Challenges and Emerging Strategies in ATMPs

Michele Malandruccolo

Alten, Bern, Switzerland

Correspondence to:
Michele Malandruccolo,
malandruccolom@gmail.com

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ABSTRACT

Advanced therapy medicinal products (ATMPs) are a significant innovation in medicine, categorized by the European Medicines Agency into four types: gene therapy medicines, somatic cell therapy medicines, tissue-engineered medicines and combined ATMPs. They hold potential for treating various conditions, including rare diseases, degenerative diseases like Parkinson's and Alzheimer's and cancers. The global market for ATMPs was valued at US$9.28 billion in 2023 and is projected to reach US$22.80 billion by 2032, growing at a compound annual growth rate of 10.50%. Gene and cell therapies are advancing rapidly, with over 1,700 approved clinical trials worldwide. Notable successes include Glybera for lipoprotein lipase deficiency and Roctavian for haemophilia. Despite limited current approvals, many gene therapies are expected to gain market approval soon. Challenges include stringent regulatory requirements, safety and ethical concerns. For example, Glybera faced multiple rejections before approval due to safety issues. Current clinical studies are exploring immune-based therapies like CAR-T, cytotoxic T lymphocytes, natural killer cells and mesenchymal stromal cells. CAR-T cell therapies, such as Yescarta and Kymriah, have shown promise in treating B-cell lymphoma. However, high development and manufacturing costs limit accessibility, exemplified by Hemgenix, a gene therapy for haemophilia B priced at US$3.5 million. Increased ATMP sales have spurred investor interest in R&D, leading to advancements in technology and manufacturing processes. Despite challenges, the future is promising with more academic and commercial ATMP clinical trials. There are now 32 approved gene therapies globally. To attract industries, the focus should shift from rare to common diseases, and alternative reimbursement models could help manage high costs. A trained workforce and public involvement are crucial for the successful delivery of ATMPs.

Keywords: ATMPs, Gene therapy, CAR-T cell therapy, Regulatory challenges, Tissue engineering

Introduction

Advanced therapy medicinal products (ATMPs) are innovative medicines either in their manufacturing process or mechanism of action and can be grouped into four major categories as defined by the European Medicines Agency (EMA):[1]

- Gene therapy medicines: they contain "recombinant" genes that are inserted into the body to treat diseases such as cancer and genetic disorders;
- Somatic cell therapy medicines: these contain cells or tissues that have been engineered to change their biological features and are not intended to be used for the same original functions in the human body;
- Tissue-engineered medicines: such medicines are characterized by cells or tissues that have been engineered to repair, regenerate or replace human tissues.

Furthermore, some ATMPs may contain one or more medical devices defined as combined ATMPs such as scaffolds or biodegradable matrixes.

ATMPs have great potential to treat multiple conditions, from rare diseases through degenerative diseases such as Parkinson's and Alzheimer's to solid and blood cancers. Over the years, there has been an increased number of ATMP clinical trials worldwide, and the global market size was valued at US$9.28 billion in 2023, with a forecast to reach US$22.80 billion by 2032 at a compound annual growth rate of 10.50% (Figure 1).[2]

If we consider gene therapies only, there are more than 1700 approved clinical trials worldwide with many success stories such as Glybera to treat lipoprotein lipase deficiency or Roctavian to treat haemophilia, for example. Despite the fact that the current number of approved gene therapies is limited, there are many products that are likely to receive market approvals in the coming years. Nonetheless, gene therapies still face several challenges, above all the regulatory requirements. In the case of Glybera, it had failed three times before the final marketing authorization. This is mainly linked to the safety and ethical concerns of such medicines, as the transfer of genes could have an impact on germ lines. Then the quality and stability of the transgene and the type of vectors used could lead to mutagenic events.

In terms of cell therapies, CAR-T therapies have shown great promise with the historical approval of Yescarta and Kymriah to treat B-cell lymphoma. The FDA has already approved 6 CAR-T products, and many other countries other than the US have followed forth. However, all these approved CAR-T therapies target mainly blood cancers such as lymphomas and leukaemia. Nonetheless, because the sales of these products have increased, many investors are now supporting R&D programmes to continuously bring in new advancements. In fact, in many instances, companies are now shifting toward technology and process improvements with more efficient supply chains or new manufacturing models such as decentralized cell therapy centres or physical hubs (e.g. Catapult) that provide infrastructures (a GMP facility is a rigorous environment with really high design costs), laboratories, offices, production and supply chain services to reduce the costs or lack of capabilities of small

Fig 1 | ATMPs' market size and trends analysis[2]

companies fuelling innovation and business growth. Around that, an ecosystem of stakeholders is being built to support such business models. For example, Miltenyi Biotec has specialized in the production of CliniMACS Prodigy devices that are vastly used in cell therapy manufacturing.

In terms of cell therapies, there are currently more than 1000 clinical studies exploring immune-based therapies on CAR-T, cytotoxic T lymphocytes, natural killer cells, mesenchymal stromal cells or using fibroblasts.[3] However, as we have seen with gene therapies, complex regulatory and developmental landscapes pose a challenge to further market approvals. Another huge challenge that ATMPs are facing is that generally the ideas are developed in academia or small startups where there is a lack of understanding of manufacturing processes (scaling up) or regulatory requirements, which later on can lead to rejection by national agencies. Furthermore, the high costs associated with ATMP development and manufacturing make them unaffordable to public and private patients, limiting access to such treatments. A clear example is the approval of Hemgenic to treat haemophilia B, the first gene therapy and most expensive drug with a price tag of US$3.5 million.

Even though the field is facing several challenges, the future is bright for ATMPs. The number of academic and commercial ongoing ATMP clinical trials has substantially increased from 2016. There are now globally 32 approved gene therapies including genetically modified cell therapies with many more at different phases of the clinical trial cycle and showing great potential to treat uncurable diseases. To overcome some of the challenges, the ATMPs' landscape has to move from rare to common diseases so that these treatments become more attractive for industries. However, one question that may arise is how can healthcare systems afford extremely expensive treatment for a common disease such as diabetes? Alternative reimbursement models could be a solution to avoid the high burden on healthcare systems but also prevent market failures and the huge costs that come with it. Better and more coordinated infrastructure is needed, physical hubs like Catapult in the UK can help in reducing the costs associated with GMP facilities, but at the same time, a trained workforce with the latest advancements is also key to successful ATMP delivery, and ultimately, but not least, patient and public involvement to increase awareness and educate the population on the benefits of such therapies.

