

# The future of gene therapies: next steps for the UK

Summary of a workshop held by the  
Academy of Medical Sciences and the  
Cell and Gene Therapy Catapult  
7 March 2019

### **The Academy of Medical Sciences**

The Academy of Medical Sciences is the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the United Kingdom's leading medical scientists from hospitals, academia, industry and the public service. We work with them to promote excellence, influence policy to improve health and wealth, nurture the next generation of medical researchers, link academia, industry and the NHS, seize international opportunities and encourage dialogue about the medical sciences.

### **The Academy of Medical Sciences' FORUM**

The Academy's FORUM was established in 2003 to recognise the role of industry in medical research, and to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM network helps address our strategic challenge 'To harness our expertise and convening power to tackle the biggest scientific and health challenges and opportunities facing our society' as set in our Strategy 2017-21. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact [forum@acmedsci.ac.uk](mailto:forum@acmedsci.ac.uk).

### **The Cell and Gene Therapy Catapult**

The Cell and Gene Therapy Catapult was established as an independent centre of excellence to advance the growth of the UK cell and gene therapy industry, by bridging the gap between scientific research and full-scale commercialisation. With over 180 experts focusing on cell and gene therapy technologies, it works with partners in academia and industry to ensure these life-changing therapies can be developed for use in health services throughout the world. It offers leading-edge capability, technology and innovation to enable companies to take products into clinical trials and provide clinical, process development, manufacturing, regulatory, health economics and market access expertise. Its aim is to make the UK the most compelling and logical choice for UK and international partners to develop and commercialise these advanced therapies. The Cell and Gene Therapy Catapult works with Innovate UK. For more information please visit [ct.catapult.org.uk](http://ct.catapult.org.uk) or visit [www.gov.uk/innovate-uk](http://www.gov.uk/innovate-uk).

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows, or the Cell and Gene Therapy Catapult.

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# Executive summary

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**Gene therapies are an emerging class of therapeutics offering treatments, and in some cases cures, for diseases with high unmet need. As new technologies there are challenges in translating promising research to commercial therapies, including acquiring funding, manufacturing and delivery, and in how these novel disruptive therapies can be adopted in healthcare systems. With gene therapies on their way to becoming a standard part of healthcare, collaboration in overcoming these challenges will ensure the UK remains at the forefront of the cell and gene therapy field.**

On 7 March 2019, the Academy of Medical Sciences and the Cell and Gene Therapy Catapult held a FORUM workshop exploring how the UK can remain at the forefront of gene therapy development in the context of recent advances in this sector. Discussions focused on four key parts of the gene therapy translational pathway:

- Discovery science bringing through the next generation of gene therapy technologies.
- Funding strategies and opportunities for evidence generation and key milestones.
- The role of private and capital investment in growing companies and allowing expansion of clinical studies.
- The scale up challenges for gene therapies, including manufacturing, regulation and integration into healthcare systems.

The key themes of discussion that emerged from the workshop were:

- The **huge potential of next-generation gene therapy technologies** for meeting unmet need in a range of therapy areas, including rare diseases and those where treatment options are currently limited. However, these next-generation technologies also bring new scientific challenges. Targeted delivery, transfection efficiency, repeated dosing and off-target effects are all examples of such challenges. As such, the approach to new technologies needs to be measured to ensure that effective therapies are produced from these new innovations.
- The need to **begin development programmes with a clear end goal of producing an effective and deliverable therapy**, and considering how this will be achieved early in the process.
- The **rich source of gene therapy research in academia**, and the need for **pull-through mechanisms** to ensure ideas started in academia can secure continued funding and navigate the complex translational pathway.

- The methods needed to ensure **stable investment in gene therapies** and attract venture capitalist investment.
- The **complex supply chain challenges** associated with gene therapies, and how these can be overcome to ensure disruptive therapies can be adopted into **existing healthcare systems**.
- The challenges in **scaling up of gene therapy manufacturing**, and the importance of **locking down manufacturing strategies** to help with the regulation of gene therapies.
- The need for **supportive and collaborative networks** within the gene therapy landscape, to ensure the UK remains at the forefront of this growing field, as gene therapies become standard in healthcare.
- **Reimbursement for novel gene therapies** remains a challenge that needs to be solved before widespread adoption is likely.
- Initiatives such as the Advanced Therapy Treatment Centres and the Cell and Gene Therapy Catapult facilities are supporting localised discovery, manufacture and delivery, but **more is needed to support the wealth of discovery research programmes**.

# Introduction

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**Gene therapies have the potential to offer new treatments, or possibly cures, for diseases with high unmet need, including rare diseases. Due to the new technologies used, including viral and non-viral delivery systems, and both *ex-vivo* and *in-vivo* approaches, there are significant challenges in moving from research to commercial therapy. These include scientific challenges, difficulties in securing funding for discovery research and early clinical development, issues in securing investment for clinical development, unique manufacturing and supply chain challenges, and regulatory challenges.**

There are many different types of gene therapies, each of which come with their own array of challenges.

Autologous *ex vivo* gene therapies use a patient's own cells ('autologous') to correct a genetic disorder. In this approach cells are taken from the patient, modified outside of the body ('*ex vivo*'), for example using a vector carrying a functioning copy of the missing or faulty gene, and then the modified cells are transplanted back into the body. In contrast, allogeneic *ex vivo* therapies use cells derived from another patient ('allogeneic') which can be genetically modified for an "off the shelf" therapy. *In vivo* gene therapies use vectors carrying a functioning copy of the missing or faulty gene to modify the genes of cells inside the patient's body ('*in vivo*').

The method used to deliver the target genes, and the delivery vehicle, all affect the characteristics of the therapy.

The development of a gene therapy from promising preclinical research into a clinical therapy typically takes many years. The first protocol for Strimvelis, the first *ex vivo* stem cell gene therapy to treat adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID), was written in 1990 and it took 26 years of development before the European Medicines Agency (EMA) recommended marketing approval for its use. Recent developments in the field have meant that we are moving rapidly towards a time where gene therapies will be a healthcare standard. It has been noted that the challenges facing the gene therapies sector going forwards are not just scientific, but involve funding, investment, and manufacturing challenges.

This workshop, held by the Academy of Medical Sciences and the Cell and Gene Therapy Catapult, focussed on these new technologies and how the UK can continue to be at the forefront of gene therapy development.

# The landscape for gene therapies – what challenges remain?

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**Dr Jonathan Appleby, Chief Scientific Officer, Cell and Gene Therapy Catapult, introduced the challenges that remain for the development of gene therapies in the UK. He stated we should be optimistic, with several gene therapies approved for clinical use and others in the pipeline. But he cautioned that there are challenges that remain to the broader application of gene therapies, and persistence is needed to drive the field forwards.**

Different types of gene therapies have different associated challenges. Dr Appleby discussed in detail what remains to be addressed for both autologous *ex vivo* gene therapies and *in vivo* gene therapies.

## General challenges for gene therapies

Dr Appleby commented on challenges when developing gene therapies in the public arena, specifically the need to manage investors' expectations to ensure they are realistic. Gene therapies usually take decades to develop, with many peaks and troughs of success on the way which can damage investor confidence. For example, Sangamo, a biotechnology company that develops gene therapies to combat haemophilia, recently released results of a complex trial involving the first successful use of *in vivo* genome editing.<sup>1</sup> Despite one patient responding to the treatment, which represented a world first, the rest of the cohort did not respond, and investors reacted negatively, not seeing the results as positive. The announcement of the trial results led to a drop in share price, illustrating the fragile confidence of investors. This is applicable to investment in both *in vivo* and *ex vivo* gene therapies.

