CELL AND GENE THERAPY EXPLAINED

A guide to cell and gene therapy and UK excellence in the field

UK BioIndustry Association

October 2018

Foreword

The 21st century is proving to be one of the most exciting and prolific periods of innovation in biosciences and healthcare. Advances across biology, technology, engineering and data science are converging to help create new, potentially life-changing solutions for individuals and societies across the globe.

Genomics – the study of our genetic material, or DNA – is enabling truly personalised medicines, designed to effectively address particular patients' disease with as few side-effects as possible. It is also paving the way to more accurate, convenient diagnostic products that help characterise and potentially prevent disease, by picking up signs much earlier.

> **The 21st century is proving to be one of the most exciting and prolific periods of innovation in biosciences and healthcare."**

As engineers and biologists join forces to build ever-more sophisticated gene-editing tools, new classes of medicines are emerging, including **cell and gene therapies**. These involve altering cells or genes, usually outside the body, to provide a patient-specific therapy that is re-injected into the patient. Scientists' growing understanding of how genes exert their influence, and of the crucial impact of multiple environmental factors on those genes ("epigenetics"), is opening up new frontiers of drug research. It has led to an explosion of activity around the gut microbiome – the colonies of micro-organisms residing in our gut – and its role in health and disease.

Genomics, **engineering biology** and related data and analytics tools are also helping fuel innovative approaches to tackling pathogenic bacteria. These may provide new, more effective and less toxic medicines for a range of life-threatening infections. Importantly, they may also help address the growing global challenge of **antimicrobial resistance**.

UK bioscience companies are at the forefront of these innovative, converging disciplines. These companies are a key part of the UK Bioindustry Association (BIA)'s membership and as the trade association for innovative life science companies in the UK, the BIA provides a home for these groups through our Advisory Committees and working groups on antimicrobial resistance, cell and gene therapy, engineering biology and genomics.

Given both this focus of our membership and the increasing external interest in how these innovations can tackle key challenges that society faces and contribute to the growth of a 21st century economy, the BIA is delighted to publish this series of four explainers on antimicrobial resistance, cell and gene therapy, engineering biology and genomics.

Within these explainers, we describe what these areas are all about, the important contributions made by UK bioscience firms, and the external environment required to ensure that these innovative approaches continue to benefit patients, the economy and society as a whole.

I hope you enjoy reading them.

Steve Bates OBE
CEO, UK Bioindustry Association

What is cell and gene therapy?

Cell and gene therapies are a transformative new category of medicines whose full potential is only just beginning to emerge. Most treatments available today are chemical compounds, such as paracetamol tablets, or biologics, like cancer drug Herceptin, taken by injection. These medicines have extended our healthy life-span and helped address many serious conditions such as cancer. Yet most of them are one-sized-fits all: we all take the same pill or injection for a particular condition. These treatments are produced in a standardised fashion, and most are relatively short-lived within the body.

