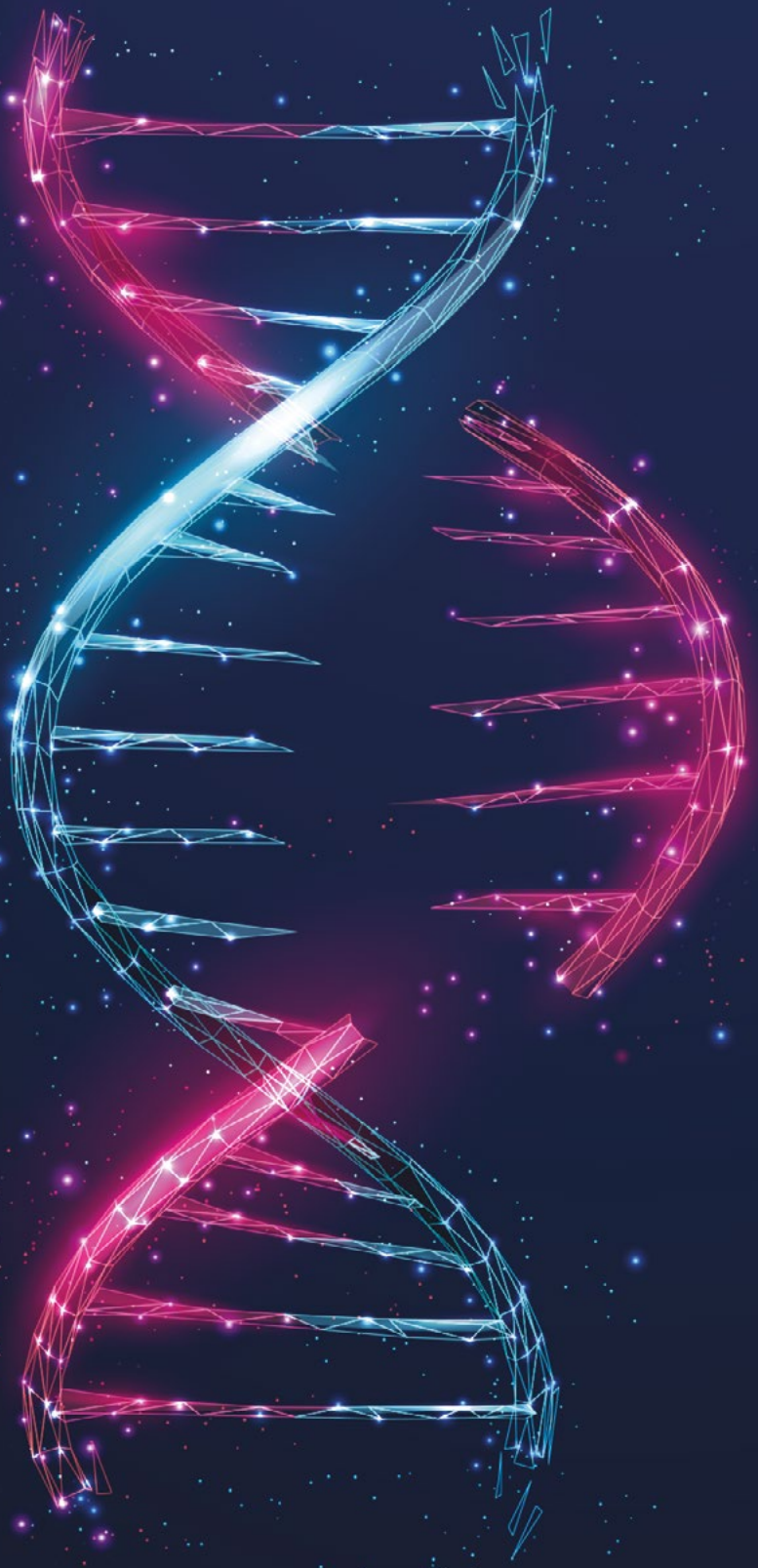
Part of the conference series
Transforming our future

Gene editing medicines

7 – 8 November 2024



THE
ROYAL
SOCIETY

Introduction

On 7 – 8 November 2024 the Royal Society hosted a hybrid conference on gene editing medicines.

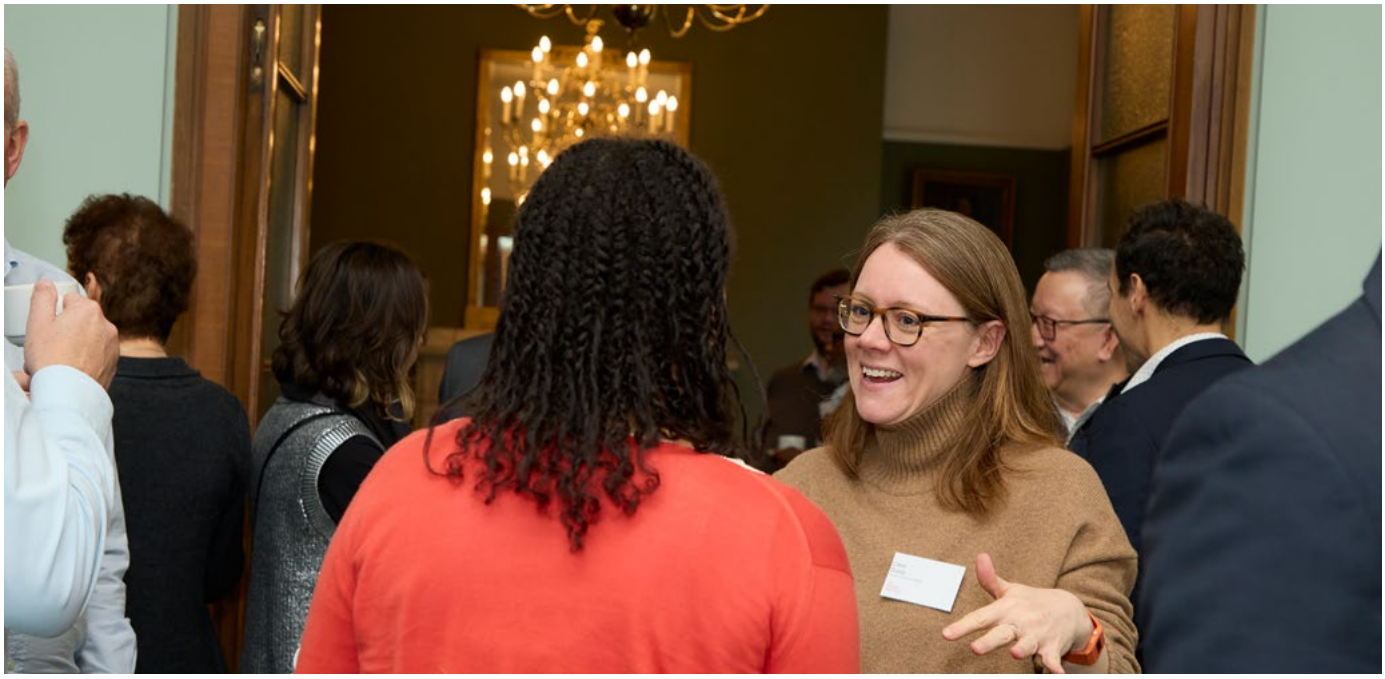


Image: Melissa Haynes Agoro, Nuffield Council on Bioethics; and Clare Duddy, House of Commons Library.

This event was delivered as part of the Royal Society's Transforming our future conference series. Meetings in this series bring together experts from industry, academia, funding bodies, the wider scientific community and government to explore and address key scientific and technical challenges of the coming decade. These conferences are organised with the support of the Royal Society's Science, Industry and Translation Committee. AstraZeneca kindly provided a sponsorship grant towards this conference, which was conceived and delivered by the Royal Society. For more details, visit: **royalsociety.org/transforming-our-future/**

Summaries of the talks and panel sessions from the conference are presented in this report. Please note, these are not verbatim records. They are intended to reflect the key points raised during presentations and discussions. Opinions and recommendations included in this report are not necessarily those of the Royal Society.

"Gene editing medicines have already transformed the future for patients – the first medicine has launched and we can look forward to many more in the years ahead."

Steve Rees OBE, AstraZeneca, conference organiser.

"The UK is in a very special position because of the NHS. There is a national referral system, treatment is free at the point of delivery, and the regulatory environment in the UK for gene editing medicines is unparalleled."

Professor Waseem Qasim, UCL Great Ormond Street Institute of Child Health, conference organiser.

Executive summary

Just 12 years after the discovery of CRISPR / Cas9, the first gene editing medicine has been approved, two candidates are in late stage clinical trials, and many more are in development. The underpinning science continues to develop at a rapid pace, and clinical applications are growing. However, the widespread roll-out of these medicines is constrained by challenges associated with manufacturing, scale-up, regulation, equitable access, health economics and safety.

The *Gene editing medicines* conference held on 7 – 8 November 2024 brought together speakers from industry, academia and the healthcare community to discuss how scientific breakthroughs in genome editing can be translated into effective strategies for improved health, including the prevention and management of chronic disease.

Two keynote presentations set the tone for the meeting. Professor Julian Gillmore, UCL, discussed recent work on CRISPR / Cas9-based gene editing for transthyretin amyloidosis, the first *in vivo* approach to be approved for phase 3 clinical trials. Professor Fyodor Urnov, University of California, Berkeley, issued a passionate call to action, highlighting the potential for gene editing medicines to cure thousands of rare, severe diseases and the need for both innovation and political courage to achieve this aim.

Additional talks and panel sessions aligned with the following themes:

- gene editing technologies;
- cell therapy engineering and gene delivery;
- patient experiences;
- clinical perspectives;
- barriers to success;
- patient access and health economics; and
- the future of gene editing medicines.

Image: Dr Laura Sepp-Lorenzino, Intellia Therapeutics, conference organiser.

> "Delivery is still a major issue for gene editing medicines. Solutions are needed if we want to expand the range of diseases that can be treated using this these therapies."
>
> Dr Laura Sepp-Lorenzino, Intellia Therapeutics, conference organiser.

Image: Professor Robin Ali, King's College London, conference organiser.

"Cell and gene therapies often must be tailored to an individual patient. Manufacturing these personalised medicines in a cost-effective way continues to be a real challenge to the scale up of these therapies."

Professor Robin Ali, King's College London, conference organiser.

Development of the programme was led by Professor Robin Ali, King's College London, Professor Robin Lovell-Badge FRS, The Francis Crick Institute, Steve Rees OBE, AstraZeneca, Dr Laura Sepp-Lorenzino, Intellia Therapeutics and Professor Waseem Qasim, UCL Great Ormond Street Institute of Child Health. The Royal Society is grateful to the organising committee for their generous contributions to this event.

Recordings of the presentations are available at **youtu.be/43BrMJo98LA?feature=shared**

"Delivery is still a major issue for gene editing medicines. Solutions are needed if we want to expand the range of diseases that can be treated using this these therapies."

Dr Laura Sepp-Lorenzino, Intellia Therapeutics, conference organiser.

"Getting a view from patients and their representatives is an incredibly important aspect of developing gene editing therapies."

Professor Robin Lovell-Badge FRS
The Francis Crick Institute, conference organiser.

OPENING KEYNOTE

CRISPR / Cas9-based *in vivo* gene editing for transthyretin amyloidosis

Professor Julian Gillmore, UCL, described his pioneering work on developing *in vivo* therapeutics to treat rare, severe diseases impacting the heart and tendons.

Image: Professor Julian Gillmore, UCL.

> "Less than ten years ago, transthyretin amyloidosis was a completely untreatable, progressive and ultimately fatal disease. Novel RNA interference and gene editing therapeutics have completely changed outcomes in this hitherto progressive and fatal disease."
>
> Professor Julian Gillmore, UCL.

Gene editing medicines are now becoming a realistic treatment option for a handful of diseases. Most CRISPR-based therapies in development involve *ex vivo* editing, in which cells are removed from a patient, edited, then infused back into the patient. This ensures that only selected cell types are edited, and avoids any long-term risks associated with having genome editing components in the body (eg immune reactions). However, *ex vivo* editing is only feasible for some cell types.

In vivo gene editing could transform the treatment of a huge number of genetic diseases, particularly those for which *ex vivo* gene editing is not an option. Recent first-in-human work has demonstrated the potential of *in vivo* gene editing to treat transthyretin (ATTR) amyloidosis.

ATTR amyloidosis

Amyloidosis is a rare disease characterised by the build-up of amyloid protein in organs of the body. There are many different types of amyloidosis. ATTR amyloidosis, now the most-commonly diagnosed type of amyloidosis, occurs when transthyretin (TTR) protein produced by the liver misfolds and deposits as amyloid fibrils in organs such as the heart. Wild-type ATTR is age-related, typically developing after age 60, and is increasingly recognized as a major cause of heart failure. If untreated, it is progressive and fatal within 2 – 7 years. Hereditary ATTR, which can affect much younger people, is caused by mutations in the *TTR* gene and is typically fatal within 2 – 15 years of the onset of symptoms.

Previous work has shown that RNA interference (RNAi) can be used to reduce production of the TTR protein thereby slowing ongoing amyloid formation. Extensive clinical data suggests that RNAi therapeutics are a safe, clinically beneficial treatment option. However, these therapies only partially knock down TTR protein levels in the bloodstream and some patients continue to experience disease symptoms and still die from the disease. RNAi treatments must be readministered regularly for the patient's lifetime.

Gene editing potential

Editing the TTR gene is an attractive alternative therapeutic strategy. It may be possible to further decrease TTR protein levels beyond what has been achieved via RNAi and thus achieve better clinical outcomes. A single dose may be sufficient. The unequivocal link between the misfolded TTR protein and ATTR amyloidosis and the fact that circulating TTR protein is exclusively produced by the liver makes it an ideal candidate for an *in vivo* gene editing strategy.

A novel CRISPR / Cas9-based *in vivo* gene editing therapy is now being developed to treat ATTR amyloidosis. Briefly, a lipid nanoparticle delivery system is used to target editing machinery to liver cells. The CRISPR / Cas9 complex causes mutations in the TTR gene that prevent it from being expressed into a protein.

A rigorous process was followed to ensure that this therapy could achieve potent on-target impact with no detectable off-target editing. This involved using computational analysis to identify potential target sites, in silico and *ex vivo* candidate analysis and stringent validation procedures. Pre-clinical *in vivo* studies suggest the treatment has a durable effect and achieves over 95% reduction in TTR protein levels following a single dose. A first-in-human study showed acceptable safety in the short to medium term and consistent, durable ~90% TTR reduction after a single dose. A phase 3 double-blind, placebo-controlled clinical trial is actively recruiting patients with ATTR amyloid cardiomyopathy to determine the clinical efficacy of the treatment.