This review article will deep dive into the most promising ATMP therapies, focussing initially on the technology, the evolution and recent improvements in the field, to move on with failure and success stories, the challenges ATMPs are facing and what emerging strategies are being developed or are already being deployed. The article will conclude with reflections and future expectations for these innovative therapeutic medicines.

Understanding ATMPs

"Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells" (EMA 2024).

ATMPs can be divided into gene therapy medicinal products that are in turn differentiated in in vivo and *ex vivo* (e.g. CAR-T) therapies; somatic cell therapy products (e.g. *ex vivo* expanded adipose stem cells); tissue-engineered products (e.g. skin drafts for burns); combined ATMPs (e.g. cells embedded in a scaffold).

In a global growing and ageing population, one in three people will develop cancer at some point in their life. There are currently 200 types of cancer, with 20 million cases and 10 million deaths worldwide every year. The economic burden of cancer treatment is equal to 25% of total global healthcare spend, with many adverse drug reactions affecting 50% of cancer patients and only one in four cancer patients responding to traditional therapy. However, survival rate has increased 2x since 1970s primarily due to:

- Prevention
- Earlier diagnosis and screening
- Better treatment and innovative medicines (personalized medicines/ATMPs)

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In recent years, there has been a growing movement towards personalized medicines whereby rather than having one treatment fits all, treatments are tailored to the patient rather than to the disease. This approach can take different forms such as immunotherapy, gene therapy, small-molecule inhibitors and the like.

In the case of immunotherapy, the disease is treated with substances that stimulate or suppress the immune response to fight cancer. Immunotherapies are divided into:

- Cancer vaccines
- Oncolytic virus therapies
- Cytokine therapies
- Immune checkpoint inhibitors
- Adoptive cell transfer (e.g. CAR-T)

The advantages of such therapies are that they can provide long-lasting responses, fewer side effects and improved efficiency than traditional therapies other than a more precise targeted action. However, there are still side effects associated with immunotherapies, and some treatments can be really expensive.

Gene Therapies

From a developmental perspective, there are currently >2000 gene therapies in the pipeline worldwide, with most of the therapies targeting rare and cancer diseases with a focus on the main areas described in Figure 2. Globally, 32 gene therapies have been approved, and the number of trials has increased exponentially in recent years.

When we talk about gene therapies, it is first important to understand the difference between *ex vivo* and in vivo applications. In *ex vivo* autologous (from the same donor) or allogeneic (from different donors), the cells are taken out of the body (mostly from the bone marrow), engineered in petri dishes and then the gene-modified cells are transplanted back into the patients. In immunodeficiencies, technologies such as CAR-T cells are typical examples. On the other hand, in vivo gene addition is characterized by the injection of gene therapy agents directly into the body through intravenous injection (IV), spinal fluid injection, muscle injection or inhalation. Diseases treated with this approach are, for example, haemophilia, cystic fibrosis and spinal muscular atrophy (SMA) (Figure 3).

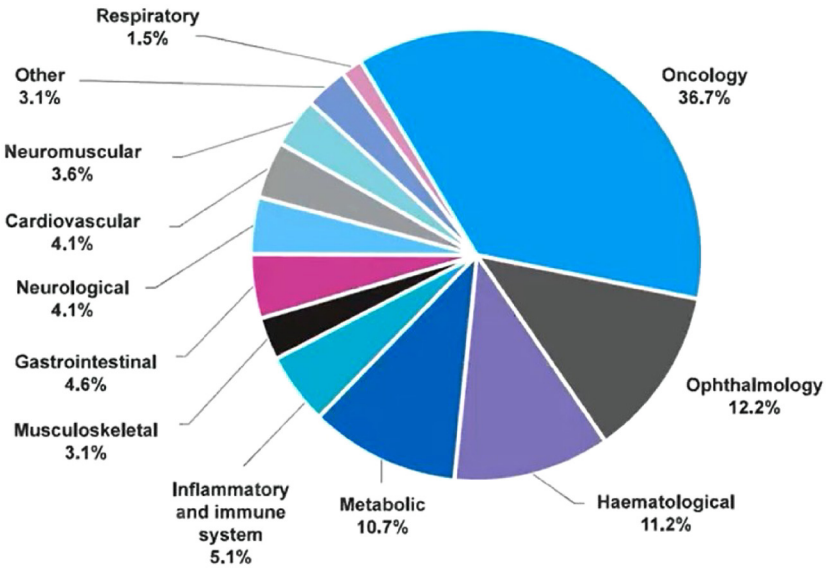

Fig 2 | Gene therapies' therapeutic areas

The gene transfer agents are typically viral vectors such as adenovirus, lentivirus or adeno-associated virus (AAV) but also non-viral vectors such as lipid, mRNA and the like. Viral vectors are engineered to be safe and not replicative through the removal of key genetic information so that diseases are not triggered by these viral vectors.

Knowing that there are several viral vector types, the question is, which viral vector should be used? This is a challenge as there are several aspects to be considered such as:

- Acute vs chronic disease
- Size of the gene (packaging capacity of each vector)
- *Ex vivo* vs in vivo
- Dividing or non-dividing target cells
- Short- vs long-term expression

A typical example of successful gene therapy where these challenges have been overcome is CAR-T cells. These engineered T cells target specific proteins (antigens) on the tumour cells, as they are armed to better recognize tumour antigens, bind to them and kill such cells. Kymriah and Yescarta are CAR-T cell products that were licenced in 2017–2018 to treat B-cell lymphomas. So far, there has been an increase in the survival rate of patients treated with these products, with reduced side effects, although it is not yet proven whether relapse issues have also improved. In paragraph 4 a more detailed explanation of this successful technology in treating blood disorders, its applications, limitations and emerging strategies for improvement will be discussed.