Other challenges that face the entire gene therapies field include; the requirement for long-term pharmacovigilance after licencing of gene therapies and the scaling up of the manufacturing of gene therapies as their use becomes more widespread throughout the healthcare system.

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<sup>1</sup> <https://investor.sangamo.com/news-releases/news-release-details/sangamo-announces-interim-results-phase-12-champions-study>

## Autologous *ex-vivo* gene therapies

The implementation of autologous *ex-vivo* gene therapies creates a complex, closed-loop supply chain. A key challenge is the transport of cells from the patient to a facility, where they are processed and modified, and then the subsequent transport back to the patient. The transport process requires the freezing and the controlled thawing of cells. This is not trivial and requires specially trained staff and specialist equipment. While an alternative approach, using allogeneic cells which come from a single donor, could help overcome these supply chain challenges it seems unlikely to happen in the near future due to the issues with immunological compatibility of allogeneic cells with the recipient's immune system.

Challenges in the autologous supply chain are being addressed by initiatives such as the Advanced Therapy Treatment Centres (ATTCs) network programme, coordinated by the Cell and Gene Therapy Catapult and initially supported by the Industrial Challenge Strategy Fund.<sup>2,3</sup> The ATTCs work with both industry partners and the NHS to develop the necessary personnel, infrastructure and processes at scale that will be needed to bring advanced therapy medicinal products, including gene therapies, to patients.

The field of immuno-oncology has grown rapidly in the last decade, and the possibility of *ex vivo* gene therapies in cancer treatment has generated a lot of excitement but these approaches still need some hurdles to be overcome. For example, the two current gene therapy treatments available are for blood cancers, specifically B-cell lymphomas, not for solid tumour cancers. There is still a need to find out how similar therapies could penetrate solid tumours effectively. Other challenges in this field include targeting specific receptor sub-types on tumours and identifying which cell types are the ideal ones to be modified.

Although there is the potential for success in autologous *ex vivo* gene therapies going forwards, failures should also be expected as the biology behind these approaches is not yet fully understood. A concern which appeared throughout the day, also highlighted by Dr Appleby, was that many of the gene therapies developed in academia might have real potential as therapies but unfortunately these are abandoned due to issues with lack of support, for example in getting follow-on funding for them. Dr Appleby suggested that there is a need for a 'pull-through' mechanism to encourage the follow through of these developments.

## *In vivo* gene therapies

One of the challenges facing *in vivo* gene therapies is their integration within the healthcare system. This includes patient management and the impact of vector shedding, where active vectors might be excreted by the patient shortly after treatment, affecting the wider population and the environment. The ATTCs can help to establish the practical procedures to overcome these point of care administration challenges.

Another of the challenges facing *in vivo* gene therapies is the development of vectors that can avoid both the innate and adaptive immune response. Vectors need to be able to reach the targeted cells and modify them without being destroyed by the patient's own immune system first. The development of new vectors capable of avoiding the immune system requires

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<sup>2</sup> <https://ct.catapult.org.uk/article-tags/attcs>

<sup>3</sup> <https://www.ukri.org/news/medicine-manufacturing-gets-multi-million-boost/>



sustained investment, not just of funding but also working with the research community, as they prefer to use well-established models and require convincing evidence to adopt newer vector systems. Some novel advances in the area of vector development are discussed in the next chapter.

The manufacturing and supply chain of *in vivo* gene therapies is simpler to scale up than for autologous *ex vivo* gene therapies. However, optimisation of the vector yield and quality control for *in vivo* therapies are still of great importance. The currently approved *in vivo* gene therapies are administered in localised tissues of the body so large volumes of vectors are not required. If larger organs and surfaces were to be targeted, the need for large volumes of vectors could lead to manufacturing challenges. For example, treating cystic fibrosis with gene therapies would require significantly more vector due to the large surface area of the lungs.

## Case study: Developing a gene therapy for ADA-SCID at UCL

Professor Bobby Gaspar, Professor of Paediatrics and Immunology, Great Ormond Street Hospital (GOSH) and Chief Scientific Officer, Orchard Therapeutics, gave an overview of the translational pathway used to develop a gene therapy for adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID). ADA-SCID is a disorder in which a single gene defect leads to abnormal immune cell development, making patients susceptible to infection and leading to patient death at a young age. The aim of the programme was to develop a gene therapy where a patient's own blood stem cells are collected, modified *ex vivo* and then returned to correct the underlying defect and grow a new immune system. Development was made easier due to the prior knowledge of allogenic bone marrow transplantation which could then be applied to gene modification of autologous cells.

In January 2007, the group was awarded an MRC research grant to develop lentiviral vectors for gene therapy of ADA SCID. Lentiviral vectors were chosen as they had a greater propensity to get into blood stem cells. Within the vector they used an EFS promoter to drive expression of the ADA gene, as this promoter expresses well in haematopoietic stem cells but also has been designed to lack enhancer activity thereby reducing the risk of oncogenic effects.

Following on from this the Translation Research Group (TRG) at UCL advised on how to take this work along the translational research pathway. In July 2009, the research group was awarded with an MRC Developmental Pathway Funding Scheme (DPFS) grant, which enabled *in vivo* studies in ADA-deficient mice. Studies showed that the lentiviral vector could correct immune defects *in vivo* and that the vector had low transformation potential *in vitro*.

Funding for a Phase I/II clinical trial of the therapy came from an MRC Developmental Clinical Studies (DCS) grant in December 2012. The clinical trial treated 10 patients, between GOSH and Mattel Children's Hospital Los Angeles, USA with manufacturing carried out at the Indiana University Vector Production Facility. The gene therapy showed high levels of safety and efficacy in patients, with increases in T lymphocytes post treatment leading to immune protection after 6-12 months.

Next in the pathway was to take this therapy out of the academic landscape to make it into an approved medicine. Here the group made use of UCL Business for advice, and decided to start-up a company, Orchard Therapeutics, with major investment from Fidelity Biosciences, and additional funding from the UCL Technology Fund.<sup>4</sup> Now Orchard Therapeutics has a pipeline of gene therapies, and it has worked to create partnerships and develop infrastructure in order to deliver their products globally.

Professor Gaspar acknowledged that a huge ecosystem is needed to develop gene therapies, and that the development pathway should be built around making sure that the treatment is the best way to treat patients.

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<sup>4</sup> <https://www.orchard-tx.com/>

# The next generation of gene therapies

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**A range of emerging technologies are being developed for use in next generation gene therapies, including novel viral and non-viral delivery methods. Alongside this, recent advances in genome editing platforms such as CRISPR-Cas9 and its derivatives are being adopted for clinical use. Next generation technologies bring many opportunities, but they also bring a range of scientific and manufacturing challenges that need to be overcome for their effective translation to commercial therapies.**

## Next generation non-viral delivery strategies

Professor Helen McCarthy, Professor of Pharmacy, Queen's University Belfast described a peptide-based drug delivery system which could be used to deliver gene therapies. She explained her ethos that 'there is no point creating a transformative drug if it cannot be delivered to the site of action', and how this has driven her to focus on novel non-viral delivery strategies.