CRISPR on drugs: pharmacological enhancement of genome editing

Dr Marcello Maresca, AstraZeneca, shared recent work on enhancing the integration of target genes through the use of small molecules that modulate double-strand break repair pathways.

Image: Dr Marcello Maresca, AstraZeneca.

> "There is still space to investigate double-strand break repair pathways to improve the efficiency of gene editing."
>
> Dr Marcello Maresca, AstraZeneca.

The CRISPR-Cas9 system is showing great promise as a tool for treating genetic diseases, particularly in cases where knocking out a gene effectively treats the disease. Diseases that require gene repair (ie 'knock-in' to create non-mutated, functional allele) are a more complicated matter.

Familial hypercholesterolemia is a condition where the liver cannot properly process cholesterol. It is caused by mutations in the LDLR gene. Over 2000 different disease-causing mutations have been identified. Designing thousands of corresponding guide RNAs to edit these mutations is a daunting prospect. Instead, it may be possible to replace the entire gene using DNA repair pathways.

DNA repair pathways

In mammalian cells, double-strand breaks in DNA tend to be repaired using non-homologous end joining (NHEJ) and alternative end joining (alt-EJ) pathways, which are error-prone. Homology-directed repair (HDR), which uses an identical or highly similar DNA sequence as the template for repair, is much more precise but less frequently employed as it is less active in non-proliferating tissues. In theory, double-strand breaks could be introduced on either side of a disease-causing mutant gene, and HDR could then be used to knock-in a similar but functional variant of the gene.

Inhibitors to enhance HDR

To enhance HDR frequency and thus facilitate more efficient gene integration, research undertaken by AstraZeneca has explored the potential of different chemical compounds to bias DNA repair towards HDR. This identified 13 compounds that inhibit DNA-PK, an enzyme involved in NHEJ. Inhibiting DNA-PK reduces the frequency of use of NHEJ repair and increases the frequency of HDR.

In a novel approach, scientists at AstraZeneca have found that by inhibiting both DNA-PK and POLQ, an enzyme involved in alt-EJ, they can substantially increase the frequency of HDR and reduce undesired insertions and deletions. Using this two-inhibitor (2i) strategy, the precision and efficiency of gene repair can be dramatically boosted.

However, there is a key limitation of this system. HDR works mainly in dividing cells; it will not work in non-dividing cells. There is also a risk that, if an imprecise nuclease is used to create double-strand breaks during gene editing, this may create double-strand breaks at various locations in the genome and the gene of interest may be integrated at off-target sites. Therefore, the use of a high-fidelity Cas9 is needed.

In vivo gene editing with ePsCas9 (eSpOT-ON)

PsCas9 has much higher fidelity than the classic SpCas9. However, a limitation of PsCas9 is that it is not very efficient and needs to be overexpressed, which is not possible with some genome editing delivery mechanisms (eg lipid nanoparticle systems).

AstraZeneca have now engineered PsCas9 to achieve a genome editing efficiency similar to SpCas9. This proprietary ePsCas9 maintains higher fidelity than SpCas9, and thus likely has a better safety profile. Preliminary work in mice shows that ePsCas9 delivered via LNP can be used to efficiently knock out PCKS9 *in vivo* highlighting the potential for a therapeutic intervention for familial hypercholesterolemia and other genetic diseases.

Genetic engineering of hematopoietic stem cells to treat human disease: state-of-the-art and future perspective

Professor Luigi Naldini, San Raffaele Telethon Institute for Gene Therapy, described his pioneering work on developing *in vivo* therapeutics to treat rare, severe diseases impacting the heart and tendons.

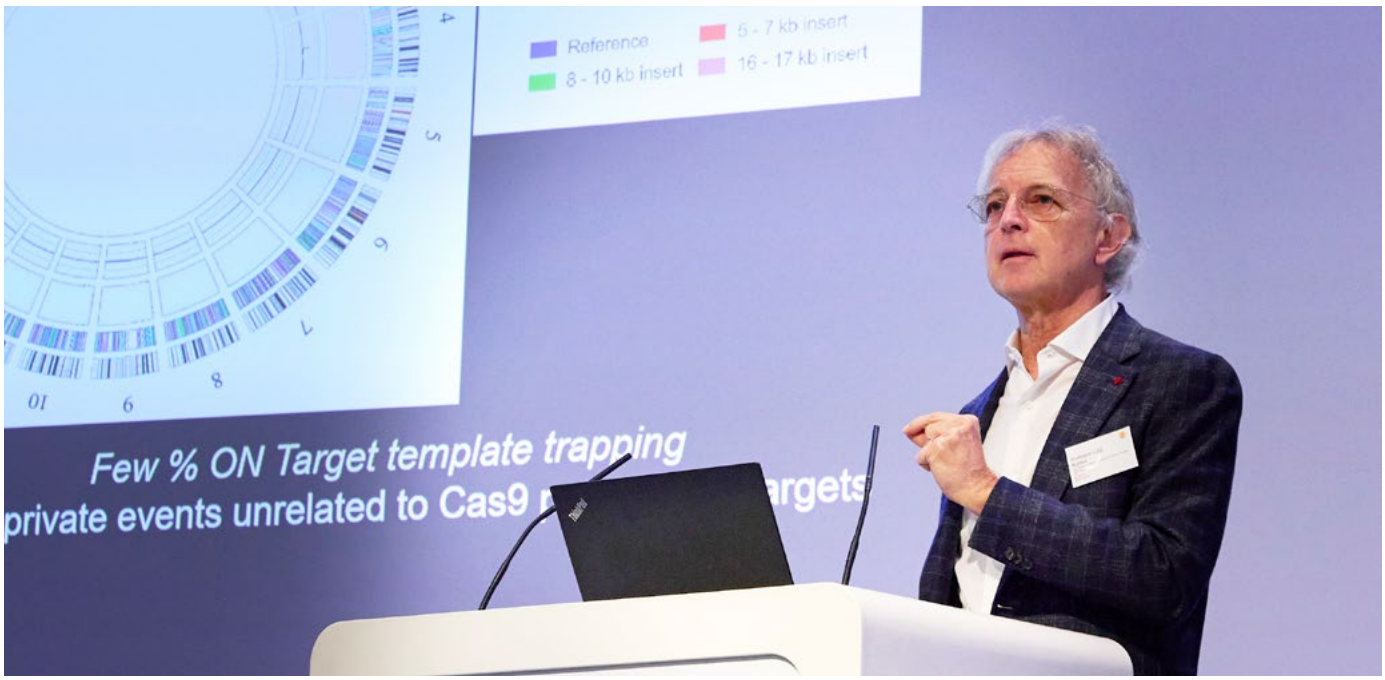


Image: Professor Luigi Naldini, San Raffaele Telethon Institute for Gene Therapy.

> "Hematopoietic stem cell gene therapy is likely to continue to advance by a combination of transformative approaches. Precision genetic engineering has the potential to broaden gene therapy applications to many diseases and patients worldwide."
>
> Professor Luigi Naldini, San Raffaele Telethon Institute for Gene Therapy.

Hematopoietic stem cells (HSC) are cells with the potential for both self-renewal and differentiation into other types of blood cells. They are found in blood and bone marrow. Using lentiviral vectors, it is possible to genetically engineer HSC (eg to insert a functional copy of a mutant gene). In this type of gene therapy, HSC are harvested, treated with the lentiviral vector, *ex vivo,* and infused into the patient.

HSC gene therapy has been providing substantial benefit to hundreds of patients affected by a wide range of severe genetic diseases, particularly blood disorders. Trials were first started over a decade ago and there are now several commercial therapies. Long-term follow-up indicates HSC gene therapy is safe and has a durable effect. However, precise engineering by gene editing may further improve the reach and safety of HSC gene therapy by achieving *in situ* gene correction or targeted transgene integration. Different editing tools are discussed below.

Nuclease-based editing

CRISPR / Cas9-mediated targeted gene editing is becoming a feasible treatment option for some diseases. Nuclease-based editing enables efficient, targeted gene disruption, typically by causing small mutations in a gene that inactivate its expression. Nuclease-based editing therapies are being investigated in clinical trials, although one CRISPR / Cas9-based medicine (Casgevy) has recently been approved for use in the UK to treat sickle cell disease. Importantly, there is a largely unknown long-term genotoxic risk associated with this type of editing due to off-target activity of the editing machinery.

An alternate nuclease-based strategy has the potential to enable treatment of diseases caused by many different mutations. To fix double-strand DNA breaks, a cell may use one of several types of DNA repair pathways. In homology-driven repair (HDR), an identical or highly similar DNA sequence is used as a template to ensure the break in the DNA sequence is correctly repaired. Homology-driven editing involves making double-strand breaks on either side of a mutant gene of interest, then providing a functional copy of the gene for the cell to use as a template for repair. This enables in situ gene correction that has the potential to be used to treat many different variants of defective gene. However, there are two major constraints:

- HDR has very low efficiency, as mammalian cells typically use other types of DNA repair pathways; and
- co-delivery of a functional DNA template may be complex, depending on delivery mechanism.

Nickase-based editors

On the other hand, the emergence of base and prime editors that bypass the requirement for DNA double-strand breaks (DSB) allows editing single / few mutant nucleotides with limited activation of DNA damage response. Base editors can change a single base-pair in a DNA sequence. Prime editors can introduce insertions, deletions or base-pair changes. These tools are still relatively early in development, as clinical trials are just beginning. However, there are still genotoxicity concerns with these editors that should be better investigated and monitored in emerging clinical applications.

Epigenetic editing

Cutting-edge R&D is exploring the potential to alter the epigenomic marks on the human genome that influence the DNA is transcribed and translated. This approach does not cut the DNA, substantially limiting damage caused by off-target effects. As of 2024, this technology is still pre-clinical.

Multiplexed CRISPR-based cell engineering to generate persistent allogeneic cell therapy solutions and improved function in solid tumors

Dr Birgit Schultes, Intellia Therapeutics, described new approaches being used to improve the efficacy and durability of therapeutics to treat blood cancers.

Cell and gene therapies have shown great success in treating a range of conditions. For some cancers and autoimmune diseases, *ex vivo* CRISPR can be used to create a therapeutic treatment. This is done by harvesting cells, editing them and infusing them into the patient. These therapies are typically autologous, meaning they involve harvesting and editing a patient's own cells to decrease the likelihood of an adverse reaction. However, this limits the speed with which the therapy can be produced and means that every batch produced is specific to one individual. These treatments cannot be created in advance of need or stockpiled.

Durable, 'off-the-shelf' cell therapy treatments that could be mass-produced in advance of need and stockpiled would be game-changing. Intellia Therapeutics are on a mission develop a scalable *ex vivo* editing platform that can be used to create potent treatments for a range of oncology and autoimmune diseases. Using this platform, allogeneic (ie donor cells) can be edited to remove factors likely to cause an immune response in the patient. However, this requires multiplexed gene editing to create multiple edits. This raises safety concerns, as each CRISPR editing step results in additional off-target changes to the DNA. To address these challenges, Intellia have adapted their system in the ways outlined below.

Delivery mechanism

A lipid nanoparticle delivery system is used to introduce the editing machinery into the allogeneic cells. This maintains high cell viability and speeds up cell recovery following gene editing compared to more traditional delivery systems (eg electroporation), which compromise cell quality. This has the potential to reduce manufacturing time. The lipid nanoparticle system also enables edits to be performed sequentially, which minimises the likelihood of chromosomal aberrations and means the different editing machineries are not in competition with one another for access to the DNA.

Image: Dr Birgit Schultes, Intellia Therapeutics.

"CRISPR has the potential to make T cells much more effective, but they must be edited in multiple ways. A single insertion or deletion is not sufficient. The true potential comes from being able to do multiplex editing."

Dr Birgit Schultes, Intellia Therapeutics.

Editing technologies

By using high-fidelity base editor Nme2Cas9, multiplex edits can be made simultaneously in the DNA sequence. Nme2Cas9 converts cytosine bases to thymine, and unlike the CRISPR / Cas9 system, this does not create double-strand breaks in the DNA. As such, unwanted / unpredicted insertions, deletions and translocations are minimised.

In cases where a gene insertion is required, the SpyCas9 nuclease can be used to create double-strand breaks at the desired location in the genome. A copy of the gene can then be integrated at that site by leveraging the cell's innate homology-directed DNA repair pathway. Site-specific integration minimises the risk of insertional mutagenesis and other off-target DNA damage.

Using multiplex editing

The multiplex strategy described above was deployed to generate allogeneic T cells that had been edited to avoid T cell- and NK cell-mediated host rejection, an unsolved challenge for other allogeneic cell therapies. Engineered T cells showed high chromosomal integrity and functional activity both *in vitro* and *in vivo* pre-clinical models.

Intellia are now exploring how this system could be used to create therapies that are effective in solid tumors. To date, T cell therapies to treat solid tumors have had limited success due to difficulties with T cell penetration, antigen heterogeneity and decreased T cell function in the immunosuppressive tumor microenvironment.

Programming permanent gene repression by epigenetic editing

Professor Angelo Lombardo, San Raffaele-Telethon Institute for Gene Therapy and Vita-Salute San Raffaele University, described his pioneering work on developing *in vivo* epigenetic editing therapeutics.

Gene expression can be altered without changing the DNA sequence, for example by adding or removing a methyl group or by modifying the histone proteins that give chromosomes their structure. These non-DNA factors that influence gene function are referred to as the epigenome.

Epigenome editing is emerging as a powerful strategy to silence gene expression. It offers an intriguing alternative to gene editing, as it does not damage the DNA and is potentially reversible (eg via pharmacological interventions).

This approach involves transient delivery of engineered transcriptional repressors (ETRs). These are chimeric proteins consisting of a DNA-binding domain fused to an epigenetic effector domain. Despite the transient delivery system, the silencing effects of ETRs can be long-lasting and inherited via cell mitosis. Two therapeutic indications for this technology are described below.