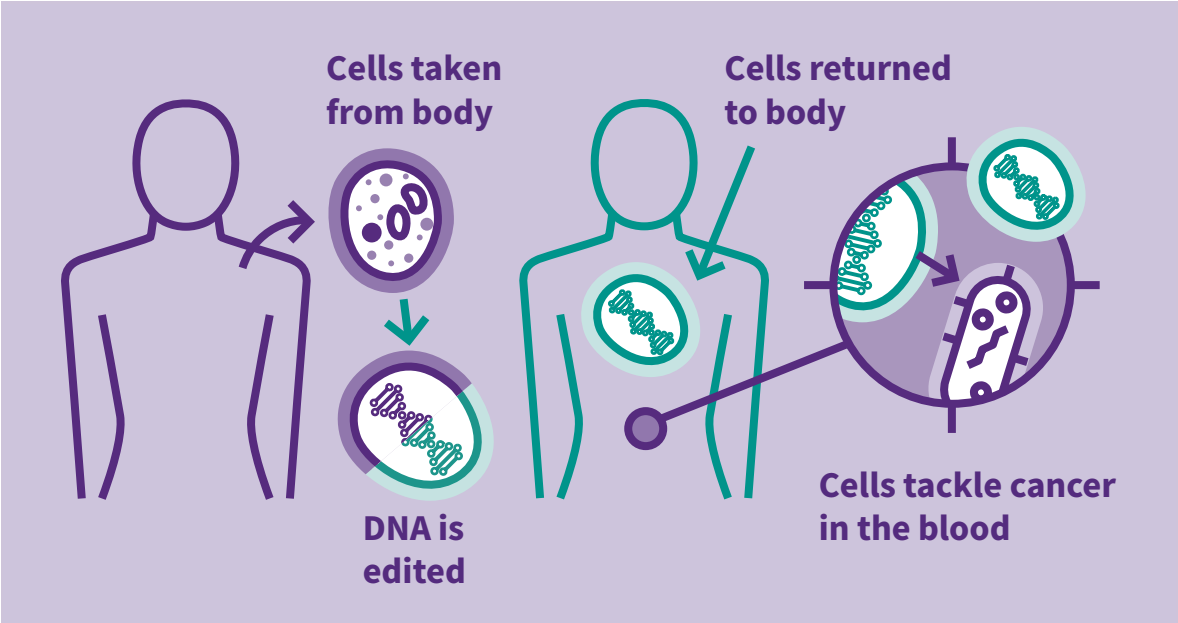
Cell and gene therapies are different. They involve extracting cells, protein or genetic material (DNA) from the patient (or a donor), and altering them to provide a highly personalised therapy, which is re-injected into the patient. Cell and gene therapies may offer longer-lasting effects than traditional medicines. They have the potential to address complex diseases, such as motor neurone disease, and many rare disorders for which there are no effective treatments.

In their simplest form, gene therapies work by replacing a faulty or missing gene that causes an inherited condition, such as sickle cell anaemia or cystic fibrosis.

Scientists have developed molecules that can deliver a repaired copy of the faulty gene for the appropriate cells, enabling those cells to function correctly again, alleviating some or all of the symptoms of the disease. It's a hot area, attracting increasing commercial and general interest.

Gene-based therapies involve corrected copies of DNA that repair or replace faulty genes. Cell-based therapies rely on modifying both genetic material and cells. For example, some of the most exciting new cell therapies involve extracting and re-programming immune cells found within each of us, to equip them to more effectively fight disease from within – Trojan horse-style.

In these new medicines, a certain type of patients' own immune cells, called T-cells, are re-programmed to make them better at detecting and killing cancerous cells. Genetic material is inserted into the T-cells, coding for a receptor molecule that can easily spot a protein found on the surface of some kinds of cancer cells. The modified T-cells are then re-infused into the patient and can kill the cancer more effectively. These modified T-cells are known as CAR-T cells, short for "chimeric antigen receptor T-cell".



CAR-T cell-based medicines include both a gene therapy element (the new receptor molecule) and a cell therapy element (the cells injected back into the patient). Enabling all the parts to work together and get to the right places requires other biological tools, some of which are being developed by UK companies.

Several new cell and gene based therapy approaches use biological engineering to improve the immune system's capacity to fight disease, while sparing healthy tissues in the body. For example, there are antibody-based therapies (antibodies are another kind of immune-system warrior cell) that can make T-cells more effective by increasing their interactions with cancer cells. Other modifications – like adding complexity to the CAR-T and cancer cell interaction – can further sharpen T-cells' cancer-targeting ability, reducing damage to normal cells.

Scientists are working on ways to expand the kinds of cancer markers that can be detected using the CAR-T cell approach, and the types of immune cell used to do the job. For example, several UK companies are working with a sub-set of T-cells found in the blood, skin and other tissues that can rapidly detect local abnormalities and recruit other immune-system players to the site. They're helped by a huge range of sophisticated tools for analysing and editing genetic material, including many from UK companies.

Regenerative medicine is another important branch of cell therapy. It enables human tissues – such as muscle, skin or cartilage – to be repaired or replaced, using appropriate cells and the molecules needed to keep them alive. Regenerative medicine may even one day allow entire organs to be grown in the laboratory – though we are not there yet.