Professor McCarthy described the development of the RALA peptide, a patented drug delivery system, which can be tuned to target certain cells types, for example tumour cells, and can transport negatively charged cargoes including DNA and small molecules to these cells. The RALA peptide is comprised of 30 amino acids and uses electrostatic interactions to encase cargo, meaning there are no cargo size limitations. The RALA peptide itself self-assembles in water to produce a RALA nanoparticle. One of the key defining features of this technology is the presence of glutamic residues which make it pH responsive. Upon uptake by cells via clathrin-mediated endocytosis, the peptide nanoparticle is transported through the endosomal system, during which endosome acidification occurs and the pH level drops, releasing the cargo. This means that the contents are non-toxic up to this point. A company, pHion Therapeutics, has now been established to further this technology.<sup>5</sup>

This next-generation non-viral delivery strategy has a range of applications, as well as potential advantages over viral strategies. This includes their non-immunogenicity, which allows repeated dosing, simpler manufacturing and scale up and their ability to carry larger cargo than viral vectors. Professor McCarthy is working with the Cell and Gene Therapy Catapult on developing this technology for use in *ex vivo* gene therapies. They have so far shown that RALA has the ability to transfect stem cells without toxicity, and they are working

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<sup>5</sup> <https://www.phiontx.co.uk/>

together on future manufacturing processes.

Finally, Professor McCarthy highlighted that her priority was now to help inform the wider community of alternative delivery vehicle technologies, such as the RALA peptide, with the aim to create promising collaborations with academia and industry.

## Next generation viral delivery strategies

Professor Eric Alton FMedSci, Professor of Respiratory Medicine and Gene Therapy, Imperial College London, described how the UK Cystic Fibrosis Gene Therapy Consortium (the Consortium) have worked on using a novel viral delivery system to develop a gene therapy for cystic fibrosis.<sup>6</sup> Cystic fibrosis is the most common, lethal, inherited disease, with those affected surviving on average to the age of 38, and death mostly attributed to repeated cycles of airway infections. Initial gene therapy strategies for cystic fibrosis used non-viral liposome-based delivery approaches and have been developed as far as early efficacy studies. Results showed that while there were no safety issues with the treatment, the moderate improvement of efficacy relative to the placebo group is unlikely to be sufficient to warrant further development.

To overcome these anticipated issues, the Consortium have developed a novel viral strategy. They initially considered Sendai virus as it has the ability to transfect airway epithelial cells, the target cells of interest, but this virus does not lead to long term expression as the dosing cannot be repeated. Professor Alton described how the Consortium, working with a Japanese biotechnology company, replaced the naturally occurring surface proteins on a lentivirus with those present on the Sendai virus (pseudotyping). This was anticipated to combine long-lasting expression, as the lentivirus components would allow integration of the transgenes into the cellular genome, with efficient transduction via the Sendai virus proteins. *In vivo* testing of this in mice demonstrated significantly superior gene transfer compared with the previous liposome-based delivery approach, with a long duration of expression and the ability for repeat dosing. Going forwards this novel Sendai-lentivirus combination will be tested in an academic first-in-man clinical trial.

Professor Alton also highlighted some of the challenges to developing gene therapies through to clinical studies, including manufacturing vectors in large enough quantities to clinical standards. In order to make progress on these multiple challenges, the Consortium have negotiated a tripartite agreement with Boehringer-Ingelheim and Oxford Biomedica. He stressed that researchers and funders should commit to a technology when there is sufficient evidence to do so and then carry this through to a clinical conclusion, rather than continually shifting focus to each new technology as these emerge. Finally, Professor Alton highlighted the need to avoid the 'cure in 5 years' time' hype, so as not to give false hope to patients.

Following on from Professor Alton's talk, Professor Amin Hajitou, Reader in Neuroinflammation and Neurodegeneration, Imperial College London, described another novel viral delivery approach this time using bacteriophages in targeted, systemic gene therapies. The use of bacteriophages, or bacterial viruses, in gene therapy delivery offers many opportunities over the standard adeno-associated viruses (AAV) or lentiviral approaches. Bacteriophages are much less expensive to manufacture at large scales, they can be targeted to specific tissues and organs, and they have a larger cloning capacity allowing them to carry larger transgenes.

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<sup>6</sup> <http://www.cfgenetherapy.org.uk/>

Professor Hajitou described how they have generated novel bacteriophage hybrid vectors, also referred to as AAV-phage. They adapted the filamentous phage, so it can enter mammalian cells via the RGD4C ligands, which are over-expressed in cancer cells but not in healthy human tissues. Using this system, they demonstrated that intravenous administration of the AAV-phage induces selective targeting to tumours, and many others have now also used this technology in systemic therapies. Initial results using the adapted phage system have shown success in treating tumours in rodents. In addition, the safety and efficacy of repeated administrations has been demonstrated in domesticated dogs following treatment of fibrosarcoma. Professor Hajitou highlighted the advantages of using domesticated animals and livestock as possible stepping stones for new human drugs and gene therapies, as they have an intact immune system compared to laboratory mice.

## Genome editing in gene therapies

Dr Nicola McCarthy, Business Unit Manager, Horizon Discovery, introduced the opportunities and challenges that CRISPR-Cas9 (CRISPR) genome editing technology brings to the gene therapy field. Horizon Discovery works mainly in the pre-clinical space, where they use CRISPR technology for a wide range of applications. The technology, while providing a robust system for research purposes, needs careful consideration for use in the clinic for a variety of reasons. However, CRISPR technology is already entering clinical trials for *ex vivo* gene therapies, including an *ex vivo* genome editing therapy for the inherited blood disorder beta-thalassemia.<sup>7</sup>

Dr McCarthy introduced some of the opportunities that CRISPR could bring when used to edit primary T-cells to improve T-cell based gene therapies. CRISPR could be used to effectively knock-in and knock-out genes to improve CAR-T cell function, for example, genes which will allow T-cells to survive longer could be knocked-in and genes which generate an immune response could be knocked out. Specifically, the removal of MHC class I antigens from the cell surface might enable the use of allogeneic cells. Using CRISPR in this way could substantially improve the quality of life of patients with diseases which require frequent hospital visits. The advent of new base editing technologies that avoid double strand breaks may also be safer than standard CRISPR approaches, as double strand breaks to DNA are often repaired inaccurately.

Many challenges remain for the use of CRISPR technology in gene therapies. It has been shown that CRISPR genome editing works well for cells *ex vivo*, but each batch of these cells requires careful quality control to check for the introduction of on-target and avoidance of off-target effects. It is important to be able to effectively detect off-target effects, including insertions and deletions as well as complex gene rearrangements that might have a long-term impact. Algorithms can help to predict these, but this becomes more challenging in whole patient genomes. Another challenge when using CRISPR for gene therapies is the delivery of this technology *in vivo*, especially for systemic diseases. Cas9 protein is known to induce an immune response, so would need to be delivered for a short treatment time.<sup>8</sup> In addition to this, the long-term effects of genome-editing need to be established, especially for its use in children. Finally, as with all gene therapies there are concerns around the manufacturing of the technology, specifically the supply of clinical grade DNA oligos and proteins which are needed to edit cells effectively.

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<sup>7</sup> <http://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-progress-clinical>

<sup>8</sup> Charlesworth CT *et al.* (2019). *Identification of preexisting adaptive immunity to Cas9 proteins in humans.* Nat. Med. **25(2)**:249-254

# The funding landscape for gene therapies

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**The development of gene therapies covers a broad range of research from discovery, to preclinical research and early clinical development. Consequently, translation of a therapy through these stages requires multiple points of funding at different milestones. At the workshop representatives from a range of funding bodies, the Engineering and Physical Sciences Research Council, the Medical Research Council, Innovate UK and LifeArc, covered the funding challenges for gene therapies, and the practical steps they have taken to overcome these.**

## Funding challenges and opportunities

One of the main challenges highlighted was that it is difficult for researchers to understand how different schemes from funding bodies link together to ensure continuity of funding. Participants in the session noted that it is very rare for one organisation to fund the whole translational pathway, from discovery research through to clinical development.