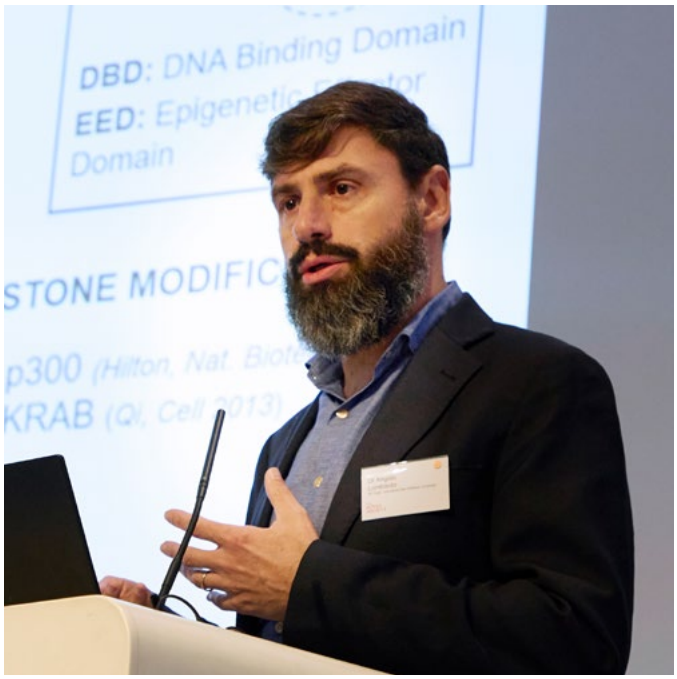


Image: Image: Professor Angelo Lombardo, San Raffaele-Telethon Institute for Gene Therapy and Vita-Salute San Raffaele University.

Liver-based epi-silencing

Current systems for delivering editing machinery (eg lipid nanoparticles) are well-designed for targeting the liver, making liver diseases an ideal initial target for epigenetic editing experiments. Early efforts have focused on the PCSK9 gene. Gain-of-function mutations in this gene may cause familial hypercholesterolemia, characterized by abnormally low cholesterol levels in the blood. Conversely, loss-of-function mutations in this gene have been shown to protect against coronary heart disease. Both RNA interference and gene editing approaches have been successfully used to inhibit PCSK9.

In vivo experiments in mice have shown that a single ETR dose results in durable, efficient silencing of the mouse Pcsk9 gene. This is accompanied by hyper-methylation at the Pcsk9 promoter. Different DNA-binding domains resulted in differing efficacy and specificity of the treatment, and for the most specific DNA-binding domains little if any off-target effect was observed. This supports the hypothesis that epigenetic editing may be a safer alternative to other *in vivo* gene silencing approaches.

> "Epigenetic editing may be a valid and indeed safer alternative to other editing approaches for *in vivo* gene silencing."
>
> Professor Angelo Lombardo, San Raffaele-Telethon Institute for Gene Therapy and Vita-Salute San Raffaele University.

Another liver disease caused by hepatitis B virus (HBV) is associated with over 800,000 deaths per year globally. It persists in liver cells as covalently closed circular DNA (cccDNA). The current standard-of-care is treatment with nucleotide analogues, which require life-long administration. A single dose epigenetic therapy could revolutionise treatment for this disease.

Screening was undertaken to identify guide RNAs able to achieve efficient (up to 90%) HBV silencing that lasts for up to 5 months. Initial validation shows that this silencing is associated with hyper-methylation of the cccDNA. This work suggests epigenetic editing could be a viable treatment option for HBV, although this work is still preliminary.

Ex vivo epi-silencing

Epigenetic editing has potential applications for engineering T cells for cancer immunotherapy. Engineering donor cells requires knocking out, knocking in and modulating the expression of different genes. This necessitates multiple edits which has a high likelihood of resulting in chromosomal translocations, the functional consequences of which are still unknown.

Early studies suggest that epigenetic editing can be used to silence multiple genes in human primary T cells. Chromosomal translocations are prevented, and the epigenetically silenced T cells retain their ability to kill cancer cells. Further work is needed to test this approach *in vitro* and *in vivo*.

Delivery of genome editing tool kits in engineered lentivirus-derived particles

Professor Jacob Giehm Mikkelson, Aarhus University, shared recent work on the use of lentivirus-derived nanoparticles for targeted DNA cleavage and its potential large scale therapeutic use.

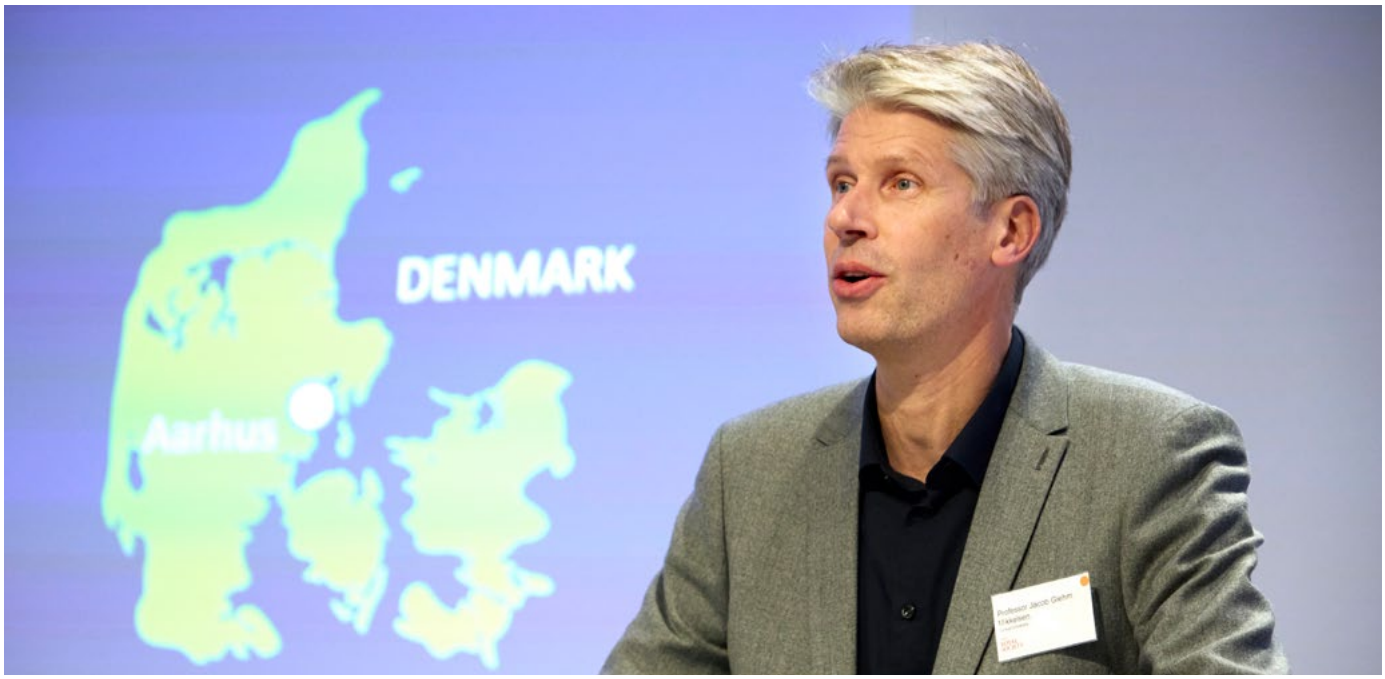


Image: Professor Jacob Giehm Mikkelson, Aarhus University.

"Early *in vivo* evidence of lentiviral-derived nanoparticle-directed gene editing in the mouse retina fuels hope that this system can be further developed and produced at scale for therapeutic applications."

Professor Jacob Giehm Mikkelsen, Aarhus University.

A major obstacle to the use of CRISPR / Cas for disease treatment is the difficulty in targeting specific cell types. Gene editing requires delivery of a Cas9 protein, a single guide RNA (sgRNA) and potentially a donor DNA template for repair into the desired cell type. Current delivery mechanisms can be used to target liver and cancer cells but targeting other cell types *in vivo* remains a challenge.

There is inspiration to be found in nature. When a retrovirus invades a host cell, it reverse-transcribes its genome and integrates a DNA copy into the host's genome, essentially editing it. This editing also requires viral proteins (ie integrase). That is, retroviruses are natural protein delivery vehicles. The proteins on the outermost layer of a virus (the viral envelope) dictate what cell types a virus can infect.

Unlike most retroviruses, lentiviruses can infect both dividing and non-dividing cells, making them uniquely useful as vectors.

Engineering lentiviruses for protein delivery

About a decade ago, exploratory work showed that lentiviral particles could be engineered to ferry a protein of interest (eg Cas9) into cells. Briefly, when a lentivirus buds off an infected cell, its proteins are packaged together as polypeptides (many Gag and fewer Gag-Pol polypeptides). After particle maturation, these are cleaved into smaller proteins. Through fusion to a polypeptide, Cas9 can be incorporated into lentiviral-derived nanoparticles (LVNPs) and delivered into infected recipient cells.

Delivery of Cas9 and sgRNA

To be useful as a gene editing delivery system, LVNPs must also be able to deliver sgRNAs. Experiments *in vitro* have shown the incorporation of sgRNAs into LNVPs requires the presence of Cas9. Together they form Cas9 / sgRNA ribonucleoproteins (RNPs) that are capable of cleaving target DNA sequences in treated cells. Targeted DNA cleavage was also detected *in vivo* when LNVPs were injected into mouse retina, suggesting this approach could be adapted for future therapeutic applications.

Co-delivery of Cas9, sgRNA and a donor template

To create small insertions or deletions, only Cas9 and a sgRNA are needed. However, to insert a long DNA sequence, a donor template is also required. After delivery into the host cell, co-delivered donor RNA can be reverse transcribed and incorporated by homologous recombination into the host genome where it has been cleaved by the gene editing machinery. Experiments have shown this approach can be used to 'knock in' a gene of interest into a recipient cell.

The LVNP platform also supports base and prime editing. Unlike Cas9-mediated gene editing, base and prime editing create changes in the genome without causing double-stranded breaks and are likely to be important in future gene editing therapies.

Targeting specific cell types

In a process referred to as pseudotyping, viral vectors can be modified to express different proteins in their viral envelope to change the types of cells they infect. Studies indicate that pseudotyped LNVPs can deliver the Cas9 / sgRNA RNP into specific cell types to induce site-specific edits.

Taken together, the past decade of LNVP research shows the promise of this system for enabling cell type-specific gene editing.

Promise of AAV-mediated gene delivery as a disease-modifying therapy

Dr Seng H Cheng, Alexion, AstraZeneca Rare Disease, discussed the potential of recombinant adeno-associated viral vectors as a mechanism for treating rare diseases.

Adeno-associated viruses (AAV) are small viruses capable of infecting humans. Several features make AAV an intriguing vector as a therapeutic modality for genetic diseases. For example, it is non-pathogenic and can infect both dividing and non-dividing cells.

For numerous AAV gene therapies, there is demonstrable evidence of clinical efficacy and durability of effect that persists for multiple years following a single treatment. Approved AAV gene therapy products are commercially available to treat diseases such as spinal muscular atrophy and retinal dystrophy.

However, safety concerns exist. Investigations indicate that high-dose AAV treatments can elicit a host immune response. This may lead to lower treatment efficacy over time, and in some cases immune-mediated toxicity has resulted in patient death. As AAV therapies have shown such great promise for addressing severe genetic diseases with limited other treatment options, finding a way to mitigate this toxicity is an important avenue for future research. Several strategies are discussed below.

Immunosuppressive regimes

A range of immunosuppressive regimes (eg corticosteroids and mTOR inhibitors) have been employed across AAV gene therapy trials. These can help limit patient immune response to the treatment, improving patient safety. However, there is a trade-off, as immunosuppression can increase the patient's risk of infection. In cases where an AAV treatment can be delivered in low doses or in a tissue-specific manner, there may be less need for immunosuppressive protocols alongside AAV gene therapy.

Image: Dr Seng H Cheng, Alexion, AstraZeneca Rare Disease.

"The potential of recombinant adeno-associated viral vectors as a therapeutic modality for genetic diseases continues to show promise."

Dr Seng H Cheng, Alexion, AstraZeneca Rare Disease.

Developing more potent and tissue-specific viral vectors

Targeting AAV therapies to the tissues where they are needed could reduce the dosage levels required to achieve the desired health outcome, thus decreasing the risk of toxicity. AAV vectors that target the liver already exist, and trials indicate that these appear to be effective and safe in providing durable therapy for a subset of genetic diseases.

Other existing AAV therapies designed to target non-liver tissues (eg skeletal and cardiac muscle cells) have struggled to achieve clinical efficacy while maintaining patient safety. There is optimism about and keen interest in advancing the next generation of AAV vectors for non-liver (ie extrahepatic) delivery. These could have the potential to generate a step-change in treatment for cardiac and neurological diseases where there is no existing satisfactory treatment.

Design of the transgene expression cassette

Judicious selection of transgene expression cassette design is yet another important consideration for an optimal clinical outcome. Careful design and validation steps can be used to create tissue-specific promoters to enhance expression of the gene of interest in specific cell types. Thoughtful design has the potential to enhance both safety and efficacy.

Lessons learned are providing a clearer path to deploying this emerging technology platform for use in the next wave of diseases with particular emphasis on those with high unmet need.

Lipid nanoparticles are enabling gene therapies

Dr Jayesh Kulkarni, NanoVation Therapeutics, highlighted recent advances in the use of lipid nanoparticles to deliver gene therapies, noting the urgent need for further innovation to enable delivery to non-liver tissues.

Image: Dr Jayesh Kulkarni, NanoVation Therapeutics.

Nucleic acids need a delivery system if they are to be used in gene therapies. On their own, they are rapidly cleared by the immune system and broken down quickly by nucleases. They show poor accumulation at target sites and are unable to cross the cell membrane.

Lipid nanoparticles (LNPs) represent an advanced drug delivery system that is now enabling gene therapies. They are small, spherical particles made up of phospholipids, cholesterols, polyethylene glycol-derived lipids and ionizable cationic lipids. Nucleic acids can be encapsulated through a charge interaction with the cationic lipids, and the fusogenic shape of the particles promotes intracellular delivery. In systemic circulation, they typically have a neutral charge.

Many factors make LNPs a desirable delivery system for medicines. They can be produced at rapidly and at scale. There are several approved formulations suitable for different types of cargo. Importantly, they are both potent and redosable, as they do not trigger an adaptive immune response.

Commercial formulations

The first lipid-based nanomedicines received regulatory approval in Europe and North America in the early to mid-1990s. These were for anticancer drugs, and the LNP delivery system enabled reduced toxicity and improved efficacy in certain instances.