Stem cells are very important in regenerative medicine and across cell and gene therapy. These cells, found in the bone marrow of children and young adults, and in the cord blood of newborn babies, have the potential to differentiate into any cell-type – heart, skin, nerve, blood, muscle, connective tissue and immune cells. Scientists can also extract stem cells from patients with genetic disorders that affect multiple physiological functions (for instance, the immune system, muscle and nerve function). Correcting the defective or missing gene in the extracted stem cells tackles the root cause of the condition. Thus re-infusing the repaired stem cells into the patient may alleviate or even eliminate many or all disease symptoms. For example, scientists are close to treating patients with beta thalassemia, an inherited disorder that affects the production of a protein in the blood that carries oxygen around the body. They harvest stem cells from the patients and edit the cell genomes to produce a fetal form of the missing protein. The stem cells are then reinfused back into the patient to restore oxygen transport.

Researchers are also developing 'off-the-shelf' stem cell (and non-stem cell) -based therapies. These don't require a patient's own stem cells to be extracted and corrected. Instead, they involve using genetically-uniform, appropriately programmed cells, expanded from a single starting stem cell, under safe and sterile conditions. These approaches may ultimately be used to treat a variety of diseases, including bone degeneration, organ failure, neuro-degenerative diseases such as Alzheimer's, and chronic obstructive pulmonary disease (COPD).

For now, cell and gene therapies are highly specialised treatments that are either experimental, or available only to specific patient populations. They are complex to manufacture and administer, and very expensive.

That will change as the techniques and support services underpinning cell and gene therapy research and drug development become more sophisticated and practical. UK companies are among those working on new ways to design, manufacture and safely administer cell and gene therapies, driving next-generation approaches. These tools include efficient cell harvesting methods, more precise gene editing, advanced manufacturing and purification processes, cell and tissue preservation techniques, and more.

These technologies are already changing healthcare – including as tools to discover and test other kinds of medicines. They also offer potential in other sectors, from agriculture to energy, industrial production and beyond.

UK excellence in cell and gene therapy

The UK is recognised as a world-leader in the discovery and development of cell and gene therapies and an ecosystem capable of operating at the scale required to manufacture and deliver these therapies to patients is now beginning to emerge.

The state of the industry in the UK

- **There are 64 advanced therapy developers in the UK – more than any other European country**
- **£1.6bn has been raised by UK cell and gene therapy companies since 2013**
- **The UK cell and gene therapy industry employs 1,500 people**
- **By 2035 the cell and gene therapy industry could be worth £10bn and provide 18,000 jobs.**

* Figures as per the Cell and Gene Therapy Catapult Annual Review 2018

As part of the broader life science endeavour, efforts to develop cell and gene therapies benefit from the UK's well-established strengths in scientific research and its commercialisation. However, in recent years there have been several additional initiatives aimed specifically at establishing and supporting a thriving cell and gene therapy industry in the UK.

As part of the broader network of Catapult centres across the UK, the Cell and Gene Therapy Catapult (CGT Catapult) aims to bridge the gap between scientific research and full-scale commercialisation. It was established in 2012, with funding from Innovate UK, the business-focused arm of the UK's national funding agency, UK Research and Innovation (UKRI), to grow the UK cell and gene therapy industry. Its vision is for the UK to be a global leader in the development, delivery and commercialisation of cell and gene therapies, where businesses can start, grow and confidently develop advanced therapies, delivering them to patients rapidly, efficiently and effectively.

One way the CGT Catapult intends to realise this ambition is by increasing the UK's cell and gene therapy manufacturing capabilities. In April 2018, the CGT Catapult opened its state-of-the-art manufacturing centre in Stevenage, with £60m of investment from government as part of the Industrial Strategy Challenge Fund. The new facility will enable companies to manufacture therapies at the scale required for late phase studies and commercial supply, complementing the UK's existing manufacturing facilities that cater for early stage clinical trials.