While funding bodies themselves work closely to ensure synergy across the landscape, this could be better communicated to researchers, as they would find flexible continued funding with clear milestones useful. At the meeting, the funding bodies presented a schematic of the funding landscape, highlighting how their schemes fit together across the translational pathway, as shown in **Figure 1**. Having a central point to access this information, including smaller charity funders alongside the larger funding bodies, was suggested as being very useful in helping academics understand the routes to commercialisation.

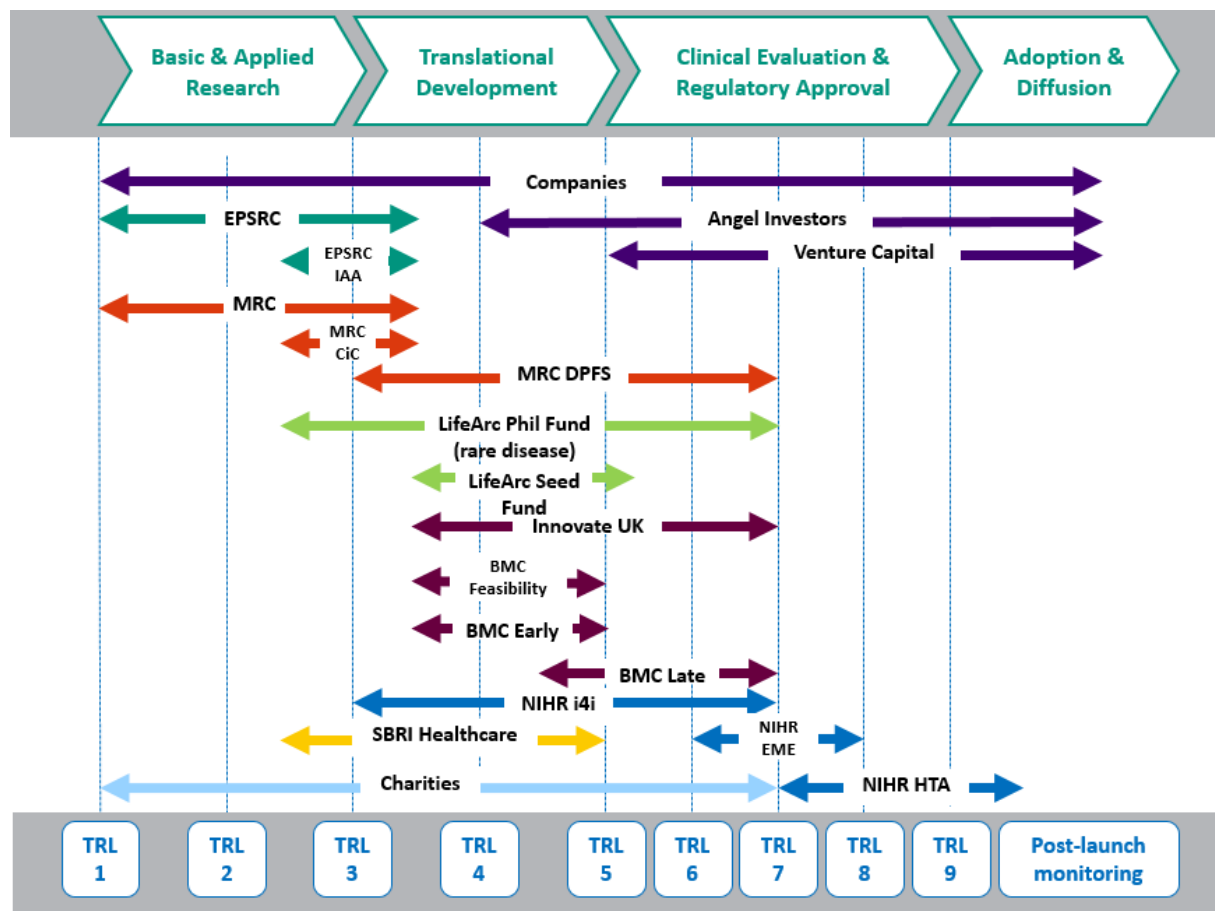


Figure 1 A schematic overview of some of the translational funding schemes available to gene therapy programmes.

## Strategies for successful funding and translation

Participants discussed a number of practical actions that both researchers and funders can take to help acquire funding and de-risk projects:

- It is important to **speak to funding bodies before applying for funding**, as they can provide information on the best places to apply and sign post applicants to the right place. UK Research & Innovation, the UK's major public research funder, have a '**no wrong door policy**' and will make introductions to other research councils.
- **De-risking early stage projects**, at either the discovery research or preclinical research stage, will help **enable continuity of funding and commercial investment**.
- Academics can also **make use of university technology transfer offices**, who will be able to advise on how to de-risk projects, although it was noted that the capacity of technology transfer offices to provide such advice varies between institutions.
- **Researchers should consider the pathway to clinic**, as technologies where this is prohibitively expensive or unrealistic are unlikely to be successfully funded. It was noted by researchers in the session that the estimation of costs of goods and returns are difficult to calculate in early stages of a research programme, especially for academics with no experience of the translation pathway.

## Case study: Commonalities between funding bodies

Dr Catriona Crombie, Philanthropic Fund Manager, LifeArc, gave an overview of the commonalities in what funding bodies are looking for in successful applications for the development of gene therapies. Despite the translational pathway being complex it is important to keep in mind that they all look for the same things in successful applications.

### **What makes a good translational research funding application?**

Dr Crombie explained that a good translational research funding application for the early development of a gene therapy, needs to be grounded on strong scientific rationale but also with a clear market pull, including patient need. An application needs to clearly articulate what the end product and goal is, with a realistic and deliverable path to get there. There also needs to be a strong team behind the application, with access to all the skills necessary for the project to deliver. Applications should give a clear review of the competition and clear acknowledgment of the risks to the project, with plans in place to mitigate and manage these. Finally, the application should highlight a sensible long-term plan and route to market.

### **What are the common failure modes for translational research projects?**

Many translational research projects, including those for gene therapies, fail for similar reasons. Dr Crombie said that the reasons for failure at the grant application stage include; pilot data not being convincing, a plan that is unlikely to yield the required evidence or a project team weak in a key area. In later stages, translational research projects fail as there is a lack of evidence for the next stage, there are problems with the proposed solution, or flawed endpoints were used in the study.



# Investment in gene therapies

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**Gene therapies pose many challenges for companies investing in them, due to the high costs of taking a therapy through clinical development and the potential risk of a lack of efficacy or unacceptable safety halting development. Participants discussed what makes a successful or 'good' investment in the gene therapy sector.**

Dr Dominic Schmidt, Partner, Syncona, described how Syncona, a life sciences investment company, approaches their investment strategies. Syncona aims to found, build and fund life science companies that have the potential to transform the delivery of healthcare in their respective markets. They set up companies to deliver marketed products and have sufficient resources to give them the flexibility to fund companies from start-up through to market delivery. Syncona has a strong focus on cell and gene therapies, with seven out of their nine portfolio companies working in this area, as these advanced therapies have the potential to revolutionise healthcare.