Gene therapies have also been successful in treating immunodeficiencies such as adenosine deaminase deficiency (ADA-SCID), a metabolic disorder and one of the rarest diseases with a ratio of 1:500,000 born babies. Because babies are prone to frequent severe infections from viruses, bacteria and fungi, they have to grow up in a very sterile environment. Also in this disease, cells are obtained from the bone marrow cells of the babies, then engineered in petri dishes *ex vivo* and gene transfer vector inserted in the engineered cells that are ultimately transplanted back into the patient (Figure 4). This is another successful story whereby the product under the name of Strimvelis was licenced in 2017 at a quite expensive price of £600k. However, the price is justified by the one-off treatment, which completely cures the disease.

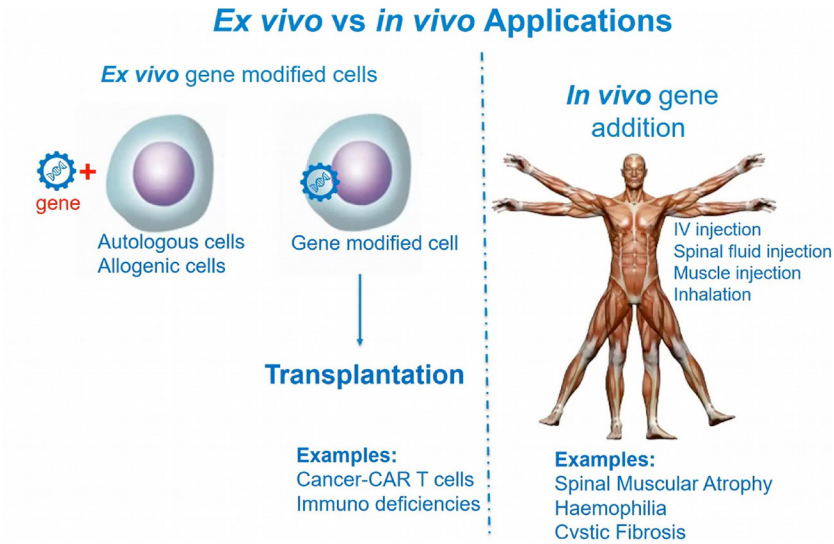

Fig 3 | *In vivo* vs *ex vivo* gene therapies

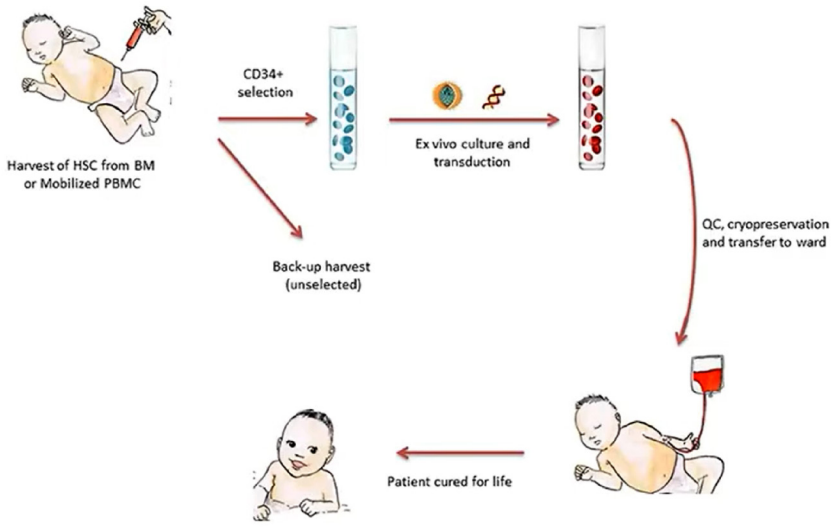

Fig 4 | *Ex vivo* Strimvelis gene therapy manufacturing process[4]

Despite the success, Strimvelis was considered a market failure as it was initially developed by San Raffaele in Italy in 2010 and then bought by GSK and approved in the EU in the same year, 2017. Orchard Therapeutics came into play and brought Strimvelis in 2018, but just after 4 years, it discontinued the product because ADA-SCID is such a rare disease that the product is not worth the investments.[4] Therefore, this is an example of how gene therapy can be successful but because of the high cost, it becomes not commercially viable for pharma companies, and patients are quite often left behind when they should be generally put at the centre of the whole process.

There are other examples of approved gene therapies that turned out to be successful but at the same time very expensive. This is the case of SMA, an inherited neurological disorder typical in children with a 95% mortality rate at 6 months. In this disease, children are characterized by rapid loss of motor neuron's function that makes them floppy. Zolgensma was successfully approved in 2019, an in vivo (IV injection) AAV SMA gene therapy able to improve children's motor function and survival rate. However, it was reported to have a list price of £1.79 million per dose. As we have seen with Strimvelis, cost is one of the main challenges the ATMP field is facing. A similar story happened with a gene therapy targeting haemophilia B (Hemgenix), an in vivo (IV injection) AAV gene therapy that was named the most expensive medicine, reaching a price tag of US$3.5 million.[5]

In conclusion, we have seen that gene therapies can work, and there are many licenced products that patients can be treated with; hence, there is a lot of potential. However, manufacturing has to be improved to reduce the costs, and long-term follow-up for patients has to be improved. Another big challenge is the transition from rare to common diseases, but we need to avoid the burden on healthcare systems (a reimbursement model could be a solution) or situations like Strimvelis to prevent any setbacks. In addition, these innovative medicines require specific infrastructure such as GMP facilities, which take a big chunk of the manufacturing costs associated with these products. Because of that, issues may arise during the manufacturing process if GMP requirements are not fulfilled, leading to major findings by regulatory bodies and further additional costs other than reputational damage.