The UK is also addressing the challenge of how to deliver cell and gene therapies to patients in the NHS. Unlike traditional pharmaceutical medicines that can be taken outside a clinical setting without supervision, the administration of cell and gene therapies will need to be performed by an experienced clinician and carefully tracked to ensure traceability and to identify potential adverse events. The UK now has a network of Advanced Therapy Treatment Centres, the first of their kind in the world, that will develop these new systems and processes. They will work together to establish best practice for the safe and effective delivery of cell and gene therapies, positioning the UK as a global-leader in terms of patient access to these treatments.

The Advanced Therapy Treatment Centres

Each centre is a joint venture between industry, academia and NHS partners.

- **Innovate Manchester Advanced Therapy Centre Hub** (iMATCH)
- **Midlands-Wales Advanced Therapy Treatment Centre** (MW-ATTC, comprising Birmingham, Wales and Nottingham)
- **Northern Alliance Advanced Therapies Treatment Centre** (NAATTC, comprising Scotland, Newcastle and Leeds)

The enclosed case studies demonstrate how companies operating in the UK are seeking to utilise cell and gene therapies to meet patient need in a range of disease areas. This is but a snapshot of the exciting innovation at work today. To discover more about the BIA's cell and gene therapy community visit: **www.bioindustry.org/bia-membership/advisory-committees/cell-gene-therapy-advisory-committee.html**

How cell and gene therapies can help tackle cancer

Cell Medica and Immunocore are both engaged in work to build on the first generation of CAR-T cell therapies. In different ways, their work seeks to broaden the reach of these new therapies, including into the treatment of solid tumours, which is integral to developing new ways to tackle cancer.

Cell Medica

Tweaking the body's own immune cells to better fight cancer is a proven, highly promising approach. Two newly-approved therapies, Novartis' Kymriah and Gilead/Kite's Yescarta, involve engineering patients' own T cells (a type of immune cell) with a specific receptor molecule that hones in on certain cancers. Known as 'chimeric antigen T-cell (CAR-T) receptor' drugs, they have shown outstanding results in certain patients with hard-to-treat blood cancers but have challenging delivery logistics.

Tweaking the body's own immune cells to better fight cancer is a proven, highly promising approach."

London-based Cell Medica's scientists are among several groups around the world seeking to improve on this first-generation of CAR-T cell therapies, potentially broadening their reach into solid tumors, as well as making these complex treatments more convenient to make and administer.

The company's AlloCAR platform is a next-generation CAR-T, utilising a specialised class of T cells called natural killer T-cells (NKT) cells, for off-the-shelf therapies to treat multiple types of solid and haematological malignancies. Current CAR-T therapies involve extracting a patient's own immune cells, engineering those cells and then re-infusing them into the same patient. This "autologous" approach – using the patient's own cells – avoids the risk of rejection by the immune system but makes these therapies difficult and time-consuming to administer.

Cell Medica's ambition is to be a leader in allogeneic (off-the-shelf) CAR-T therapies. The specialised class of NKT cells they work with have properties that make them ideally suited to this.

In particular, type 1 NKT cells have certain kinds of receptors that are invariant, meaning that donated cells are unlikely to be seen as foreign and rejected by the recipient. This opens the door to potentially transformative therapies that face far fewer logistical hurdles than autologous CAR-T treatments.

Furthermore, these NKTs are preferentially found inside tissues, rather than only in the blood, so may also be more appropriate for solid tumour targets, says Karen Hodgkin, Cell Medica's Chief Operating Officer.

Cell Medica's lead autologous, NKT-cell therapy candidate, CMD-501, has just started human testing in patients with neuroblastoma – a solid cancer of the nerve tissue. CMD-501 is in a first in human safety and efficacy (Phase I/II) trial sponsored by the Baylor College of Medicine at Texas Children's Hospital in the US.

On August 1, 2018, Cell Medica appointed CEO Chris Nowers to guide the company as it progresses into later-stage clinical development and toward commercialisation. Mr Nowers, who takes over from founder Gregg Sando, previously built and ran European operations for Kite Pharma, developer of CAR-T therapy pioneer Yescarta. Kite was acquired by Gilead in 2017.