Dr Schmidt highlighted that the 'hype cycle', where new therapy modalities may initially generate inflated expectations, is true for any new technology, including those in the biotechnology sector. Investing too early may mean getting caught up in the hype cycle, therefore it is important for both investors and researchers to know the technology's location in the cycle. From the point of view of investors, key moments that transformed the systemic gene therapy field include; Professor Amit Nathwani and his team's 2011 publication of the first systemic adeno-associated virus (AAV) clinical trial showing sustained expression, and Professor Robert MacLaren's work published in 2014 showing clinical proof-of-concept for gene therapies in choroideremia.<sup>9,10</sup>

## **What makes an attractive investment?**

Dr Schmidt highlighted some of the key drivers that make for an attractive investment. These include a therapy that has a clear unmet clinical need, and also some initial data that the therapy could offer transformative outcomes to patients compared to standard care. In addition, there must be the ability to take the product through to market, where it will be globally competitive. Syncona also look for an aligned founder with whom they will be able to build a company.

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<sup>9</sup> Nathwani AC *et al.* (2011). *Adenovirus-associated virus vector-mediated gene transfer in hemophilia B*. N Eng J Med. **365(25)**:2357-65

<sup>10</sup> MacLaren RE *et al.* (2014). *Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial* Lancet **383(9923)**:1129-37

### **What makes investing in gene therapies challenging?**

Dr Schmidt noted that there are several major challenges facing the gene therapy sector which might impact on future investment and investor confidence. Currently the size of transgenes that can be accommodated into single vectors is limited, meaning that gene therapies are not possible for many diseases that require large transgenes. There is also the challenge of pre-existing neutralising antibodies being present, in particular in adult patient populations, meaning that only a portion of patients will be able to receive treatment and that re-administration of an *in vivo* gene therapy is not currently possible. Questions also remain about how to increase the potency of gene therapies without increasing their toxicity. For example, for a low expressing protein it is reasonably straightforward to obtain the right expression level, but if a large amount of protein needs to be produced this can be more challenging. Additionally, gene therapies are currently primarily focused on treating recessive monogenic conditions, expanding the use of gene therapies to treat dominant diseases and those caused by multiple genes is important to ensure widespread market applicability.

Finally, one of the key challenges facing gene therapies is the industrialisation of manufacturing, especially if gene therapies start being used to treat systemic common diseases where large amounts of vectors are required. Investors need to see that a potential therapy has a route through to market and part of this is ensuring that the manufacture of vectors can be scaled up to ensure widespread patient delivery. To ensure a successful route to market, manufacturing needs to be high quality, but also cheaper than it is currently. Progress is being made on manufacturing and scaling-up processes, but the current pace is not sufficient to ensure that these therapies can be used widely across the healthcare sector. Wide scale uptake in healthcare will also require reimbursement structures that account for these one-time, potentially curative treatments.

## Case study: Academic strategies for advanced therapy translation

Dr Pamela Tranter, Head of the Translational Research Group (TRG), Translational Research Office (TRO), University College London (UCL), described how the TRO at UCL supports academics who have developed advanced therapies to progress through the translational pathway.

The TRO is an experienced support group with extensive industrial science and innovation expertise which enables UCL to capitalise on academic discoveries. The TRO's mature biomedical translation portfolio includes 46 active projects, and almost 50% of these are in advanced therapies. Within the TRO, the TRG establishes and maintains a portfolio of funded translational projects, assisting with project management and milestones.

The TRO uses a range of funding schemes, both internal and external, to support the translation pathway for advanced therapies. The internal funding schemes available include the UCL Therapeutic Acceleration Scheme, which funds around 18 projects a year for proof-of-concept work at the discovery stage of development. For these projects, a manager works closely with the research team, and assists in ensuring timely applications for the next stage of funding, allowing continuity. Internally, the TRO also has a Biomedical Research Centre (BRC) fund and EPSRC Impact Acceleration Award funding. The TRO also makes use of internal venture funding, from the UCL Technology Fund and the Apollo Fund, which both fund at the pre-clinical/early clinical phase of development.

Externally, the TRO mainly uses the MRC Developmental Pathway Funding Scheme (DPFS) to fund projects at the pre-clinical stage and those in early clinical trials. The TRO have found the MRC to be very responsive in outlining the milestones required to secure the next round of funding. Other external funding schemes used by the TRG include; the NIHR Invention for Innovation (i4i) scheme, charity schemes (Wellcome, LifeArc, BHF), and industry partnerships.

Therapeutic Innovation Networks (TINs), have been set up at UCL to bring together researchers and build expert communities around certain modalities in order to drive translational networks. The Cell, Gene and Regenerative Medicine TIN at UCL carried out an extensive scoping exercise to identify the portfolio of advanced therapy projects at UCL. This has enabled them to articulate the wealth of ongoing academic studies and to highlight the increasing demand for GMP manufacture for viral vectors in particular.

Through these schemes UCL has developed strength and depth in cell and gene therapy translation, with pioneering first-in-human studies and several high profile spin-out companies. The main challenges for the TRO going forwards is ensuring a sustainable pipeline through which success at UCL can be continued, and to minimise delays and gaps in funding for translational projects.

## Case study: how did GSK divest their rare disease gene therapy portfolio?

Dr Jon Ellis, VP Business Development, GlaxoSmithKline (GSK), described how GSK divested their rare disease gene therapies portfolio. GSK has been involved in developing gene therapies for over 20 years.

GSK was initially interested in working with Professor Jim Wilson from the University of Pennsylvania on the vectorising of adenoviruses for vaccines and the use of adeno-associated viruses (AAVs) for gene therapies. GSK collaborated with Professor Wilson for a number of years. However, in 2009 GSK deprioritised in-house research into AAV gene therapies, and together with the University, licensed rights in the AAV platform to ReGenX BIO, which has continued to develop the technology.

In 2010, GSK returned to gene therapies, this time in the development of *ex vivo* gene therapies, leading to a long and productive collaboration with the San Raffaele Telethon Institute for Gene Therapy eventually ending in Strimvelis, the first *ex vivo* stem cell gene therapy to be approved as a commercial product to treat ADA-SCID. In this time period they also started working with Adaptimmune on their T-cell receptor work in cancer immunotherapy, a collaboration which is ongoing.

In 2018, GSK divested their rare disease gene therapies portfolio to Orchard Therapeutics. This came after an internal review into the prioritisation of research and development at GSK which came to the conclusion that GSK was not the best company to commercialise these products, as the development of rare disease gene therapies is a specialised business. GSK ran a competitive process to find a partner who shared their drive to get these treatments through to patients. They struck a competitive deal with Orchard Therapeutics, which was structured in a way that aligns GSK's long-term economic interest with Orchard's and the success of these therapies going forward. Currently GSK's internal gene therapy focus is on oncology.

Despite gene therapies being a new field, with many twists and turns and setbacks on the path so far, Dr Ellis noted that with persistence, high quality science and smart strategy, the potential of these therapies will be fulfilled. He also noted that the major strategic hurdle going forwards is the profitability of gene therapies, as sustainable profitability is fundamental to continuing to attract investment and innovation into the field.

# Manufacturing and scale up of gene therapies in the UK

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**There are major challenges associated with the scale up of gene therapy manufacturing, the regulation of this process and how manufacturing will work in healthcare scenarios. Participants in this session highlighted the key challenges associated with each of these and what options are available to overcome these.**

## Small scale manufacturing

Professor Farzin Farzaneh, Professor of Molecular Medicine, King's College London (KCL), described how the small-scale manufacturing facility at King's supports the rapid transition of products to clinical studies, by having the capability to manufacture large numbers of vectors in small batches. The facility has the ability to produce vectors for clinical studies, under Good Manufacturing Practice (GMP) standards, and for each of the last three years the facility has produced around 20 viral vectors.