Solutions to reduce such costs could be outsourcing some activities to contract, development and manufacturing organizations (CDMOs) or within physical hubs that provide the infrastructure in compliance with regulatory requirements (e.g. Catapult centre in the UK). Automation and robotics are also making the production of such therapies more scalable and cost-effective, whilst big data and AI are optimizing clinical trials, pushing towards more personalized treatments and away from the traditional one-size-fits-all approach. The use of CRISPR-Cas9 has also enabled more precise gene editing and cell reprogramming with many pharmaceutical and biotechnology companies transforming their approach to drug development and patient care. This is especially true for the field of drug discovery, whereby predictive analysis through machine leaning models could reshape the industry and accelerate the process from drug discovery to commercialization. Nonetheless, it is important to continuously innovate, bring in technological advancements, and at the same time invest and involve stakeholders across industries. The ATMPs' market value is forecast to reach US$60 billion by 2027, and the growth will primarily be driven by increasing investments in R&D and tech advancements.[6]

CAR-T Therapies

Among immunotherapies, chimeric antigen receptor T-cell therapy (CAR-T cells) has revolutionized the

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outcomes for haematological malignancies, with 90% response in otherwise incurable diseases. Autologous CAR-T requires the collection of T cells from the same donor by apheresis, followed by the introduction of the CAR encoding sequences and the *ex vivo* expansion of the resulting CAR-T cells that are then infused back into the same patient (Figure 5).[7]

CARs usually consist of a single-chain variable fragment (scFv) fused to a spacer, a transmembrane anchor and the intracellular signalling domain of the CD3 z chain (Figure 6). Antigen recognition occurs via the scFv, while activation of the CAR itself occurs through the intracellular domain signalling domains of CD3 z and costimulatory receptors.[8]

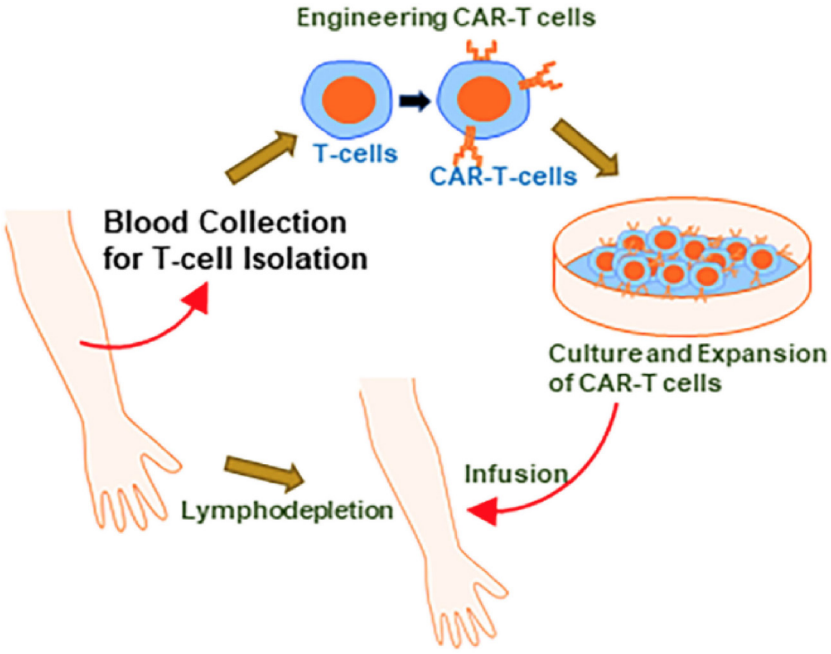

Fig 5 | Chimeric antigen receptor T-cell manufacturing process[7]

There are four generations of CAR-T cells. The first generation has only the CD3 z intracellular signalling domain, while second-generation CARs possess an additional costimulatory signalling domain (e.g. CD28). Third-generation CARs have two costimulatory domains, while fourth-generation CARs incorporate a cytokine signalling module to signal cells. The composition of the CAR varies depending on the target and generation of CAR chosen.

Most of the commercialized CAR-T are fourth-generation products, and the EMA has already approved six of them, but mainly targeting haematological malignancies and multiple myeloma, and only 5% are aimed at other cancers. In fact, solid tumours represent 90% of all cancers, but there has been little success with alternative therapies such as CAR-T, mainly due to physical barriers of the tumour mass, hostile tumour microenvironment, lack of specific tumour-targetable antigens and T-cell exhaustion. To improve such technology, CRISPR is, for example, being used to reduce T-cell exhaustion by targeting the programmed cell death protein 1, a T-cell receptor, or tumour penetrating peptides are being experimented with to overcome the tumour hostile microenvironment. Although one of the main challenges in treating solid tumours with CAR-T is associated with the high costs of autologous (from the same patient) CAR-T therapy in comparison to allogeneic (coming from different donors) strategies that could drastically reduce the costs, in this case, the graft vs host disease is still a bottleneck as they can lead to immune reactions after transplantation. Regulatory CAR-Treg are, for example, a solution to this problem, as they have shown enhanced transplantation and offer potentials for allogeneic treatments.

Another limitation of CAR-T therapies is that they are extremely expensive (in Spain, for example, the price is >€330K per patient), and there are concerns about viral safety, particularly for chronic cancers. Furthermore, there is a need for better biomarker identification for efficacy and toxicity purposes.