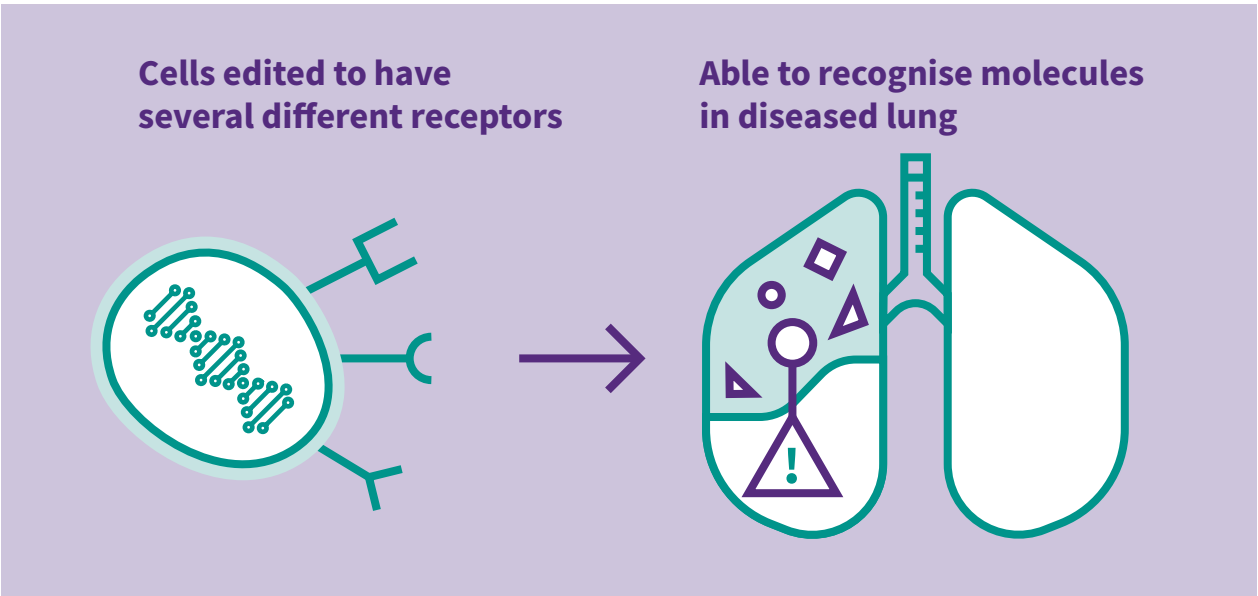
Cell Medica raised £60 million in private funding in March 2017.

Immunocore

Cell-based therapies such as engineered immune cells that include the recently-approved chimeric antigen receptor T (CAR-T) cell therapies offer exciting new cancer treatment options. But they also present challenges. Most are expensive and time-consuming to manufacture and administer and face constraints around mode of administration and dose-control. To date, they have shown limited clinical efficacy in solid tumours.

Immunocore has developed a new class of immuno-oncology agents that have the potential to overcome some of these challenges. ImmTAC ('Immune mobilising monoclonal TCR against cancer') molecules are small, soluble molecules formed of an engineered T-cell receptor (TCR) fused to a CD3-antibody fragment. The TCR portion acts as a highly tuned detector that seeks out and targets cancer antigens – molecules that signal the cancer's presence. The CD3-antibody fragment engages, re-directs and activates T-cells to kill the cancer cells. The result is a targeted immune system attack on cancerous cells.

Solid tumours, such as those in lung, skin, breast or prostate, build multiple physical and physiological barriers to avoid detection by the immune system. For instance, they reduce the number of danger-signalling antigens presented on the surface of tumour cells. Since ImmTAC molecules are small and soluble, they are better able to penetrate solid tumours than larger, cell-based therapies.



Moreover, the TCR component of ImmTAC molecules can recognise a much wider range of cancer antigens than CAR-T cell therapies and other antibody-based therapies by recognising intracellular antigens that are processed and presented as small peptides on the surface of the cancer cells. Thus, TCR-based therapies such as ImmTAC molecules have the opportunity to open many more doors into the solid tumour.