The facility at KCL works to fast track innovation in manufacturing on a small scale. For example, they have developed an approach which uses paramagnetic beads to concentrate retroviral vectors.<sup>11</sup> Professor Farzaneh's lab are currently working on a range of new initiatives to overcome the outstanding problems in all manufacturing systems, these include; using more stable producer cell lines, using cell lines which are more suitable for large scale manufacturing, and using vectors with altered tropism for *in vivo* applications. These are innovative approaches although it remains to be seen if they are translatable to large scale manufacturing systems when a product is in the later stages of development.

Small scale academic manufacturing centres, similar to Professor Farzaneh's, underpin the leading position of the UK in gene therapy. They enable the rapid transition of new therapies into clinical research, where there can be fast evaluation of the safety and efficacy of these therapies, enabling efficient handover of manufacturing to spin-out companies. In collaboration with University College London, Imperial College London and Queen Mary University of London, Professor Farzaneh's facility provides manufacturing facilities for rapid clinical evaluation in the UK. This has provided a rapid route to move candidate products into advanced clinical studies, and has contributed to the UK having more regulatory approved clinical trials in cell and gene therapies than the rest of Europe. More widely, this provides a recipe for industrial success by giving the opportunity for associated business development.

Professor Farzaneh highlighted that the main challenge for the gene therapies sector is

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<https://www.kcl.ac.uk/lsm/research/divisions/cancer/research/groups/haematooncology/services/celltherapysuite>

ensuring the rapid passage from proof-of-concept studies to clinical studies. For this there needs to be reliability in manufacturing allowing robust planning and the use of a scalable manufacturing strategy from early on, which is suitable for the safe, efficient and rapid transition from Phase I clinical trials through to a marketed product.

## Scaling-up gene therapy manufacturing

Mr Peter Coleman, Chief Executive, Cobra Biologics, highlighted the challenges in scaling-up gene therapy manufacturing for a contract development and manufacturing organisation such as Cobra Biologics. The main challenge is the complexity of the supply chain, often consisting of fragmented development and manufacturing systems, with multiple partners required. This complex supply chain is further compounded by scarce capacity for producing DNA and viral vectors, a critical component in the supply chain. Alongside this, there is also diversity within the gene therapy sector; both dose levels and patient numbers can vary widely, and there is a range of different vector types in use. These challenges need to be overcome to allow the rapid development of manufacturing systems and to enable timely commercialisation.

Another challenge facing scale-up of gene therapy manufacturing is that the sector sits in an emerging regulatory landscape. Regulators have highlighted that a lot of the complexity in the field comes from product-related issues and not clinical issues. Mr Coleman noted that it is never straight-forward to transfer technology from research to GMP grade material, with regulatory authorities strongly advising organisations to lock down their manufacturing process early on in product development. Industry needs to work with academia to ensure manufacturing systems are in place from an early stage to enable a seamless transition from research grade to commercial grade manufacturing.

Dr Jim Faulkner, Senior Vice President, Head of Product Delivery, Autolus, expanded on some of the challenges identified by Mr Coleman. Autolus is a leader in T-cell programming and manufacturing technology, developing the future generations of T-cell therapies targeting both haematological cancers and solid tumours. Dr Faulkner noted that from early in Autolus' development there was a strong focus on manufacturing, as patient benefit is contingent on successful delivery of gene therapies.

Autolus were the first company to make use of the Cell and Gene Therapy Catapult Manufacturing Centre in Stevenage, UK, to manufacture their products and are now producing clinical-grade products from it. Currently they are launching their own manufacturing facility close to Stevenage. Dr Faulkner noted that they have located the new facility close to Stevenage due to the need to remain close to the talent pool. He noted one of the main challenges not yet mentioned, in terms of manufacturing, was the low number of skilled workers available in the manufacturing of gene therapies.

## Regulation of gene therapy manufacturing

Dr Graham McNaughton, Senior Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency (MHRA), described the approach of the MHRA to new technologies including gene therapy manufacturing. Dr McNaughton noted that regulators such as the MHRA need to be made aware of the regulatory complications for new sectors, which are dealing with new technology, new product types, and new manufacturing processes. Through early engagement, they can support the sector to ensure that progress with new therapies is not stifled because they do not fit into an established pathway.

In order to regulate advanced therapies effectively the MHRA needs to understand where the risks are, and how to balance these with the benefits new therapies could bring. In addition, the MHRA needs to be able to understand the impact of manufacturing changes, including scaling-up and automation, on products for patient delivery, and they require data showing this impact to enable them to evaluate these changes fully.

Dr McNaughton, explained the actions the MHRA take to anticipate the challenges faced by new therapies. This includes interacting with communities, and using internal horizon scanning to look at signals which may reveal gaps in expertise or regulations. The MHRA also encourages the community to support regulators through meetings with the innovation office; more details on this are available in the case study below.

## Case study: MHRA Innovation Office

Dr Graham McNaughton, Senior Pharmaceutical Assessor, MHRA, encouraged research communities working on new therapies, such as gene therapies, to support regulators through interaction with the Innovation Office.

The MHRA Innovation Office was set up in 2013 to provide a single point of access to expert regulatory information, advice and guidance to all organisations that develop innovative medicines, medical devices or novel manufacturing processes, particularly where these might challenge the current regulatory framework. The service helps to make regulatory information clear and accessible, ensuring that the UK remains a world leader in the development of life sciences projects. The MHRA Innovation Office is a free service, but follow-on scientific advice is charged for.

Dr McNaughton urged participants at the meeting to engage through the MHRA Innovation Office early in the development process, as this enables a two-way conversation where problems can be pre-empted and resolved. He noted that it is much better for the MHRA to see a new therapy at this point than for the first time at a clinical trial application, allowing de-risking of the development process. Participants at the meeting supported Dr McNaughton's comments, describing how they have found the experience of working with the MHRA Innovation Office to be very beneficial to product development, as they were provided with pragmatic advice and could have an open dialogue.



## Adoption of gene therapies into healthcare

Dr Jacqueline Barry, Chief Clinical Officer, Cell and Gene Therapy Catapult, described the challenges associated with adopting gene therapies, and other advanced therapies, into current healthcare models. Initially, she highlighted the scale-up challenge being faced. In 2018, around 200 patients were treated with cell and gene therapies, mainly through clinical trials, by 2028 around 10,000 patients will be treated, with the delivery of these embedded into healthcare.

Dr Barry described the barriers which stand in the way of patient access to gene therapies. One of the challenges she identified was the lack of development and maturity in the analytical methodologies used to characterise gene therapies, which could support manufacturing and provide data to regulators. Ensuring these systems are set-up well from early in the development process will ensure there is enough good quality data to support both licensing, reimbursement and post-licensing follow-up.

Highlighted again was the challenge of reimbursement of gene therapies by healthcare systems. Several licensed therapies have been withdrawn from the market largely due to challenges in securing reimbursement, there are few of these products with formal reimbursement in place. Compared to other EU Countries, the UK is doing well on this front with the following products approved for reimbursement; Yescarta, Kymriah, Spherox, Strimvelis, Imlygic, and Holoclar.

Dr Barry also highlighted the importance of maintaining a skilled workforce to drive forward the adoption of gene therapies. These skilled workers are needed at all stages of development, from discovery through to commercial manufacturing, and are crucial to be able to ensure routine supply to the healthcare system.