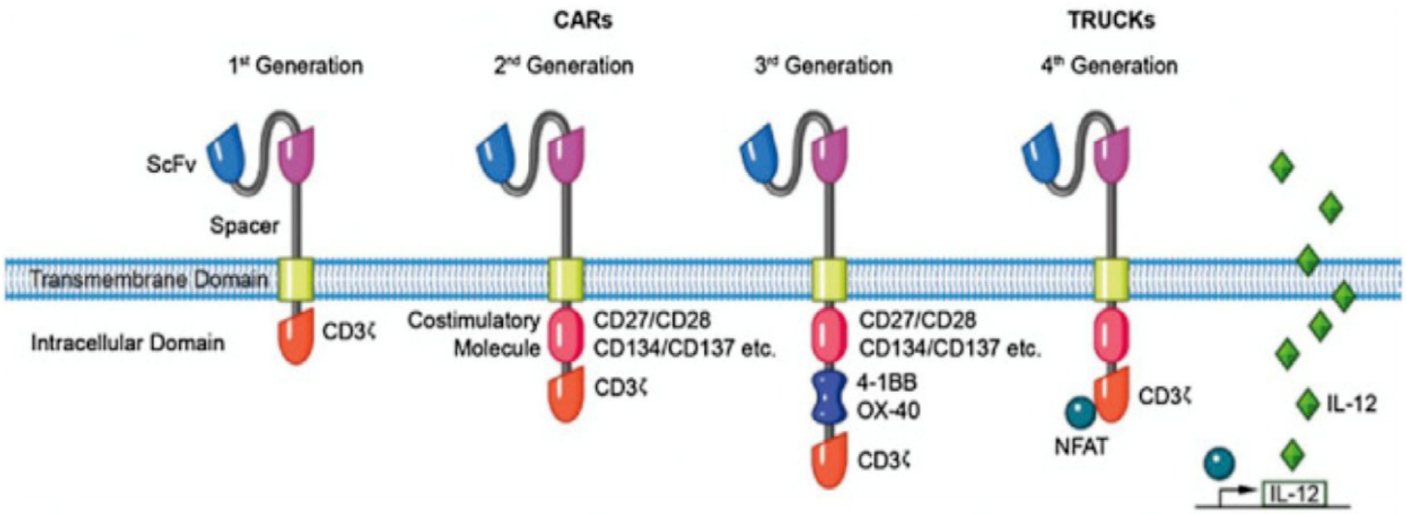

Fig 6 | Chimeric antigen receptors' architecture[8]

Viral vectors (e.g. gamma retrovirus and lentivirus) play a crucial role in the introduction of genetic material that encodes the CAR, but these vectors have several limitations. To address such a challenge, non-viral vectors (NanoCART) are much cheaper, easier to scale and less toxic. Regarding this latter, mini-circle DNA is being used rather than plasmid for the delivery of genetic material as they have no bacterial sequences, hence they are less toxic systems. Although the potential exists, NanoCART approaches need electroporation so that the genetic material is absorbed via endocytosis by the cells. This process has high T-cell death with a lower CAR delivery than viral vectors; hence, different nanomaterials have to be assessed in order to overcome such limitations. Current emerging strategies being developed to overcome toxicity issues are also the use of RNA CAR-T cells or allogeneic haematopoietic stem cell transplantation to restore haematopoiesis.

Recent ATMP strategies are also focussing on better and more targeted biomarker identifications, as >50% of CAR-T-treated patients relapse within 2 years. In this regard, multi-omics (genomics, transcriptomic, metabolomic etc.) approaches coupled with machine learning algorithms can be an innovative solution for the early identification of patients that will respond to CAR-T treatments in a predictive manner (integrate and harmonize huge amounts of data to discover novel biomarkers). In addition, to reduce the rate of relapse, the use of kinase inhibitors along with dual antigen-cotargeted CAR-T cells is being experimented, whilst continuous improvement of CRISPR/Cas9 systems may increase the precision and longevity of CAR-T therapies. Lastly, with the implementation and advancements in the field of precision medicine, CAR-T limitations can be further overcome and more unmet patients' needs addressed.

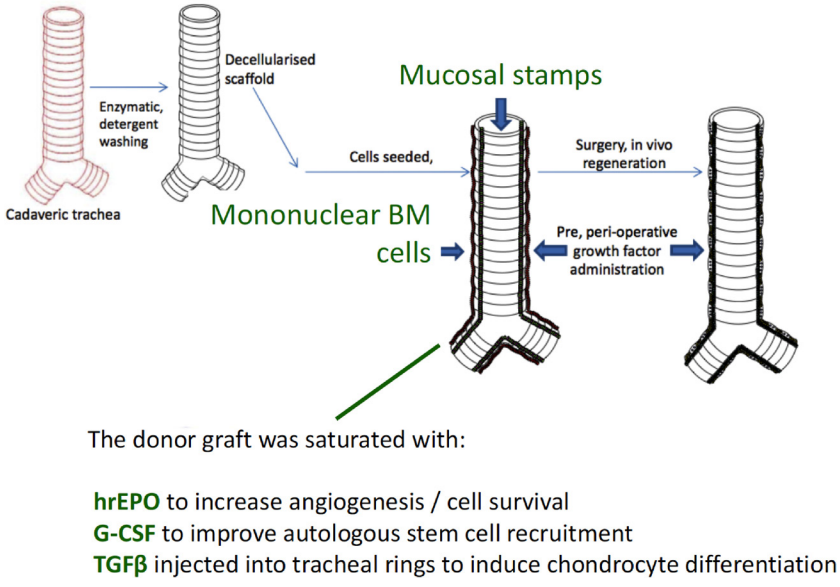

Fig 7 | Engineered trachea[9]

Tissue Engineering and Combined ATMPs

Another typical, more complex ATMP therapy is tissue engineering. This technology has been deployed in many areas with successes such as a tracheal transplant that occurred in 2010 to a child hospitalized at Great Ormond Street Hospital (GOSH) in London, UK.[9] It is a typical example of combined ATMPs whereby the use of scaffolds like cadaveric trachea is initially decellularized, bone marrow stem cells seeded (in this case cells of the same patient to avoid rejection), and then, with the help of growing factors and other molecular stimulators, the engineered trachea is implanted through surgery. In the GOSH case, further growing factors were given to the patient following the transplant to boost the growth of stem cells in vivo (Figure 7).