More recently efforts have focused on using LNPs to deliver nucleic acid-based medicines. Onpattro was designed to deliver short interfering RNA to the liver using LNPs to treat hereditary transthyretin amyloidosis. It was the first-ever approved RNA interference therapeutic and was cleared for use in the NHS in 2019, although newer drugs with simpler dosing regimens are now recommended.

Further advancements of these systems through optimization of the LNP have enabled their use in the messenger RNA vaccines commercialized by Pfizer / BioNTech and Moderna.

Future possibilities

While substantial advancements have resulted in several medicines for liver diseases and vaccines, the critical barrier to treating or even curing disease is the ability to deliver nucleic acids in a precise manner to non-liver tissues.

Adsorption of apolipoprotein E onto the LNP surface facilitates their accumulation in the liver. Typical LNP formulations do not circulate in the bloodstream for very long. Within about 15 minutes of being introduced into the body, LNPs rapidly accumulate in the liver. This severely limits their ability to deliver medicines to non-liver tissues. Work is now being done to develop 'long-circulating' LNPs that extend the circulatory half-life of the LNP from 15 minutes to about six hours, which increases their accumulation in tissues other than the liver.

Improving the therapeutic index is another key challenge. If this technology is to be used to deliver gene editing medicines, reducing the potential toxicity and thus improving patient safety is of paramount importance.

> "The limit is really only what we can dream of doing with an LNP-RNA system, and how well we can engineer them to get to non-liver targets."
>
> Dr Jayesh Kulkarni, NanoVation Therapeutics.

PANEL DISCUSSION

Patient experiences

Professor Robin Lovell-Badge FRS, The Francis Crick Institute, chaired a panel discussion that explored the experiences of three people whose lives have been impacted by severe genetic diseases.

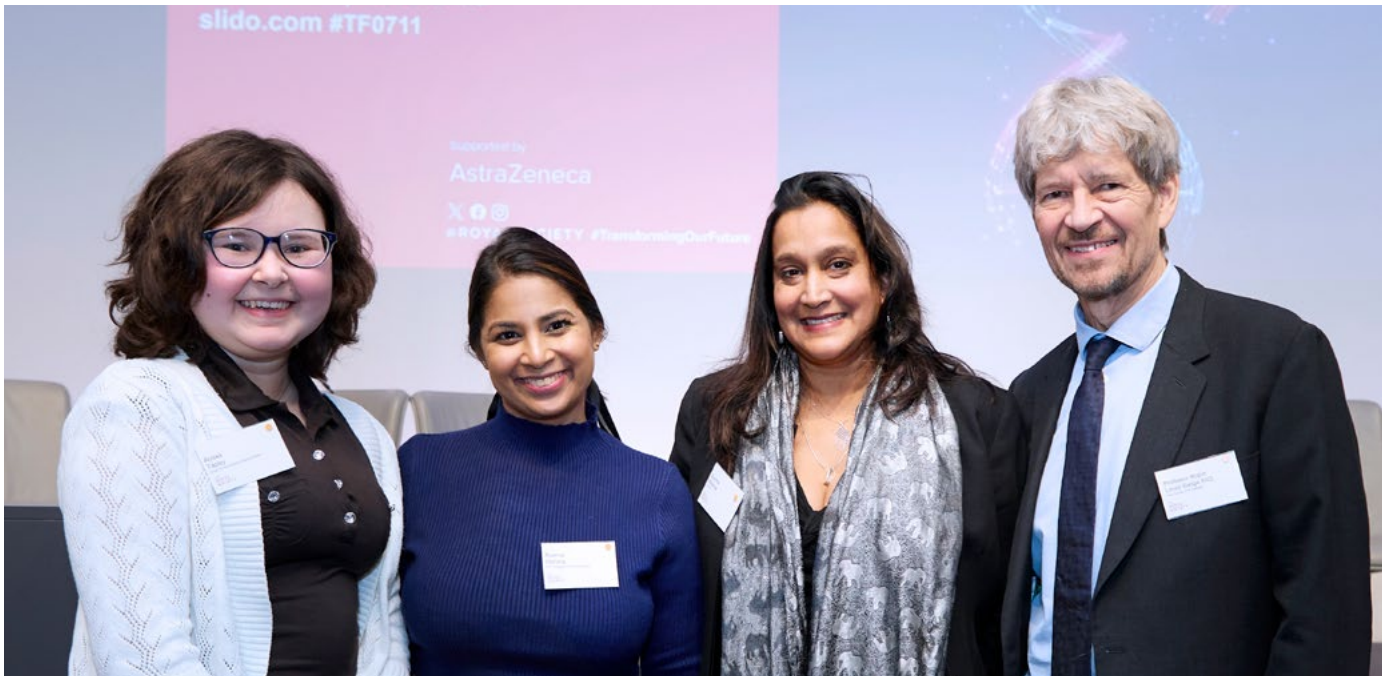


Image: (left to right) Alyssa, Roanna Maharaj, Sharmila Nikapota and Professor Robin Lovell-Badge FRS, The Francis Crick Institute, conference organiser and panel discussion Chair.

Perspectives from patients, potential patients and their representatives are crucial to any discussion on the future of gene editing medicines. Incorporating their views as early as possible during the research and development phase is important to ensure these therapies are meeting the needs of the communities they intend to benefit.

In this panel session, Roanna Maharaj, Sharmila Nikapota and Alyssa shared their personal experiences with rare genetic diseases. They discussed the need for innovative therapies and how they have been involved in recent advances in this field.

This wide-ranging conversation covered many topics, including:

- The emotional toll on patients with rare genetic diseases, as well as their families.
- The importance of patient advocacy in spreading hope amongst those being impacted by these diseases as well as inspiring the research community.
- The timing of treatment in a patient's life can have a huge impact on outcome. Therapies applied earlier, before a disease progresses and secondary conditions develop, have the potential to more effectively treat and possibly even cure some genetic diseases. Patient communities are desperate for therapies that stop disease progression.
- The need for regulatory bodies such as MHRA and NICE in the UK to listen to patient voices. There are examples of where this has been done well (eg removing age limits from the NICE recommendation for the gene editing medicine Exa-cel to be included on the NHS). However, many patient groups remain frustrated by their interactions with regulators and feel as though their involvement is only a 'tick-box' exercise.
- Considerations of the commercial viability of genomic therapies must consider all costs associated with long-term care of those with chronic conditions. The true cost (eg of all the appointments and medications needed) are typically not factored into these calculations.

- Patient uptake of novel gene editing therapies is difficult to predict and comes down to the individual. Some may be happy to take up an experimental treatment, but others may prefer to continue with current standard-of-care therapies as there are so many unknowns associated with innovative therapies. The age of the patient and the degree of disease progression may impact that decision-making process.

Roanna Maharaj

Roanna was diagnosed with thalassemia as a baby. Thalassemia refers to a group of conditions that result in the production of little to no haemoglobin, an important component of red blood cells that enables them to carry oxygen. Patients with the most severe form of this condition require regular blood transfusions, as well as daily chelation therapy to remove the excess iron from the transfusions. The development of secondary conditions, such as organ dysfunction and failure, is common.

Roanna is a dedicated patient advocate. She is deeply passionate about education and tackling the health disparities faced by the thalassemia and rare disease communities. She holds a master's degree in health psychology and is now pursuing a PhD. Her experience includes serving as Vice Chair of the UK Thalassaemia Society, where she led initiatives in public health, education, and patient advocacy for over 20 years.

Through her advocacy work, Roanna emphasises the importance of incorporating the patient's voice throughout the continuum of care, from preventive measures to curative therapies. In August 2024, an important milestone for the thalassemia community was reached: NICE recommended the novel gene editing therapy Exa-cel for individuals living with transfusion-dependent thalassemia to be made available through the NHS.

> "The NICE patient journey needs to be better. I had to do a course in health economics to understand the language to be able to represent my community in the way they deserve."
>
> Roanna Maharaj.

> "Watching my daughter Sohana suffer the agonising pain of EB every day is my incentive to push for research to find a treatment."
>
> Sharmila Nikapota.

Sharmila Nikapota

Sharmila's eldest daughter Sohana was born with epidermolysis bullosa (EB), a rare and very painful inherited disease that causes the skin to become fragile. Even minor friction can cause the skin to blister and tear, leaving burn like wounds. In severe types internal skin is also affected and blisters form inside the mouth and oesophagus leading to significant difficulties eating. There is currently no cure for EB, and treatment options are limited.

The chronic underfunding of EB medical research led Sharmila to set up a dedicated research fund which became Cure EB. She is the driving force behind Cure EB, planning fundraising activities, organising research dissemination meetings and speaking at events. Cure EB's goal is to maximise research progress towards effectively treating EB by funding promising projects and building collaborations between researchers, biotech companies and other funding bodies.

As EB is caused by mutations in any of at least 20 genes, gene therapies are being explored as potential treatment options. A number of potential therapies, both *ex vivo* and *in vivo*, are in development, and continuing advances in this field are giving hope to patients and their families.

Alyssa

Alyssa was 12 when she was diagnosed with T-Cell Acute Lymphoblastic Leukaemia. This is an aggressive disease in which a large number of immature, non-functional T cells accumulate in the bone marrow and prevent the development of healthy blood cells. After chemotherapy failed to treat Alyssa's cancer, she underwent a bone marrow transplant. When that also failed, her cancer was diagnosed as terminal.

However, Alyssa's consultant suggested one more therapeutic option. Great Ormond Street Hospital was seeking patients to receive an experimental T cell CAR-T therapy in which T cells from a healthy donor are base-edited to enable them to destroy cancerous T cells. The edited cells are then infused into the patient. After careful contemplation, Alyssa consented to the trial and was the first person in the world to receive this innovative treatment.

Alyssa is now 15 and has been in remission for two years. She loves spending time with her family and her Labrador Holly, riding her bike and enjoying life as much as possible. In addition to studying for her GCSEs, Alyssa enjoys working with charities to help them raise more money for life-saving research. She hopes to one day work in blood cancer research.

> "I had a lot of questions before the trial, as anyone would. The doctors answered them as best they could. My mum and dad told me I could choose whether to participate in the trial, and I decided to do it. I hoped that even if it didn't help me, it might help others, and I viewed it as the reason I was put on Earth."
>
> Alyssa.

Precise gene correction for Primary Immunodeficiency Diseases

Dr Suk See De Ravin, National Institutes of Health, described her first-in-human clinical work using gene editing tools to treat inborn errors of immunity.

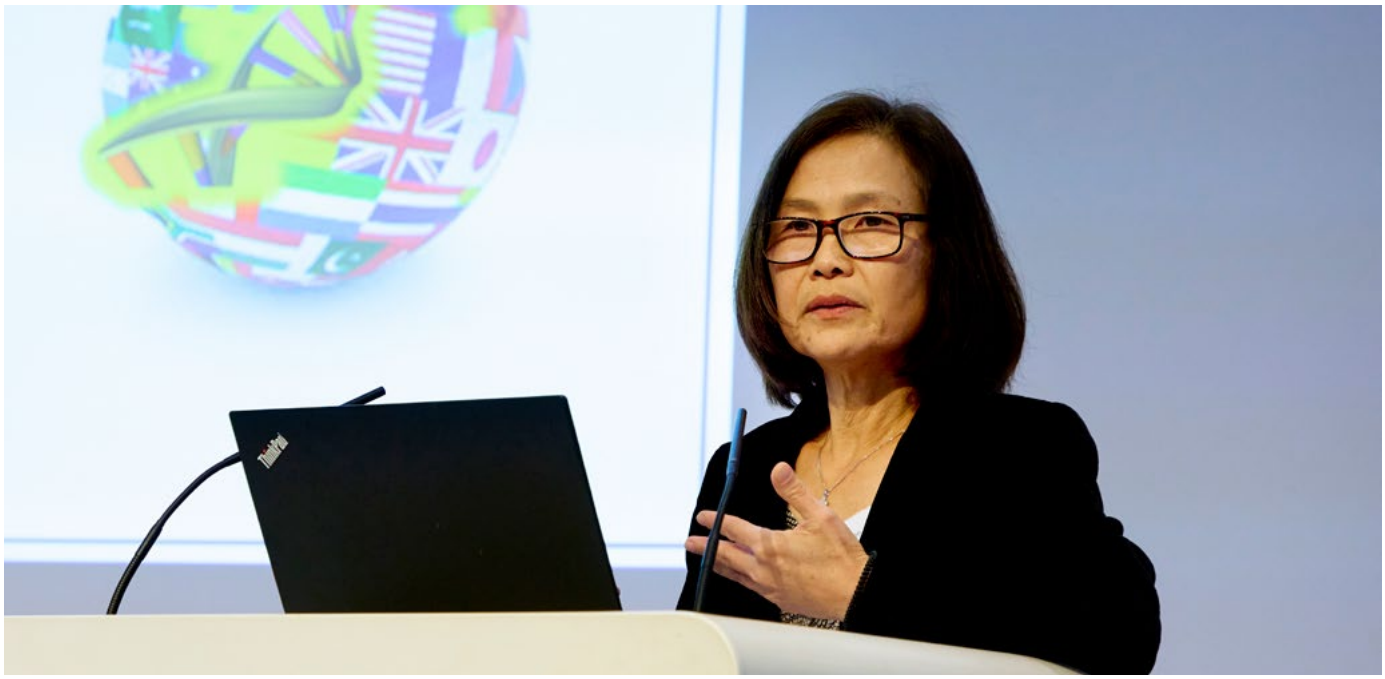


Image: Dr Suk See De Ravin, National Institutes of Health.

> "Our goal is simply to do better than what is currently available. Patients cannot wait years for a treatment to be perfected."
>
> Dr Suk See De Ravin, National Institutes of Health.

Inborn errors of immunity (IEIs) are monogenic disorders characterized by defects in the immune system that lead to increased susceptibility to infections, as well as autoinflammation, hyperinflammation, allergies and malignancies. They can cause significant morbidity and, in severe cases, early mortality. As of 2022 there are 485 genes linked to different IEIs.

Hematopoietic stem cells (HSCs) are the root of all blood and immune cells. If mutations in these cells can be corrected, there is hope of a cure. HSC transplants using healthy donor cells can be lifesaving, but are limited by graft rejection, graft failure, graft-versus-host disease or a lack of suitable donors. Gene therapy using a patient's own HSCs could mitigate these problems.