The ATTC network, described earlier, is also involved in overcoming the challenges in the network supply chain, and are working with the London Advanced Therapy Network. Currently, the ATTC network is focussed on increasing the ability of the NHS to deliver gene therapies at scale to patients across the NHS, by developing easy-to-run and ready-to-use systems within NHS trusts and hospitals. Lessons learnt from these initial centres will be passed on to other centres in the UK to improve institutional readiness and ultimately patient access to gene therapies.

# Conclusions

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Workshop co-chairs Dr Melanie Lee FMedSci, Chief Executive Officer, LifeArc, and Professor Uta Griesenbach, Professor of Molecular Medicine, Imperial College London, concluded the workshop by highlighting that it was clear that the UK is at the forefront of gene therapy development. They also noted that in bringing the community together for the workshop, they were able to cover the many challenges which need to be overcome to ensure that the UK remains at the forefront.

Dr Lee commented that there is a rich source of gene therapy research from academia and this is supported by a lot of activity in supporting translation, however she noted that there is confusion in this area and that this could be alleviated by better coordination and communication by funding bodies. There is also a need to create resources to keep academics committed, motivated and supported through the long journey of developing a gene therapy from discovery through to clinical application. More supportive networks within the gene therapy community could help to do this. It was also noted that work needs to be done to bridge the worlds of academic science and translation, and this could be done by ensuring teams have the broad set of skills and disciplines which are needed at different stages of development.

Big scientific challenges remain for gene therapies, for example, in the repeated administration of gene therapies, and the need for new vectors and new delivery systems, with Dr Lee noting that we might be staring at some obvious alternatives but these are missed due to fixation on certain technologies. She also noted that the gene therapy sector benefits from starting with discrete patient populations, giving a significant source of learning for future therapies in other areas which are not yet recognised as discrete genetic diseases.

Dr Lee was excited by the fact that we are moving towards a stage where gene therapy will be a standard in healthcare. And concluding her comments, Dr Lee noted that you need to be able to see the way through the development pathway for successful translation to occur, with patient need being a key driver behind innovation.

Professor Griesenbach gave an academic's perspective of the gene therapies landscape, noting that there is clearly a need for universities to have dedicated teams, like the UCL TRO, in order to help academics navigate the translation pathway. These teams also help to link researchers up, to prevent silos, and allowing better coordination of research activities. These are vital to keep the UK as a strong player in this field, and an attractive environment for industry investment.

Finally, she also noted that the scaling-up of gene therapy manufacture is a major challenge, but that many initiatives are underway in this area that will drive change, including the ATTC networks. Alongside this, workforce training is essential across the board to ensure expertise in the workforce so the UK can remain at the forefront of this field. Professor Griesenbach noted that this was particularly important in the context of academia to keep the pipeline of translation open.

# Annex 1: Attendees List

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## Co-Chairs

**Professor Uta Griesenbach**, Professor of Molecular Medicine, Imperial College London

**Dr Melanie Lee CBE FMedSci**, Chief Executive Officer, LifeArc

## Speakers and panellists

**Professor Eric Alton FMedSci**, Professor of Respiratory Medicine and Gene Therapy, Imperial College London

**Dr Jonathan Appleby**, Chief Scientific Officer, Cell and Gene Therapy Catapult

**Dr Jacqueline Barry**, Chief Clinical Officer, Cell and Gene Therapy Catapult

**Mr Peter Coleman**, Chief Executive, Cobra Biologics

**Dr Catriona Crombie**, Philanthropic Fund Manager, LifeArc

**Dr Jon Ellis**, VP & Head, Science & Technology Licensing, GlaxoSmithKline

**Professor Farzin Farzaneh**, Professor of Molecular Medicine, King's College London

**Dr Jim Faulkner**, Senior Vice President, Head of Product Delivery, Autolus

**Professor Bobby Gaspar**, Professor of Paediatrics and Immunology, Great Ormond Street Hospital

**Dr Amin Hajitou**, Reader in Neuroinflammation and Neurodegeneration, Imperial College London

**Dr Iain Larmour**, Senior Portfolio Manager, EPSRC

**Dr Kath Mackay**, Director Ageing Society, Health & Nutrition, Innovate UK

**Dr Nicola McCarthy**, Business Unit Manager, Horizon Discovery

**Professor Helen McCarthy**, Professor of Pharmacy, Queen's University Belfast

**Dr Graham McNaughton**, Senior Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency

**Dr Steve Oakeshott**, Head of Innovative Technologies, Medical Research Council

**Dr Dominic Schmidt**, Partner, Syncona

**Dr Pamela Tranter**, Head, Translational Research Group, University College London

## Attendees

**Dr Kate Adcock**, Director of Research and Innovation, Muscular Dystrophy UK

**Dr Rubina Ahmed**, Head of Research, Fight for Sight

**Dr Tauhid Ali**, VP Global Program Leader, Takeda

**Ms Kate Arkell**, Research Development Manager, Retina UK

**Dr Mariana Arroja**, Regulatory Medical Writer, Kinesys Consulting

**Professor Metin Avkiran**, Associate Medical Director (Research), British Heart Foundation

**Dr Eva Barkauskaite**, Senior Consultant, Pricing and Market Access, PAREXEL

**Dr Chris Boyd**, Reader, University of Edinburgh

**Dr Mark Briggs**, Head of Cell & Gene Therapy, Welsh Blood Service

**Dr David Bull**, Director of Research, Duchenne UK

**Dr Rob Clemmitt**, Head, Cell & Gene Therapy Medicine & Process Delivery, GlaxoSmithKline

**Dr Elisa Corritore**, FEAM Forum Policy Officer, Federation of European Academies of Medicine

**Dr Silvana Cossins**, Research Collaboration Manager, NIHR Office for Clinical Research Infrastructure

**Professor Giulio Cossu FMedSci**, Professor of Regenerative Medicine, University of Manchester

**Dr John Counsell**, Research Associate, University College London

**Ms Nicola Courtenay**, External Program Director, Takeda

**Dr Bryan Deane**, Interim Head of Product and Process Innovation, Association of the British Pharmaceutical Industry

**Mr Matthew Durdy**, Chief Business Officer, Cell and Gene Therapy Catapult

**Dr Andrew Gennery**, Clinical Reader and Consultant, Great North Children's Hospital

**Dr Francesca Gliubich**, Director, London Advanced Therapies Programme

**Professor Simon Howell**, Director of Academic Estates Strategy for Health Campuses, King's College London

**Dr Shoshanna Isaacson**, Grants Manager, GOSH Children's Charity

**Dr Beki James**, Consultant Paediatric Haematologist, Leeds Teaching Hospitals NHS Trust

**Dr Minesh Jobanputra**, Director, Medical Affairs, Bluebird Bio UK

**Mr James Lawford-Davies**, Partner, Hill Dickinson

**Dr Natasa Levicar**, Senior Research Advisor, British Heart Foundation

**Dr Nicole Mathon**, Head, Opportunity Assessment Group, LifeArc

**Dr Bettina Mavrommatis**, Senior Scientific Officer, Department of Health and Social Care

**Mr Dominic McDonagh**, Senior Policy Manager, Investment and Engagement, Office for Life Sciences

**Dr James Miskin**, Chief Technical Officer, Oxford BioMedica

**Dr Penny Morton**, Programme Manager for Translational Research, Medical Research Council

**Professor Jo Mountford**, Cellular Therapies Group Lead, Scottish National Blood Transfusion Service

**Ms Megan Mullaney**, Research and Communications Officer, Duchenne UK

**Professor Stuart Nicklin**, Professor of Cardiovascular Therapy, University of Glasgow

**Dr Grace Okoli**, NIHR Clinical Lecturer, Queen Mary University of London

**Professor Richard Piercy**, Professor of Comparative Neuromuscular Diseases, Royal Veterinary College

**Mr Ian Rees**, Unit Manager, Inspectorate Strategy & Innovation, Medicines and Healthcare products Regulatory Agency

**Dr Gregory Robinson**, Chief Scientific Officer, NightstaRx

**Dr Simon Rothwell**, Consultant, Pricing and Market Access, PAREXEL

**Dr Klaus Rudolf**, Director, Research Beyond Borders, Boehringer-Ingelheim

**Professor Stephanie Schorge**, Chair in Translational Neuroscience, University College London

**Dr Fiona Thistlethwaite**, Medical Oncology Consultant, The Christie NHS Foundation Trust

**Dr David Venables**, Chief Executive Officer, Synpromics

**Dr James Warburton**, Country Medical Director - Oncology, Novartis

**Ms Alison Whitehorn**, Senior Regulatory & Strategy Consultant, Kinesys Consulting

**Dr Luke Williams**, Strategy and Policy Officer, Bioscience for Health, Biotechnology and Biological Sciences Research Council