Since trachea rigidity can be a challenge, to speed up the recovery of structural rigidity, emerging strategies are aiming at creating synthetic scaffolds, using animal tracheas and/or improving the use of stem cells since they provide a platform for the successful transplantation of these regenerative approaches. In fact, contractility of the cells plays an important role in the recellularization of the trachea but also in the flexibility of the transplanted scaffold. As such, closed (for sterility reasons) and efficient systems (cutting-edge bioreactors are used to provide the right microenvironment) are necessary to improve the contractility of cells after recellularization. These tissue engineering medicines, or combined ATMPs are currently being assessed in other instances such as oesophageal replacement, the creation of human lung tissue or heart tissue engineering. It is this latter that is taking momentum, as heart failure impacts 38 million people worldwide, and by 2030, around 187 million people will be affected by cardiovascular diseases.[10] In the United States, heart disease is the number one killer for adult men and women, and the increase in healthcare spending is forecasted to increase by 25% by 2030 for people aged 50–69 years. In addition, in babies, heart defect is also the most common birth defect with a ratio of 1:125, with congenital heart defect accounting for 10% of spontaneous abortions and affecting nearly 1% of all newborns worldwide. It is, therefore, not a surprise that new strategies and technologies are needed to tackle such a global burden.[11]

Human-induced pluripotent stem cells are being assessed in cardiac regenerative medicine, mostly aimed at replacing lost cardiomyocytes. The use of specific cardiac regulators or growth factors such as BMP4, FGFs and the like is being used to drive differentiation towards a cardiomyocyte phenotype. However, most of the current protocols have poor representation of the in vivo cardiovascular environment, as technical barriers like tumorigenesis, transplant rejection and arrhythmogenesis can really impede the success rate of these approaches (Figure 8).[12]

To overcome these obstacles, emerging strategies are shifting towards more complex systems, like the

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type of scaffold used, the cells needed to regrow the scaffold and the combination of molecular factors to trigger their growth. Indeed, defining the best cell system, vascularization and animal models are key aspects in making these therapies safer and more effective. Bioreactors are constantly being improved as they are critical devices to provide an in vitro environment that mimics in vivo conditions for the growth of tissue substitutes (Figure 9).

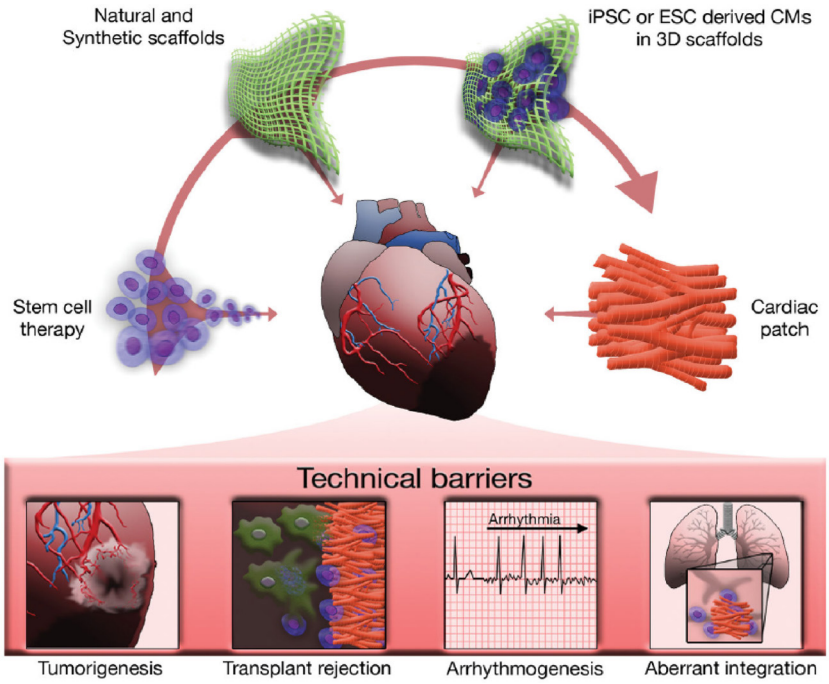

Fig 8 | Tissue engineering and technical barriers in cardiac regenerative medicine[12]

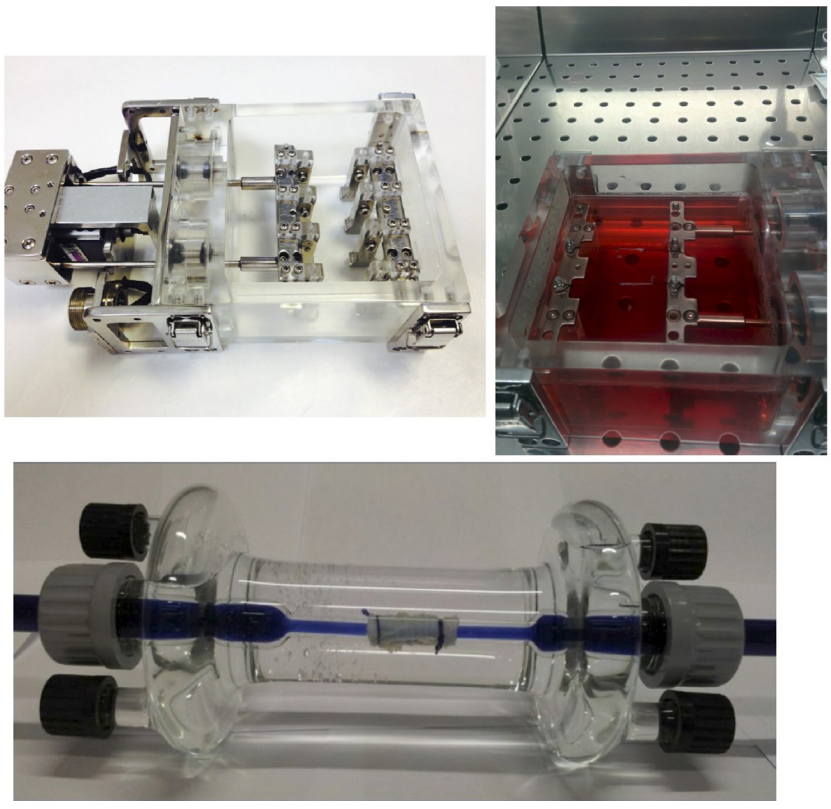

Fig 9 | Bioreactor examples[13]

At the same time, further new approaches are being developed to decellularize the scaffold matrixes and avoid patients' immune responses or inflammation that will lead to myocardial scarring. Decreasing antigenicity and increasing the capacity to recellularize may lead to more durable constructs. These technological advancements are currently being tested in animals, but there is a long way before bioartificial hearts will become a reality in humans, although there have been promising results in recent years.[13] Nonetheless, a better understanding of the molecular pathways of the heart's regenerative capacities and epigenetic regulations is needed for better translation into clinical practices.