Early gene therapy treatments for IEIs

The earliest HSC gene therapy clinical trials used oncoretroviral vectors to insert therapeutic transgenes. These inadvertently activated nearby oncogenes and caused leukemias.

The field has now moved on to the use of lentiviral vectors that reduce some of the risks associated with retroviral vectors. The first lentiviral gene therapy for X-linked severe combined immunodeficiency (XSCID) was reported in 2000, and there have been several trials since.

However, these lentivectors can integrate throughout the genome, including within actively transcribed genes where they can cause aberrant fusion transcripts. Targeted genome editing would help avoid random insertions and could potentially restore endogenous gene regulation. As there is much still to be learned about how and why gene expression is modulated, the value of this is priceless.

Use of CRISPR / Cas9-mediated gene editing

Experiments have compared traditional lentivector treatment for XSCID with a novel gene editing approach, where CRISPR / Cas9 is used to create a double-strand break in the DNA. This allows a functional copy of a gene of interest to be inserted at a specific location within the genome. Results indicated that the CRISPR / Cas9 edited HSCs showed superior functional recovery. However, analysis of the genome post-editing showed that multiple copies of a gene of interest may be inserted at the target location, and that double-strand breaks increase the likelihood of foldback fusion (joining of sister chromatids). As such, alternatives to CRISPR / Cas9 are now being explored.

The promise of base editing

Next-generation genome editing tools like base editing provide precision and efficacy that should address random integration concerns without causing double-strand breaks.

Preclinical base editing studies using HSCs from patients with Chronic Granulomatous Disease (CGD) confirmed that base editing supports highly specific and efficient mutation repair. Post-editing genome analysis identified primarily bystander edits (ie close to the editing site), but at low frequency. Subsequent first-in-human clinical trials supported the efficacy and safety of this base editing treatment.

As base editing has proven effective for treating CGD, work is now being done to explore whether it can be used to treat XSCID. Early results appear promising, indicating that base editing shows great potential as a broadly applicable and efficient tool for treating genetic diseases.

Hacking T cells to fight leukaemia

Professor Waseem Qasim, UCL Great Ormond Street, discussed how gene editing tools can be used to alter multiple genes in T cells from healthy donors to treat different types of leukaemia.

Most patients with leukaemia can be successfully treated with chemotherapy. However, for a minority of patients the disease can relapse and may become 'hard-to-treat'. Recent advances in CAR T cell therapies have revolutionised the outlook for these patients.

CAR T cells

T cells are a critical group of white blood cells that protect us from infections. They work together with B-cells, which produce antibodies against antigens that they detect via receptors on their cell surface.

To create CAR T cells, T cells are collected from the blood. Most approaches have used viral vectors to engineer T cells to display synthetic binders or receptors (ie chimeric antigen receptors, CAR) on the cell surface. These CAR T cells can then be infused back into the patient, where they are able to recognise certain target cells for destruction.

There are limitations and risks associated with current CAR T cell treatments:

- the antigen that the CAR T cells target can mutate and binding might be lost;
- it may be difficult to harvest sufficient quality and quantity of T cells;
- patients may develop side effects such as cytokine release syndrome and neurotoxicity while the immune system is very active; and
- patients may be more susceptible to infections while normal immunity is reduced.

CAR T cell therapy typically uses a patient's own cells, and each batch of cells produced is specific to an individual and cannot be shared. Creating banks of 'ready-made' products from healthy donors that can be used for multiple patients would allow these treatments to be produced more quickly, consistently and at scale. Genome editing is key to making this vision a reality.

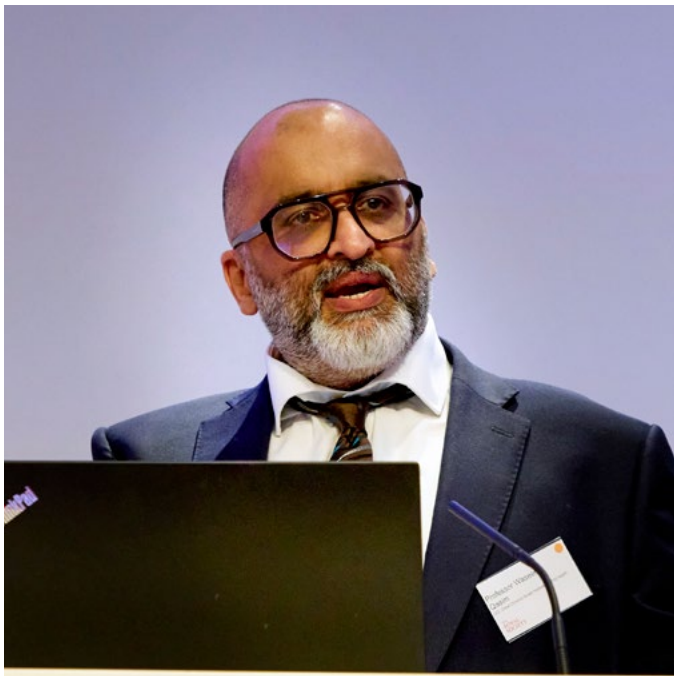


Image: Professor Waseem Qasim, UCL Great Ormond Street, speaker and conference organiser.

"Genome editing technologies can be used to simultaneously 'hack' multiple genes in T cells from healthy donors so that they can be pre-manufactured and used to treat different types of leukaemia."

Professor Waseem Qasim, UCL Great Ormond Street.

TALENS and CRISPR / Cas9

About a decade ago, a major milestone was achieved. Transcription activator-like effector nucleases (TALENS) were used to create genome edited T cells targeting B-Cell Acute Lymphoblastic Leukemia (B-ALL). This approach has since been used in trials to treat both children and adults.

More recent efforts have employed CRISPR / Cas9-mediated genome editing to engineer CAR T cells to again target B-ALL. Clinical trial data is again promising. However, both TALENS and CRISPR / Cas9 edit the genome by creating double-strand breaks, increasing the likelihood of unwanted genetic changes such as translocations. This can destabilise and disrupt the genome, and the clinical consequences are largely unknown.

Base editing

The recent development of base editing could provide an even more precise, safer treatment option. Base editing can be used to precisely change a single base pair in the DNA sequence without creating double-strand breaks and can deliver multiple edits at the same time.

In 2022, the first patient was treated in a Phase 1 trial of a base edited CAR T cell therapy. The teenage patient had previously had an unsuccessful bone marrow transplant, and her leukaemia was classified as 'hard-to-treat'. She received a single dose infusion of CAR T cells that had been base edited, was monitored in the hospital for 28 days, then received a bone marrow transplant from same initial donor. She has now been in remission for two years, and other patients have also been through the trial of this product which is only available in the UK through the NHS as part of this trial.

Therapeutic gene editing for cardiovascular and metabolic diseases: from the leading cause of death to *N*-of-1 disorders

Professor Kiran Musunuru, University of Pennsylvania, shared his ambition to establish a protocol for the rapid development of personalised, liver-directed editing therapies to treat inborn errors of metabolism.

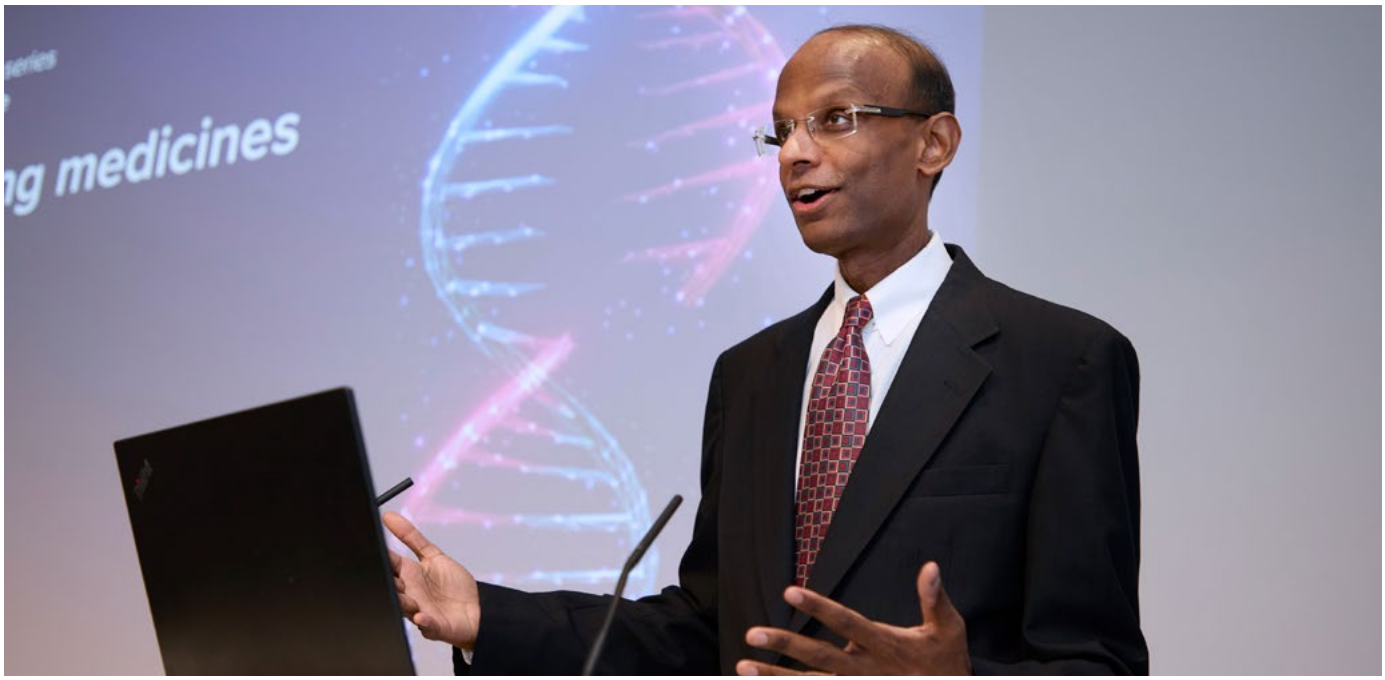


Image: Professor Kiran Musunuru, University of Pennsylvania.

"There's a good argument to be made that we should try to diagnose and treat patients while they're still in the womb, before they're born, so they avoid any negative consequence of their disease whatsoever."

Professor Kiran Musunuru, University of Pennsylvania.

Inborn errors of metabolism (IEMs) are rare, devastating disorders arising from pathogenic variants in genes encoding enzymes of key biochemical pathways. The liver plays an important role in the pathogenesis of over 150 IEMs, often failing to metabolize a toxic metabolite that can injure secondary organs, such as brain. Liver transplantation is employed in some IEMs; however, its utility is limited by scarcity of donors and lifelong risk of post-transplant complications.

To address the unmet medical need of IEM patients, the aim is to develop an overarching protocol for the rapid development of personalised genome editing therapies to treat severe, rare liver-related IEMs. This work will draw on early clinical success in developing a liver-directed editing therapy to treat and prevent atherosclerotic cardiovascular disease, the leading cause of death worldwide.

Protecting against the world's leading killer

Cardiovascular disease is associated with high cholesterol levels in the blood. Using gene editing, it is possible to turn off the expression of cholesterol genes in the liver. Initial studies used CRISPR / Cas9 to edit the PCSK9 gene in the liver in monkeys. Within a week of treatment, cholesterol levels had fallen by 60%. Data taken over the course of three years indicate the reduction achieved by this single treatment is stable, suggesting the effect may be lifelong. Clinical trials in humans are in early stages but show a similar effect. Importantly, this demonstrates that the precise editing of a gene *in vivo* can be used to treat a genetic disease.

Gene editing to treat rare genetic disorders

Lessons learned from the use of gene editing tools to treat cardiovascular disease can be applied to rare, severe genetic disorders. In the autosomal recessive disorder phenylketonuria (PKU), impaired phenylalanine (Phe) catabolism in the liver induces neurotoxic Phe accumulation. PKU is caused by numerous genetic variants of the PAH gene, which is predominantly expressed in the liver. In proof-of-concept studies, single doses of base editing therapies completely and durably normalized Phe levels in humanized PKU mice with two genetic variants. An additional three variants were shown to be amenable to base editing *in vitro*. However, more than 1000 other disease-causing variants exist.

Translational justice and *N*-of-1 disorders

In the United States, before a new gene editing medicine can be used in clinical trials it must first be subject to a series of Investigational New Drug (IND)-enabling studies to demonstrate safety. Currently, IND-enabling studies must be repeated each time the editing machinery is changed (ie to target a different mutation in the same gene). This is hugely expensive and time-consuming.

An alternative approach would be to establish a platform regulatory framework where IND-enabling studies for a 'leader' editing therapy also support programs for varied 'follower' indications. The leader and follower therapies will differ only in patient-variant-specific guide RNA sequences. A platform regulatory approach is essential to develop therapies in time to meaningfully improve outcomes for patients with rare, severe genetic diseases who typically suffer significant early morbidity and mortality. In some cases, the disease is so severe that the patient dies immediately after birth, and treatment with an editing therapy before birth would be the best way to help the patient.

CRISPR cures for all: an actionable path

Professor Fyodor Urnov, University of California, Berkeley, shared his vision of a future where gene editing platforms can be used to rapidly treat thousands of rare, severe genetic diseases.

Genome editing using CRISPR is beginning to fundamentally change the landscape of disease treatment. As of 2024, a CRISPR-based medicine has been approved in the UK to treat sickle cell disease, and Phase 3 trials are currently underway for the first-ever *in vivo* gene editing therapy.

Despite these successes, the field of gene editing medicine is in crisis. Funding for the sector is shrinking as investors shift to lower risk assets and markets. Leading companies, including Intellia, Beam Therapeutics, Editas and Caribou Biosciences, have announced plans to reduce their workforce and narrow the focus of their research programmes. Pipelines for new medicines are small and shrinking.

Approval pathways for gene editing medicines

Companies are increasingly focusing on a small number of diseases, and only a small number of the numerous mutations that cause these diseases. This is due to how gene editing medicines are reviewed and approved by regulators. Currently, gene editing therapies are assessed on their ability to treat a given disease by repairing a specific mutation. If the editing components are changed, even if it is just to use a different guide RNA to target a different mutation in the same gene, it is by law a new product and requires the initiation of a new, independent approval process. This can take years and involves restarting the preliminary non-clinical work and repeating pre-clinical studies.