#### **Secretariat and staff**

**Dr Abigail Bloy**, Policy Officer, Academy of Medical Sciences

**Dr Elizabeth Bohm**, Head of International, Academy of Medical Sciences

**Dr Emanuela Costigliola**, Head of Marketing and Communications, Cell and Gene Therapy Catapult

**Dr Shaun Griffin**, Interim Head of Policy, Academy of Medical Sciences

**Dr Gizem Osman**, Executive Research Assistant, Cell and Gene Therapy Catapult

**Dr Rachel Quinn**, Director of Medical Science Policy, Academy of Medical Sciences

**Dr James Squires**, FORUM Policy Manager, Academy of Medical Sciences

**Ms Cristiana Vagnoni**, Policy Intern, Academy of Medical Sciences

**Ms Beverley Wilson**, Policy Intern, Academy of Medical Sciences

# Annex 2: Agenda

Thursday 7 March 2019, 09.30-17.00, 11 Cavendish Square, London, W1G 0AN

09.30-10.00	<b>Registration and refreshments</b>
10.00-10.10	<b>Welcome and introduction</b> Dr Melanie Lee FMedSci, Chief Executive Officer, LifeArc and Professor Uta Griesenbach, Professor of Molecular Medicine, Imperial College London (co-chairs)
<b>Morning session</b>	
10.10-10.35	<b>Case study: the translational pathway for gene therapies</b> Professor Bobby Gaspar, Professor of Paediatrics and Immunology, Great Ormond Street Hospital and Chief Scientific Officer, Orchard Therapeutics
10.35-10.50	<b>The landscape for gene therapies – what challenges remain?</b> Dr Jonathan Appleby, Chief Scientific Officer, Cell and Gene Therapy Catapult
10.50-11.50	<b>The next generation of gene therapies</b> <i>Exciting developments in gene therapies and the challenges and opportunities for viral vs. non-viral vectors.</i>  <ol style="list-style-type: none"> <li>1. Professor Eric Alton FMedSci, Professor of Respiratory Medicine and Gene Therapy, Imperial College London</li> <li>2. Dr Nicola McCarthy, Business Unit Manager, Horizon Discovery</li> <li>3. Professor Helen McCarthy, Professor of Pharmacy, Queen's University Belfast</li> <li>4. Dr Amin Hajitou, Reader in Neuroinflammation and Neurodegeneration, Imperial College London</li> </ol>
11.50-12.10	<b>Tea and coffee</b>
12.10-13.10	<b>The funding landscape</b> <i>What is needed to secure funding for the early development of gene therapies – followed by discussion with the delegation.</i>  <ol style="list-style-type: none"> <li>1. Dr Iain Larmour, Senior Portfolio Manager, Engineering and Physical Sciences Research Council</li> <li>2. Dr Stephen Oakeshott, Head of Innovative Technologies, Medical Research Council</li> <li>3. Dr Kath Mackay, Director – Ageing Society, Health and Nutrition, Innovate UK</li> <li>4. Dr Catriona Crombie, Philanthropic Fund Manager, LifeArc</li> </ol>
13.10-14.00	<b>Lunch</b>
<b>Afternoon session</b>	
14.00-15.15	<b>What makes a good gene therapy investment?</b> <i>What makes a successful or 'good' investment - followed by discussion with the delegation on the challenges to investment.</i>  <ol style="list-style-type: none"> <li>1. Dr Pamela Tranter, Head, Translational Research Group, University College London</li> <li>2. Dr Dominic Schmidt, Partner, Syncona</li> <li>3. Dr Jon Ellis, VP, Business Development, GlaxoSmithKline</li> </ol>
15.15-15.45	<b>Tea and coffee</b>
15.45-16.45	<b>Key UK capabilities for manufacturing and scale up</b>

	<p><i>What are the challenges associated with scale up and manufacturing of gene therapies – what options are available to researchers? Followed by discussion with the delegation.</i></p> <ol style="list-style-type: none"> <li>1. Professor Farzin Farzaneh, Professor of Molecular Medicine, King's College London</li> <li>2. Mr Peter Coleman, Chief Executive, Cobra Biologics</li> <li>3. Dr Graham McNaughton, Senior Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency</li> <li>4. Dr Jim Faulkner, Senior Vice President, Head of Product Delivery, Autolus</li> <li>5. Dr Jacqueline Barry, Chief Clinical Officer, Cell &amp; Gene Therapy Catapult</li> </ol>
16.45-17.00	<p><b>A roadmap for the future and next steps</b>  <i>A summary of the key points and next steps from each discussion.</i>  Dr Melanie Lee FMedSci, Chief Executive Officer, LifeArc and Professor Uta Griesenbach, Professor of Molecular Medicine, Imperial College London (co-chairs)</p>
17.00-18.30	<p><b>Drinks and networking reception</b></p>

# Annex 3: Glossary

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- ADA-SCID – Adenosine deaminase deficiency – severe combined immunodeficiency. A rare, autosomal recessive metabolic disorder that results in an impaired immune system.
- AAV – Adeno-associated virus – a specific virus which is known to infect humans but cause no disease or symptoms.
- Allogeneic therapy – where the cells administered to a patient have come from another, genetically non-identical donor.
- ATTC – Advanced Therapy Treatment Centre.
- Autologous therapy – where the cells administered to a patient have come from the patient's own tissues.
- Bacteriophage – a virus that selectively infects bacteria.
- BHF – British Heart Foundation.
- CAR-T therapy – Chimeric antigen receptor T-cell therapy – an autologous cell therapy where T-cells are genetically modified outside the body to be able to recognise and fight the patient's cancer.
- CGTC – Cell and Gene Therapy Catapult.
- CRISPR – a genome editing tool used in both *ex vivo* and *in vivo* research and therapies.
- EMA – European Medicines Agency
- EPSRC – Engineering and Physical Sciences Research Council
- *Ex vivo* modification – where cells are modified outside of the body.
- GMP – Good Manufacturing Practices. A set of minimum regulatory standards that govern the manufacturing of cell and gene therapies to ensure that they meet the required quality.
- *In vivo* modification – where cells are modified while still *in situ* in the body.
- Lentivirus – a family of retroviruses.
- Liposome – a small vesicle, composed of lipids, that can be used to encapsulate other molecules.
- MRC – Medical Research Council.
- NIHR – National Institute for Health Research
- Sendai virus – a group of viruses used as models for infecting or inducing cancerous cells in animals.





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