To conclude, current treatments for many disorders are inadequate, and they put a substantial economic burden on healthcare systems. Tissue engineering and combined ATMPs hold promise for the treatment of such disorders. The future will involve first in-human trials, followed by limited patient trials in cases where conventional therapy has been unsuccessful.

Conclusion

ATMPs hold a great promise in treating many diseases. Worldwide, 95% of rare "orphan" diseases have no drug treatment, and there are 7,000 different types of rare diseases and disorders. As such, the orphan disease indications are driving up costs and competition, with global pharmaceutical spending up to US$1 trillion and 1.3% of global gross domestic product. Current traditional treatments are not effective, with only 30–70% of patients responding to drugs. Considering the costs necessary to make a drug available following the different clinical trial phases, which on average last 10–15 years, it is no surprise that the return on investment (ROI) in pharma R&D is on the brink of terminal decline (Figure 10).

The more the standard of care is improved, the more difficult and costly it becomes to improve further, so we spend more to get diminishing incremental benefits and added value for patients with a declining ROI, which is directly linked to growth. Since this pharma business model is broken, alternative models have to be proposed with a shift towards more disruptive innovation whereby tissue engineering and regenerative medicine, as anticipated, could be the next big thing (Figure 11).[14]

With the advent of AI and ML technologies, personalized medicine or precision medicine can help in better understanding the overall health problems, the disease risks that come with it and ultimately predict better treatment responses. In fact, traditional medicine focuses on what treatments work for most patients, whilst personalized medicine focuses on what treatments work for this individual patient. In that regard, genetics is driving treatments to predict future disease risk by providing the population with

many tests that can drive preventative measures such as mammography, surgery and the like. The use of digital platforms embedded with AI algorithms can also help in increasing knowledge and awareness in patients about their hereditary risks so that they can increase treatment adherence with genetic diagnosis. Combining clinical procedures (molecular biology, sequencing technologies and medical technologies) with information technology (big data, processing capacity and connected technologies) can really push the field forward, repurpose the drug discovery process and through novel therapeutic approaches, enable the patients to get the right drug, at the right dose, at the right time and in the long term (monitored through the use of portable health devices).

Putting the patient back at the centre of the whole clinical trial process is another key aspect (Figure 12). Stratifying them in groups based on a greater likelihood of responding to a particular therapy or avoidance of side effects based on their unique genetic and environmental profile can lead to more efficient, safer and cheaper clinical trials, reducing the burden on healthcare systems and increasing the chances of survival or remission for patients worldwide.

For the success of such innovative models, many stakeholders need to work together and, towards the same goal, make these innovative medicines more affordable, effective and safer for everyone. Ethics committees are needed so that the selection eligibility criteria are fair and to avoid exposure of patients to high-risk treatments or misconducts during the trials. Regulatory challenges can also be a bottleneck in the release of ATMPs, hence the need for stable and qualitative products, experienced personnel (e.g. many qualified persons are used to small molecules and large batches with less experience with ATMPs, same for manufacturers and clinicians) and robust quality management systems and processes. The right GMP

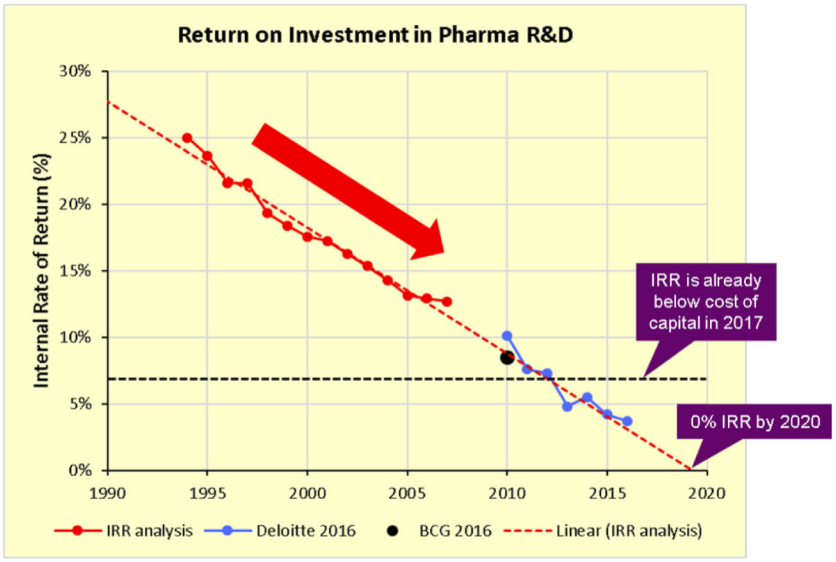

Fig 10 | Pharma ROI analysis[14]