There is potential to transform this system. In theory, gene editing medicines could instead be assessed and approved based on their ability to treat a syndrome, a collection of clinical features that consistently occur together. Under this proposed 'basket' system, regulatory approval could extend to all editors repairing any mutations that cause a specific disease.

Image: Professor Fyodor Urnov, University of California, Berkeley.

> "Can gene editing be used for thousands of other severe diseases caused by single mutations? In a research lab the answer is a firm "yes" - but what about in the clinic?"
>
> Professor Fyodor Urnov, University of California, Berkeley.

The Danaher-IGI Beacon for CRISPR Cures

Danaher and the Innovative Genomics Institute (IGI) have partnered to streamline the research, development and regulation of CRISPR therapies to treat hundreds of genetic diseases. Companies in the Danaher portfolio make every component required for a gene editing medicine, and IGI has cross-functional teams with expertise in treating inborn errors of immunity, which is the disease space this collaboration will initially focus on. The high-level ambition of this public-private partnership is to develop a platform approach that could be used to rapidly produce new gene editing therapies for any genetic disease.

The scientific exchange

To advance policy and practice, the FDA together with the Alliance for Regenerative Medicine and the International Society for Cell and Gene Therapy hold invite-only multi-stakeholder workshops. The aim is to co-create solutions to key issues for the field and lay the groundwork for further developer and regulatory evolution. In a meeting held in November 2024, the focus was on advancing the development of gene editing platforms to streamline therapy development. A platform approach has the potential to provide much-needed cures to severe diseases as they are needed. Collaboration and innovation are needed to realise this vision.

Innovation and challenges in chemistry, manufacturing and controls with new technology platforms – the gene and cell therapy case

Dr Dafni Bika, AstraZeneca, described the complexity of the manufacturing processes for cell and gene therapies, making a case for continued investment to support innovative solutions.

Image: Dr Dafni Bika, AstraZeneca.

> "Cell and gene therapies turn cells into medicine. The manufacturer is, in a sense, the human body. While amazing, this creates many challenges that affect scalability, stability, reliability and safety."
>
> Dr Dafni Bika, AstraZeneca.

Traditional pharmaceutical products have well-defined chemistry, manufacturing and controls (CMC) deliverables. Their development follows proven and accelerated clinical pathways to assess safety and efficacy. They have well-established manufacturing processes, fit into a well-defined regulatory framework and use resilient supply chains. This supports predictable cost structures and pricing.

CMC challenges for cell and gene therapies

In contrast, cell and gene therapies (CGTs) often involve complex and individualized manufacturing processes that can lead to significant variability in yield, production timelines and costs. They also face unique challenges in scalability, quality controls, regulatory compliance and supply chain logistics. For companies to develop these therapies and make them available to patients, innovation in CMC is required to ensure their production is consistent, quick, scalable and cost-effective.

Case study: Autologous cell therapy

Briefly, autologous cell therapy involves collecting a patient's cells, isolating and activating T cells, engineering those T cells so they will attack cancer cells, growing the number of T cells, undertaking quality control and quality assurance (often the most time-consuming step), then infusing the patient with the engineered T cells.

This therapy is challenging and expensive to provide to the patient. The starting material (cells from a patient) may be highly variable in terms of disease state, which in turn imposes significant variability in manufacturing inputs and outputs. Production volumes are small, as each batch is tailored to an individual. Cells are collected and later infused in the hospital, however the other steps in this pathway often take place a specialist facility thus costly cold chain transportation is required. There is a tight turnaround time, as the total process is typically completed within 25 days. However, there is no inventory to buffer variability.

One possible future innovation could be the development of 'universal effector cells'. This would involve using healthy donor cells, knocking out patient-specific genes, activating T cells, then administering these T cells to patients in need of treatment. This would essentially make cell therapy an 'off the shelf' option that could be stockpiled and would thus be ready to go for patients on demand.

Collaborative innovation

The CGT community, including the diverse stakeholders involved in therapy development and distribution, must work together to overcome manufacturing challenges and support the integration of CGTs into standard healthcare practices. Key ambitions for the future include:

- digitise and connect supply chains to ensure they are resilient and agile;
- strengthen partnerships and collaborate to respond quickly to demand;
- accelerate use of digital technologies, data and AI for real-time insights and decision making; and
- act on ethical dilemmas and improve regulations.

Innovating manufacturing solutions, such as automation, standardization and advanced bioprocessing technologies, are essential. Continued investment in manufacturing capabilities and cost-effective strategies will be crucial for integrating these groundbreaking therapies into standard healthcare practices.

Commercialising advanced cell and gene therapies - challenges and opportunities

Christopher Vann, Autolus Ltd, explained the complex supply chains involved in delivering gene therapies and described the need for collaboration amongst all stakeholders to overcome the challenges in manufacturing and delivery.

Image: Christopher Vann, Autolus Ltd.

> "Given that thousands of patients are poised to benefit from CAR-T therapies across the globe, we are reaching the point at which we must address what is needed to fully 'industrialise' the provision of these treatments."
>
> Christopher Vann, Autolus Ltd.

While advanced cell and gene therapy (ACGT) products have the potential to offer transformational outcomes to patients with limited or no treatment options, their delivery is fraught with challenges. There are numerous reasons for this, outlined below.

Novel systems

ACGT products are innovative medicines with unique modalities that cannot be produced using standard pharmaceutical manufacturing pathways. Complex requirements often necessitate bespoke systems that include expensive steps (eg cold chain logistics, cell orchestration, long-term safety follow-up platforms). For some therapies such as autologous CAR T cell therapy, each batch of medicine must be tailored to an individual. The economies of scale and speed available for other medicines have yet to be realised for most ACGTs.

Complex patient journey and management

To receive an ACGT, patients must embark on a complicated journey involving many contributors. Even just the first step, involving referral to and enrolment in a clinical programme, can be lengthy. A patient must first be identified as a potential recipient for an ACGT product. Screening and diagnostic mechanisms exist in some cases, but it can take years for a patient to receive a correct diagnosis. There may also be an eligibility assessment, where the clinical team evaluate a patient's disease status and other health markers to ensure they are a suitable candidate. Subsequent steps in the patient journey (scheduling and preparing for treatment, receiving treatment, follow-up post-treatment) involve interactions with and input from the clinical team, non-clinical stakeholders(eg couriers, lab staff) and the manufacturer of the drug.

Establishing treatment centres

The current treatment process is inefficient and costly. There may be delays in the transfer of information between stakeholders (eg scans, reports), and capacity limitations in hospitals and laboratories can cause additional lags. Support for patients' families may be lacking, and they may face substantial travel and accommodation costs.

Dedicated treatment centres have the potential to improve the delivery of advanced therapies. The Advanced Therapy Treatment Centres network is coordinated by the Cell and Gene Therapy Catapult and consists of four centres dedicated to providing ACGT products to patients. These centres are driven by collaboration between the NHS, industry and academia, and learnings from the centres can be disseminated more broadly across the healthcare system.

Reimbursement and market access

Like other products with transformational outcomes, ACGT products typically have accelerated approval based upon single-arm studies (ie all patients receive treatment, there are no results included from people with a disease who did not receive treatment). The NHS, as a single national provider of healthcare, is well-placed to take a holistic view of the value of new treatments, for example by weighing the high upfront costs of these medicines against the longer-term costs of caring for untreated patients. There is also the potential to explore novel (eg instalment-based) reimbursement mechanisms to share risk.

Overcoming manufacturing and regulatory challenges in multicomponent gene editing technologies

Dr Vanessa Almendro-Navarro, Danaher, explored the dual challenges of manufacturing and regulation in gene editing, focusing on the urgent need for new technologies and regulatory pathways.

Gene editing technologies present unique and complex manufacturing challenges. Their production is essentially incompatible with current drug development models, biomanufacturing technologies and healthcare systems.

Gene editing therapies are inherently complex, comprising multiple biological components such as guide RNAs, nucleases, and delivery systems, all of which must adhere to rigorous quality and safety standards. This complexity poses significant manufacturing challenges, particularly at small scales, where existing technologies are often inadequate for producing the tailored treatments required for rare diseases and personalized medicine. The absence of efficient small-scale manufacturing solutions has created a critical bottleneck, resulting in inefficiencies, increased costs, and extended development timelines.

Alternative development frameworks are needed

The ideal personalized genomic therapy would directly target a genetic mutation, feature modular design with independent and well-characterized components, and leverage streamlined regulatory processes and cost-efficient manufacturing altogether enabling economies of scale and scope.

The development and implementation of this vision face significant challenges, including limited access to comprehensive genetic testing, inadequate data analytics capabilities, and prolonged research cycles due to insufficient disease models and natural history data. Additionally, the lack of prior knowledge to inform dosing, modular and cost-effective manufacturing solutions, and clear regulatory guidelines further hinders progress. Compounding these issues are unsustainable funding and reimbursement models, underinvestment in N-of-1 therapies, low disease awareness, poorly established referral systems, and the absence of centralized databases

> "We need alternative development frameworks combined with advanced biomanufacturing innovation to advance genomic medicines for rare disorders from discovery to patients in a sustainable manner."
>
> Dr Vanessa Almendro-Navarro, Danaher.

The Danaher-IGI Beacon for CRISPR Cures seeks to streamline the development of gene editing medicines, addressing major gaps and inefficiencies in their biomanufacturing. The approach is to create repeatable gene editing platforms that can be adapted in relatively minor ways to create multiple therapies, each targeting a different genetic disease. This would mean non-clinical data and manufacturing information from one product may be used for another, simplifying and standardizing the development and regulation of gene editing medicines. A key promise of the platform approach is that gene editing medicines will be developed with urgency to treat patients with a lack of therapeutic options.

Regulators are trying to adapt

Regulatory bodies are increasingly supporting more flexible and efficient pathways to expedite the approval of genomic medicine drug products. A notable advancement is the Platform Designation Omnibus (PDO) passed by the U.S. Congress. The PDO is a pivotal regulatory framework designed to streamline the development and approval process for innovative therapies, particularly in genomic medicine. For developers of these therapies, the PDO can lead to shorter development timelines by minimizing the need for repetitive submission of similar data for therapies based on the same product and manufacturing platform. This could lower development costs and encourage greater investment in genomic medicines manufacturing and clinical development. Tools like the PDO are driving the integration of hardware, reagents, and consumables into unified platform approaches, paving the way for more efficient and scalable manufacturing. Addressing the interconnected challenges of regulation and manufacturing will be key to unlocking the transformative potential of gene editing and accelerating the delivery of life-changing therapies.

Cell and genetic therapies: global regulatory strategies and lessons learned

Dr Stephanie Krogmeier, Vertex Pharmaceutical, reviewed the global regulatory strategies and lessons learned on the journey to gaining approval for a novel gene therapy.

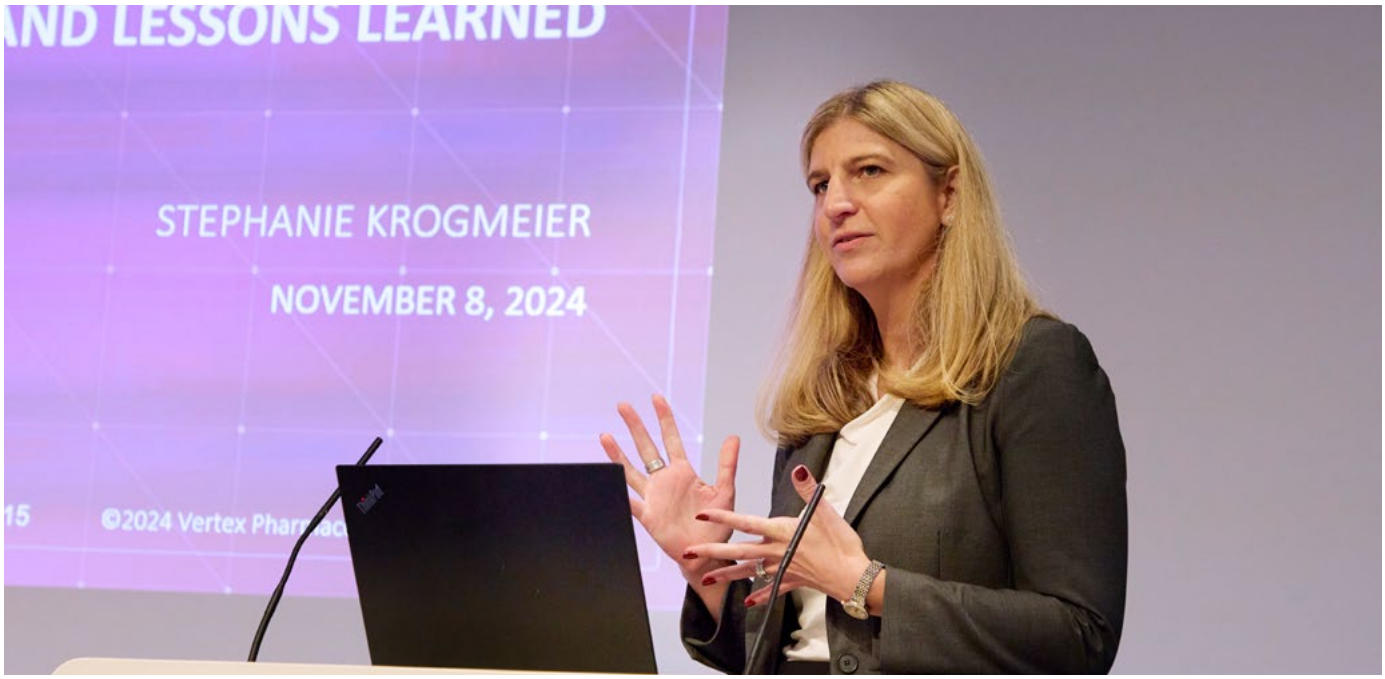


Image: Dr Stephanie Krogmeier, Vertex Pharmaceutical.

> "Development of cell and genetic therapies requires a robust and cross-functional approach, as well as early and often engagement with regulators."
>
> Dr Stephanie Krogmeier, Vertex Pharmaceuticals.

Vertex invests in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets. They focus on validated targets that address causal human biology, create predictive lab assays and clinical biomarkers, and identify efficient pathways to registration and approval.

Cell and gene therapies (CGTs) are novel products, and innovators must learn together with regulators to ensure mutual understanding of the science and uncertainties associated with these treatments.

Getting from trials to approval

Developing a comprehensive preclinical package is an essential step in the drug development process. To proceed to clinical trials, the innovator must have sufficient evidence to indicate efficacy and safety. This may not be straightforward for CGTs. They are often produced using novel manufacturing processes and some of the components of these medicines may not have been previously used or tested in preclinical studies. As such, traditional preclinical approaches for testing efficacy and safety may not apply. Early engagement with regulators to clarify and align with their requirements will help to ensure studies do not have to be repeated. This may take multiple rounds of discussion.

Novel and complex manufacturing processes directly impact the process descriptions and release strategies required for clinical trials and marketing application submissions. Rarely is the manufacturing process used in preclinical work appropriate for commercial launch, and these changes to manufacturing are a big deal for regulators. Data and methods used to demonstrate comparability between preclinical and commercial processes are often new for CGTs and thus subject to high scrutiny. These methods must be developed early and agreement with regulators must be sought promptly to ensure they understand the approach being taken. In addition to traditional release strategies, potency assay(s) must be developed early to facilitate alignment with health authorities and support manufacturing processes.

Although the potential for CGTs is clear, they can raise novel safety concerns due to their unique mechanisms of action. Discussing the emerging benefit-risk profile of a medicine with regulators early and often in the development process can help ensure any safety concerns are identified and addressed in a timely manner.

Engaging with regulators

How can innovators ensure discussions with regulators are effective? The following factors are important:

- Come prepared. Well-executed meetings with regulators take significant preparation and resources. It takes time to ensure messages are delivered concisely and clearly.
- Bring cross-functional teams to the table. Ensure the different teams involved in drug development are engaged with the regulators and with one another. Coordination and communication are vital.
- Clarity of communication. What is the key message, what are the proof points? Focus on clearly explaining the meaning of relevant data rather than providing as much data as possible. Think about the regulators and what they need to see to make decisions. Spend time going through the guidance documents as they explicitly state what regulators need.

Ensuring safety in genome editing: innovations in detecting and mitigating off-target effects

Professor Toni Cathomen, University of Freiburg, Germany, described the methods used to assess the presence and impact of on- and off-target effects of gene editing therapies.

Image: Professor Toni Cathomen, University of Freiburg, Germany.

"On- and off-target effects of genome editing can differ between cell types and editing platforms. Cas9 nuclease should not be used as a surrogate for off-target analysis for other platforms."

Professor Toni Cathomen, University of Freiburg, Germany.

Early evidence suggests that genome editing can be efficacious and safe. However, questions remain about the longer-term safety of these treatments. Before gene-edited products can be administered to patients, it is essential to thoroughly evaluate the wider changes in the genome caused by editing technologies. Genome editing carries risks of unintended off-target effects and considerable on-target aberrations that may have consequences for patient health. In the worst-case scenario, genome editing could unintentionally result in the activation of proto-oncogenes or the inactivation of tumor suppressor genes, which may lead to cancer.

The CAST-Seq assay

A recently developed biological assay, CAST-Seq, can be used to identify changes in a genome after it has been edited. CAST-Seq can discover on-target aberrations, identify translocations that have been induced by a genome editor, and pinpoint where the off-target activity has occurred. CAST-Seq is highly sensitive (ie it can detect a single chromosomal aberration event in 10,000 cells).

This assay has worked on all primary cell types examined so far and can be used to examine the effects of different types of editing technologies (eg nucleases that make cuts to DNA, base editors that can modify a base pair without being dependent on a double-stranded break in the DNA, and primer editors that can swap one DNA sequence for another). Based on what changes are seen at the genome level, a risk analysis can then be performed. It is difficult to predict the clinical relevance of many of these unintentional changes to the genome. However, their presence does not necessarily mean a therapy should not proceed to clinical trials. Nevertheless, the development of more specific editors with fewer unintended genomic changes is encouraged. Ultimately, the use of bioassays to assess on- and off-target effects may help to further derisk genome editing approaches.

On-target chromosomal aberrations

Editing technologies, particularly those that involve creating double-strand breaks in DNA, can cause large, unintended changes in the genome at the site that is being edited. Large aberrations (eg deletions and inversions) are present in up to 60% of edited on-target sites. Importantly, these effects are not detected by short-read high throughput sequencing, and there is no known mitigation strategy to prevent these impacts thus far.

Off-target effects

CAST-Seq can pinpoint where in the genome off-target activity (eg translocation) has occurred. By analysing edited cells during preclinical trials, therapy developers can see if their nuclease has a high rate of off-target effects. If so, they can re-design the nuclease to increase specificity.

Editing technologies that cause DNA double-stranded breaks (eg nucleases) are associated with a higher risk of translocations. The risk of off-target effects can be reduced by using nick-based editors (eg paired nickases, base editors), which do not rely on double-stranded breaks. However, use of these nick-based editors appears to cause a different quality of on-target aberrations (ie more large insertions), and in rare cases may also induce translocations, suggesting that nicks are converted to double-strand breaks.

Preliminary work suggests that both cell type and choice of editing platform impact the number and type of off-target effects observed. Furthermore, Cas9 cannot be used as a surrogate for predicting off-target effects for other types of editing technologies, such as base or prime editors.

Precision medicine and HTA: an overview of the barriers and solutions in evaluating Advanced Therapy Medicinal Products (ATMPs)

John Spoors, NICE, shared the role his organisation plays in assessing the clinical and cost-effectiveness of cell and gene therapies.

Image: John Spoors, NICE.

"A balance must be struck between accelerating access to these high-potential therapies and addressing the uncertainties and financial risk associated with their often-limited evidence base and implementation requirements."

John Spoors, NICE.

The National Institute for Health and Care Excellence (NICE) provides national guidance to the NHS and the wider health and care system to help practitioners and commissioners get the best care to people fast while ensuring value for the taxpayer.

For a gene therapy to be made available through the NHS, it must first undergo a health technology evaluation by NICE. They evaluate gene therapies as part of their Technology Appraisal (TA) and Highly Specialised Technologies (HST) programmes.

The current ATMP pipeline

The Specialist Pharmacy Service (SPS) provide the NHS with enhanced horizon scanning of new medicines. For the current two-year period (2024 and 2025), it is anticipated that 722 new products / indications will be made available in the UK. Of that total, approximately 3% are Advanced Therapy Medicinal Products (ATMPs).

NHS England and NICE are currently tracking 24 ATMPs that are expected to go through NICE assessment by the end of 2026. However, these timeline estimates are subject to frequent change. Horizon scanning analysis has shown that approximately 75% of ATMPs are delayed, discontinued or never launched, compared to just 25% of non-ATMP products. This attrition often happens before formal assessment by NICE, with a number of technical, commercial and clinical reasons driving this. It is worth noting that of those ATMPs that have been submitted to NICE for a health technology evaluation, the vast majority (~80%) have thus far been approved for use.

Addressing challenges associated with the development of ATMPs

Market access does not finish with regulation or health technology evaluation. Even after a product launches, the market for medicines continues to evolve. Collaboration is vital to ensuring the end-to-end pathway delivers timely medicine access for patients. By providing horizon scanning information early (eg three years before expected launch date) and continuing to engage throughout product development, manufacturers can help ensure the NHS is ready to regulate, evaluate and crucially implement new products.

Health service preparedness takes time. New technologies may require major pathway redesign for delivery. If screening and diagnostic tools and protocols are not in place, it may not be able to identify target patients in the therapeutic window of opportunity. Also, patient demand is complex, and patient desire for a novel therapy is not always a given, depending on the clinical scenario. Early engagement with healthcare systems and patient advocacy groups is therefore crucial to understand patient perspectives and the holistic care pathway.

A challenging balance for healthcare systems

Healthcare systems must strike a balance between accelerating access to ATMPs and thoroughly assessing the associated risks and uncertainties. To ensure financial sustainability, they must consider the opportunity cost / financial risk if a product fails to deliver the health benefits promised at launch. However, by creating systems to optimise access to ATMPs, healthcare systems such as the NHS can tackle unmet patient needs, provide positive signals to therapy developers that the UK is an 'early adopter' market, and improve clinical trial capabilities for these novel medicines.

What makes a successful commercial genetic medicine?

Professor Bobby Gaspar, Orchard Therapeutics / UCL, examined why some gene therapy programmes have successfully secured access for patients while other programmes have faced difficulties.

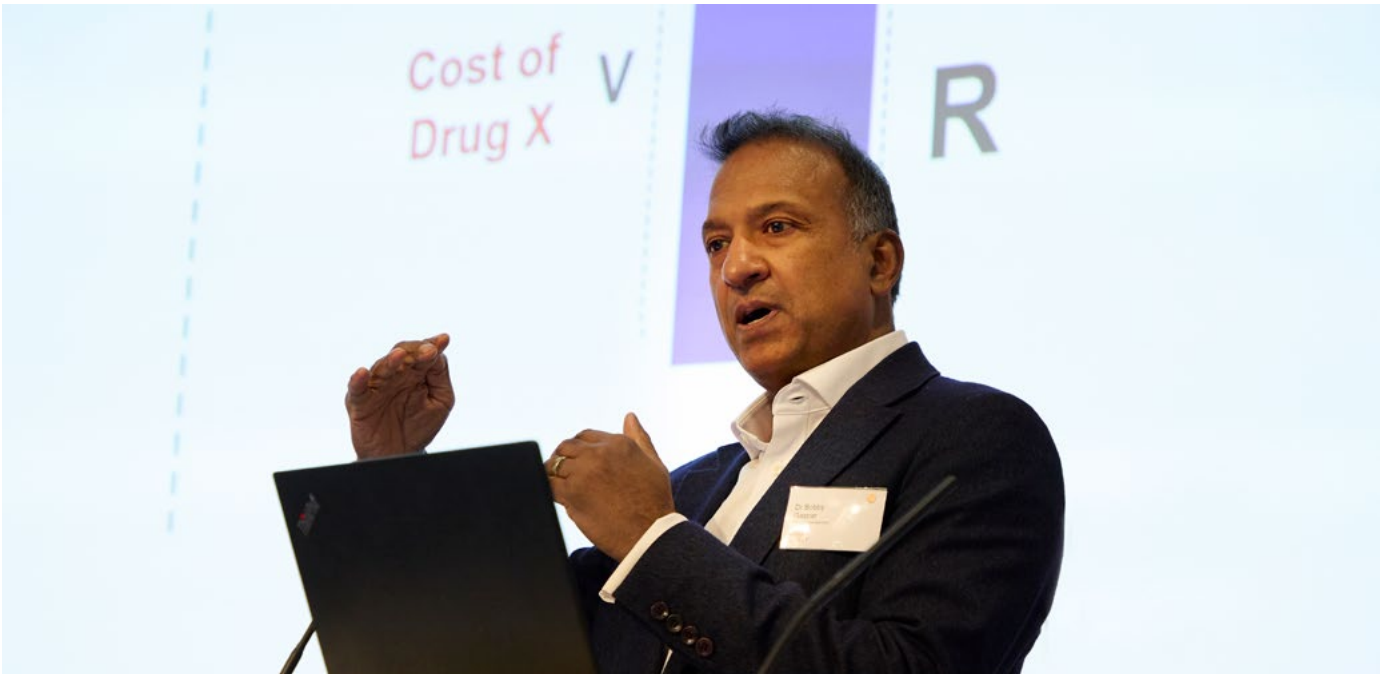


Image: Professor Bobby Gaspar, Orchard Therapeutics / UCL.

> "Great science and great clinical data are not the only pre-requisites for a successful medicine."
>
> Professor Bobby Gaspar, Orchard Therapeutics / UCL.

Over the past decade, we have seen many gene therapy successes but equally many failures. Intriguingly, there have been programmes that have shown clinical efficacy but have not been able to achieve either regulatory or commercial success.

What makes a gene editing medicine a success?

Success can be measured in many ways. For the purposes of this discussion, a successful medicine is one that gains regulatory approval, is commercialised and is accessible to patients. Revenues and return on investment are not considered.

Having an indication (that is, a valid reason for using a medicine) is key to success. When developing a new therapy, innovators must be able to articulate how their medicine offers substantial improvements in both safety and efficacy compared to existing treatments. For most ultra rare diseases for which there are either no or limited treatment options, the value proposition for new gene therapies is likely to be compelling. However, a gene therapy for treating a disease for which a high standard of care already exists (eg where bone marrow transplants are a useful treatment) is likely to face many barriers to commercialisation.

Case study: Commercialising 'Drug L'

Metachromatic leukodystrophy (MLD) is a devastating rapidly progressive genetic disease. Children with MLD die within first or second decade of life. A gene therapy, 'Drug L', has been shown substantially prolong life and halt the progress of the disease in children treated early.

To provide evidence that there was a strong indication for using 'Drug L', the developers considered:

- **Burden of illness**
  MLD is a severe disease with limited treatment options. Although rare, it has a large economic healthcare burden (eg nursing care costs).
- **Innovation**
  Based on clinical benefit, 'Drug L' has been recognised as a highly innovative therapy by the National Institute for Health and Care Excellence.
- **Cost-effectiveness**
  'Drug L' offers substantial gains in both number and quality of years of life compared to other technologies.
- **Price analogues**
  'Drug L' follows the same price to disease prevalence relationship as other life-long rare disease treatments. Although expensive, it is potentially a one-time intervention.
- **Budget impact**
  MLD occurs in about 1 in 100,000 individuals per year. In the UK, this is ~2 patients per year. The cost of providing treatment corresponds to a small fraction (~1/6250) of the UK pharmaceutical budget.
- **Sustainable access**
  The developers of 'Drug L' are willing to share financial risk with payers. Payment options exist, although most agencies have opted to pay a lump sum up front.

'Drug L' has been approved in the EU and six treatment centres have been established. Patients must be in early stages of the disease or pre-symptomatic to get the most benefit. This requires effective screening protocols, which are now being piloted in different parts of Europe. The aim is to identify all children at birth with this condition, completely changing the lives of these children and their families and removing the healthcare burden.

Economic aspects of access to gene therapies for ultra-rare diseases: an impossible riddle

Stefano Benvenuti, Fondazione Telethon, discussed a not-for-profit commercialisation model for gene therapies with the potential to complement the standard pharmaceutical development pathway.

Image: Stefano Benvenuti, Fondazione Telethon.

> "A not-for-profit model for patient access to gene therapies for ultra-rare diseases is possible, but it cannot solve everything."
>
> Stefano Benvenuti, Fondazione Telethon.