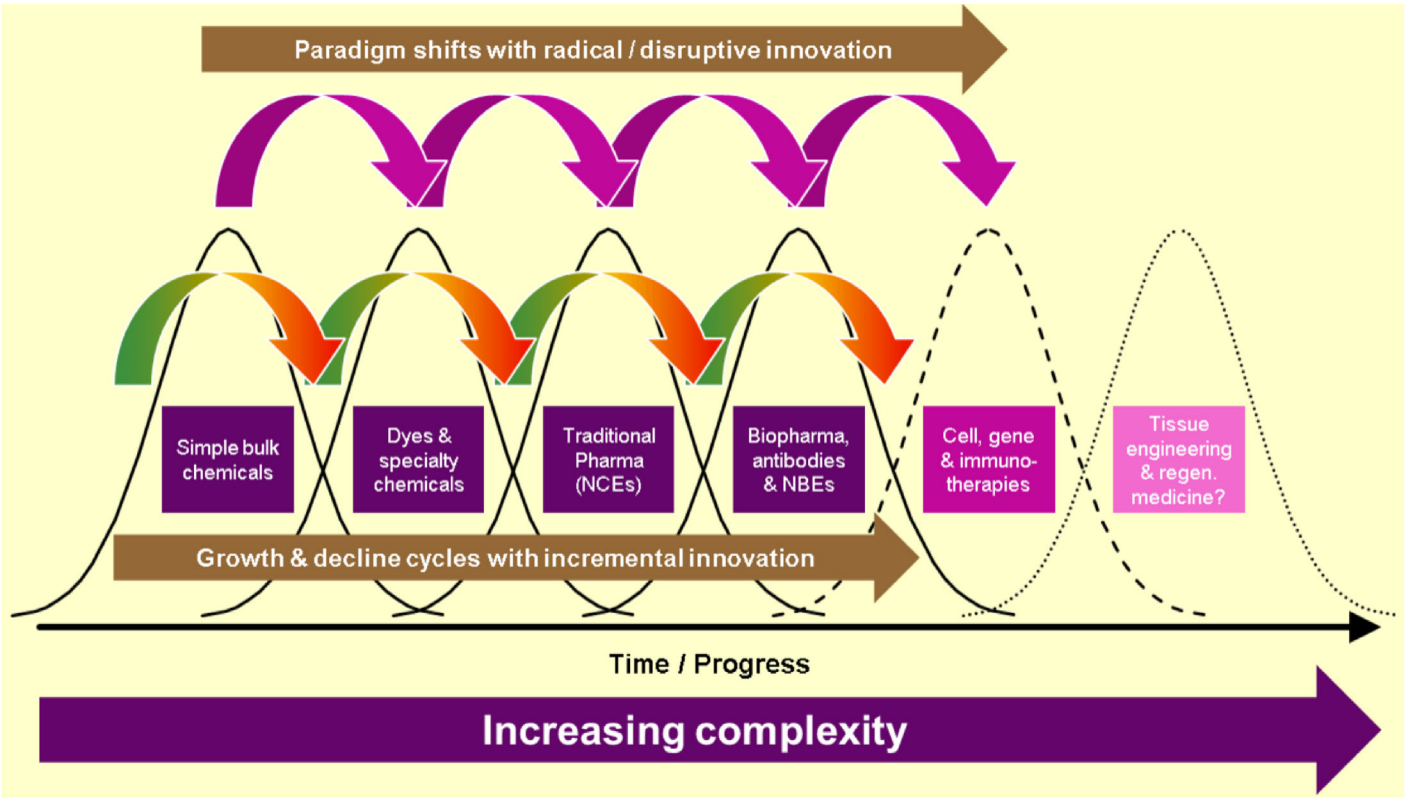

Fig 11 | Pharma cycles from bulk chemicals to tissue engineering and reg. medicine[14]

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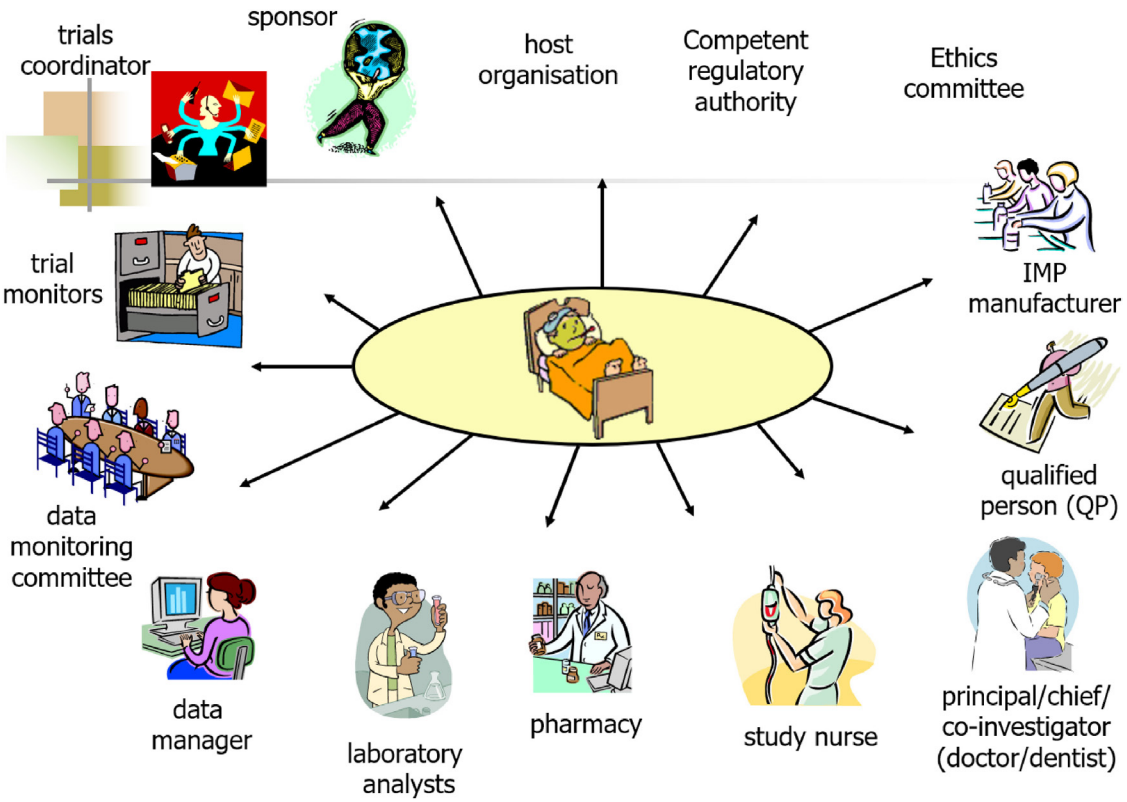

Fig 12 | Stakeholders' involvement in the clinical trial process

infrastructures and supply and logistics services are also fundamental and require a collaborative effort and coordination across industries to really move towards more disruptive and innovative solutions.

Industries like contract research organizations, CDMOs, contract manufacturing organizations or even start-up companies with innovative ideas but not the facility infrastructure must collaborate to bring down the costs of these therapies and avoid market failures, as we have seen in the case of Strimvelis. The future is bright for ATMPs, many emerging strategies including new frameworks (e.g. CIRM's framework)[15] are being developed, tested or deployed to repurpose the current pharma model. However, continued innovation, investments and stakeholders' collaboration across industries will be crucial in overcoming the challenges ahead and ensuring that these groundbreaking therapies are available and accessible to the unmet needs of many patients worldwide.

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