In 2000, an Israeli child became the first patient to receive an ex-vivo gene therapy developed by the San Raffaele Telethon Institute for Gene Therapy, a joint venture between Fondazione Telethon and the Ospedale San Raffaele. The child had adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID), an extremely rare immune system disorder that is typically fatal in infants. This pilot study saved the life of this first patient and others with ADA-SCID.

Commercialising the gene therapy

By 2010, there was sufficient data to indicate this gene therapy was effective. To register the therapy with the European Medicines Agency, Fondazione Telethon partnered with GlaxoSmithKline (now GSK). In 2016, this treatment became the first ex-vivo gene therapy to be approved in the EU. However, after only one year, GSK announced its plans to exit the rare disease drug development market, and the therapy was passed to Orchard Therapeutics. Another upset for ADA-SCID patients arrived in 2022, when Orchard Therapeutics discontinued investment in its programs in rare primary immune deficiencies because they were not economically viable.

Despite being a not-for-profit organisation, Fondazione Telethon made an official request to be transferred the marketing authorisation for this gene therapy to ensure continued patient access. The transfer was approved in 2023.

A new model for distributing gene therapies

As marketing authorisation holder for the therapy, Fondazione Telethon is now responsible for providing it to eligible patients in the EU. In its approach to pricing, it does not need to cover R&D costs as these are supported by grants and donations, nor does it seek a profit. However, it must take product-specific costs (eg operational expenditure) and pricing risks (eg loss of innovation status) into account.

This pricing model cannot apply to commercial entities who need to payback their investment in R&D. As evidenced by decisions made by GSK and Orchard Therapeutics, gene therapies for ultra-rare diseases do not typically offer a competitive return on investment compared to other activities these companies could undertake.

Improving return on investment is incredibly difficult, as the volume of product is capped by the number of patients (low for rare diseases), and the price is effectively capped by regulators who are unlikely to approve a medicine that is not cost-effective. There is a need for a different model of investment. Gene therapies will never be attractive enough for standard capital investors, and their manufacture and distribution cannot be wholly achieved using grants and donations.

Other mechanisms that may improve the economic and patient access issues associated with gene therapies include:

- define special incentives (not just market exclusivity) for gene therapies;
- support innovation procurement systems that pay for therapy development. This investment could then be discounted from the final price of the therapy;
- use reimbursed early access schemes to provide the treatment to patients while the discussion on price and reimbursement is ongoing;
- move patients to ‘centres of excellence’ to receive treatment, where experienced practitioners can treat patients safely and efficiently; and
- set-up an international system for mutual recognition of marketing authorisations.

Effective clinical development to enable patient access for gene editing therapies

Dr Benit Maru, SSI Strategy, examined how challenges associated with patient access and reimbursement could be mitigated earlier in a product lifecycle through the adoption of a 'new' clinical development mindset.

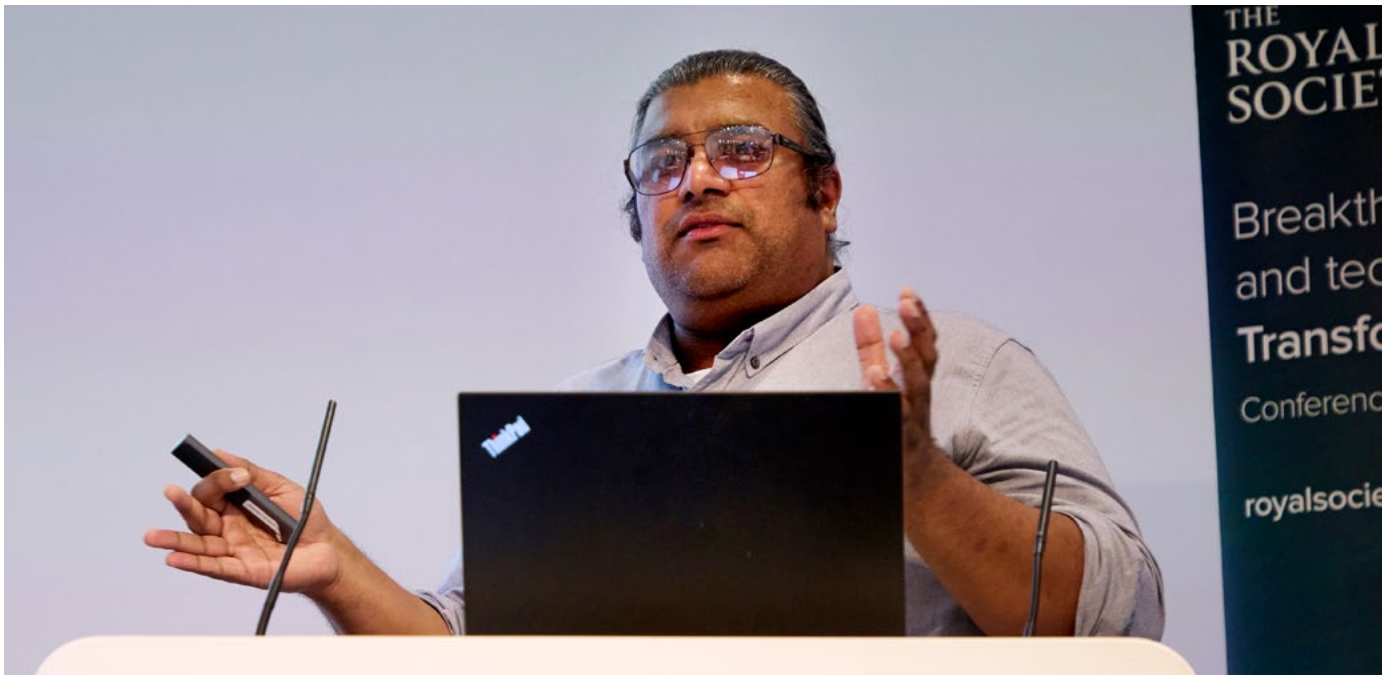


Image: Dr Benit Maru, SSI Strategy.

> "If there are no utility measures of health for the disease you are working on, you can generate your own data in-house – publish it. NICE hang their hat on referenceable material."
>
> Dr Benit Maru, SSI Strategy.

Gene editing therapies have the potential to revolutionise the treatment of genetic disorders. However, there are several challenges associated with commercialising these medicines and making them available to patients.

Reimbursement challenges for high-cost therapies

For UK patients to be able to access advanced therapies like gene editing medicines, these novel treatments typically must be funded by the NHS. In England, the National Institute for Health and Care Excellence (NICE) assesses new medicines to examine their efficacy, safety and cost-effectiveness. If NICE recommends a medicine for approval, the results of their assessment will then inform pricing and reimbursement decisions for that medicine.

Challenges with reimbursement for advanced therapies typically result from uncertainties around patient need, clinical value and cost-effectiveness. As part of their assessment process, NICE will examine clinical evidence and ask questions such as:

- What are long-term benefits of this therapy?
- What is the durability of effect?
- Is the treatment curative?
- Does it improve quality of life?
- How and when is the data being collected?
- Is the clinical trial population representative of the wider potential patient population?

Many of these uncertainties arise from the limited use of a therapy – it hasn't been in use for very long, and it may be intended to treat a very small number of people, initially in clinical trials.

Development timelines for traditional vs advanced therapies

The development of new therapies requires involvement of different stakeholders at distinct stages. In traditional product development, there is often sequential involvement of teams focused on non-clinical (eg research), clinical, patient advocacy, medical affairs, health economics and outcomes research, and market access aspects. Timelines vary, but it typically takes 10 – 15 years to develop a traditional pharmaceutical product.

In contrast, recent advanced therapies have had substantially truncated development timelines. For example, the development of Casgevy (a treatment for sickle cell disease) took about 8 years. This would have required the various teams involved in therapy development to work in parallel, rather than sequentially. Chemistry, manufacturing and controls activities would have been significantly accelerated.

How companies could address uncertainties affecting reimbursement

To mitigate some of the uncertainties that can impact approval and reimbursement decisions and speed up the development process, the following approaches may be useful:

- proactive and adaptive development mindset – for example, early consideration of the evidence needs of different stakeholders and understanding the gene therapy approval landscape;
- early cross-functional alignment and interactions – this includes alignment on an overall corporate strategy and value narrative and continuous interaction and collaboration throughout the development lifecycle; and
- creative data generation – this could involve collected data to produce utility scores and patient vignettes to describe quality of life, or leveraging non-clinical animal data and disease modelling to address concerns about durability.

Regulation and encouraging innovation in gene and advanced therapy medicinal products (ATMPs)

Julian Beach, MHRA, described the need for a continually evolving regulatory framework to adapt to fast-paced developments in gene therapies.

Image: Julian Beach, MHRA.

> "The role of the MHRA is to enable innovation and get medicines to patients. Come talk to us, bring us in."
>
> Julian Beach, MHRA.

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring medicines meet set standards for safety, quality and efficacy before they are made available to patients in the UK. A balance must be struck between enabling groundbreaking scientific innovation and safeguarding public health, and a transparent process is critical to maintaining public trust.

Existing regulations for gene editing medicines

In the UK, medicinal products manufactured using gene editing approaches have thus far been classified as advanced therapy medicinal products (ATMPs) and have been regulated under the Human Medicines Regulations 2012[1]. As advances in gene editing medicines accelerate, updates or changes to regulations may be needed. The MHRA is committed to evolving their regulatory framework to adapt to fast-paced developments in gene editing medicines so that patients can access these much-needed treatments in a timely and safe manner.

In regulating gene editing medicines, the MHRA considers why a treatment may work by seeking to understand the disease process, the pharmacological properties of the proposed therapy, and the potential patient benefit. They also consider treatment safety, particularly the potential for toxicological effects and how they may be controlled / limited. For companies developing innovative medicines, the MHRA strongly recommends early engagement. Through their Innovation Office, they can provide free and expert regulatory advice.

The number of ATMP submissions received by the MHRA is rapidly increasing. In 2022-23, they had 31 submissions, jumping in 2023 – 24. To date, 17 cell and gene therapies have been licensed in the UK.

Review of Casgevy

The list of approved ATMPs includes Casgevy, a gene therapy that is used to treat sickle cell disease and transfusion-dependent beta thalassemia. The MHRA were the first regulator to approve this first-of-its-kind CRISPR-based therapy.

1. UK Government. (2012) *Human Medicines Regulations 2012*. See www.legislation.gov.uk/uksi/2012/1916/made (accessed 7 March 2025).

During the 2022 – 2023 review, the MHRA sought to examine Casgevy's safety, quality and efficacy. This process ncluded:

- consideration of its manufacture;
- consideration of its mode of action;
- consideration of its preclinical safety, including the potential for off-target editing and genotoxicity;
- consideration of its clinical efficacy and safety profile; and
- risk management plan agreed.

The MHRA initially granted a conditional licence which was renewed after one year.

The future of ATMP regulation

In October 2024, a Statutory Instrument was laid in Parliament to amend the Human Medicines Regulations 2012. The aim is to develop a new regulatory framework to enable innovative medicines to be manufactured at or near where a patient receives treatment, rather than in a centralised facility. This could be a ground-breaking advancement for medicines with very short shelf-lives and highly personalised medicines.

Global harmonisation of regulations for ATMPs would be hugely beneficial for their clinical development and deployment to those who need them. The Cell and Gene Therapies Discussion Group, managed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, aims to provide a roadmap for future harmonisation efforts.

PANEL DISCUSSION

The future of gene editing medicines

Steve Rees OBE, AstraZeneca, chaired a panel discussion focused on the revolutionary potential of gene editing medicines in the next decade and beyond.

Image: (left to right) Professor Kiran Musunuru, University of Pennsylvania; Dr Birgit Schultes, Intellia Therapeutics; Steve Rees OBE, AstraZeneca, panel discussion Chair and conference organiser; Professor Fyodor Urnov, University of California, Berkeley and John Spoors, NICE.

To close the meeting, four speakers were invited back to the stage to share their reflections on the conference and discuss their visions for the future of gene editing medicines.

Professor Kiran Musunuru, University of Pennsylvania, Dr Birgit Schultes, Intellia Therapeutics, John Spoors, NICE and Professor Fyodor Urnov, University of California, Berkeley offered insights from the clinical, industry, regulatory and research perspectives, respectively.

Some of the topics discussed included:

- The potential for a single treatment to give lifetime protection against a genetic disease will be transformational for human society. Pre-emptive treatment before symptoms emerge is a particularly exciting vision for the future.
- Technological advances in gene editing therapies have been rapid and impressive. However, the speed of delivering these medicines to patients is impeded by expensive and time-consuming regulatory requirements.
- Gene editing therapies are not being used for chronic conditions with well-established standard of care medicines. Instead, they have the potential to transform the lives of patients who do not have other options and may die without timely treatment. Proportionate regulation is needed that takes these benefit vs risk considerations into account. Regulators increasingly recognise the need to adapt to the unique qualities of this field of medicine.
- There are lessons the gene editing community can learn from the development and deployment of Covid-19 vaccines. In two years, the world managed to produce and distribute millions of doses of a novel therapy. Self-contained, portable manufacturing units are showing promise as a mechanism to support local vaccine production. In theory, similar approaches could in future be adapted to produce novel gene editing medicines when and where they are needed.
- Investment in early phase clinical trials is crucial to continuing to advance this field. Safety and efficacy can only truly be tested by treating patients, and hearing from these patients can both inspire and inform future research efforts.

- Similarly, fund off-the-wall ideas to test the limits of what is possible. For example, experimental research has shown that while lipid nanoparticles have limited delivery capabilities in adults (eg to target the liver), the fetal context is entirely different and those same lipid nanoparticles can be used to target a huge range of tissues.

Gene editing medicines are now a reality, albeit for a small number of patients. The challenge to the community is to continue working at pace towards a future where thousands, if not hundreds of thousands of patients stand to benefit from this work.

The Royal Society is a self-governing Fellowship of many of the world's most distinguished scientists drawn from all areas of science, engineering, and medicine. The Society's fundamental purpose, as it has been since its foundation in 1660, is to recognise, promote, and support excellence in science and to encourage the development and use of science for the benefit of humanity.

The Society's strategic priorities emphasise its commitment to the highest quality science, to curiosity-driven research, and to the development and use of science for the benefit of society. These priorities are:

- The Fellowship, Foreign Membership and beyond
- Influencing
- Research system and culture
- Science and society
- Corporate and governance

For further information
The Royal Society
6 – 9 Carlton House Terrace
London SW1Y 5AG

T +44 20 7451 2500
W royalsociety.org

Registered Charity No 207043

Issued: March 2025 DES8920_5