Soluble ImmTAC molecules are available as 'off-the-shelf' reagents unlike cell therapies such as CAR-T cells, which require extraction and manipulation of the patients' own immune cells prior to treatment. ImmTAC molecules also offer more flexible dosing options and better control in the instance of adverse events. Immunocore's most advanced ImmTAC molecule, IMCgp100, targets a melanoma-associated antigen and is currently in pivotal trials for the treatment of patients with metastatic melanoma which affects the eye, with poor prognosis and with limited treatment options. Early studies of IMCgp100 have reported a one-year overall survival rate of 74%, significantly higher than expected in this patient population.

TTCR-based therapies such as ImmTAC molecules have the opportunity to open many more doors into the solid tumour."

Immunocore has a number of other proprietary and partnered oncology programmes. These include a study in metastatic cutaneous melanoma with AstraZeneca using IMCgp100 combined with checkpoint inhibitors, a type of targeted cancer treatment, as well as multi-target collaborations with GlaxoSmithKline, Roche and Eli Lilly. A second ImmTAC programme partnered with GSK is due to enter the clinic targeting the NYESO antigen for treatment of diverse indications, including Non-Small Cell Lung Cancer (NSCLC), urothelial carcinoma and synovial sarcoma.

Immunocore is headquartered at Milton Park, Oxfordshire, UK, with an office outside Philadelphia, USA. The company is privately held by range of international investors.

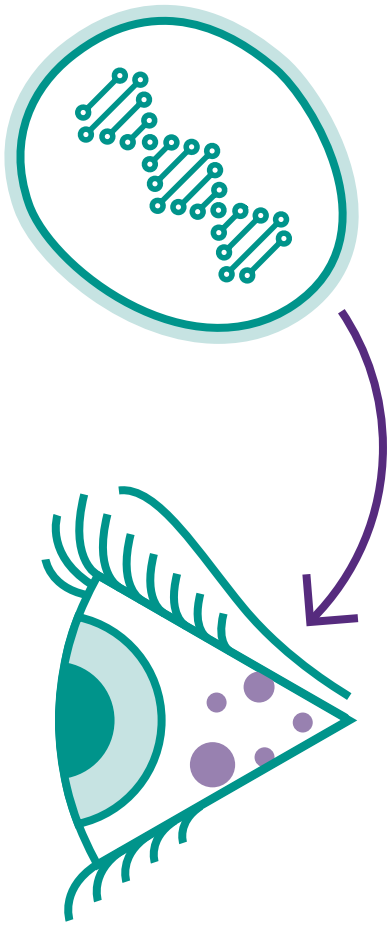
How cell and gene therapies can help tackle rare conditions

Nightstar Therapeutics is developing gene therapies to treat rare, inherited eye diseases.

NightStar Therapeutics

Nightstar Therapeutics is developing gene therapies to help restore the vision of patients with rare, inherited eye diseases. Their programmes could be life-changing for people with conditions such as choroideremia, a genetic disorder characterised by progressive vision loss. Patients with choroideremia, which typically manifests in childhood, currently suffer in the knowledge that they can do little to slow the deterioration of their eyesight, which will almost inevitably lead to blindness.

Edited cells remove waste product build up from the back of the eye



Choroideremia is caused by damage to light-sensitive cells in the retina, situated at the back of the eye. Because of a defective gene, these retinal cells lack a protein needed to help eliminate waste products. In the absence of this protein, the cells gradually die, leading to vision loss.

Nightstar's lead gene therapy programme, which is in the final stage of clinical testing, inserts a working copy of the gene. It uses a benign virus to deliver the new gene into the retinal cells, ideally leading to higher levels of the housekeeper protein and thus a healthier retina. The therapy, administered using sub-retinal surgery, has already been shown to limit vision loss among some patients. In several cases, it has improved visual acuity, suggesting that the treatment can reverse early damage to some retinal cells.

The eye is particularly well-suited to gene therapy approaches. It is a relatively small, isolated compartment, separated from the rest of the body and the blood-stream by physical barriers. That means that only small doses of therapy are required, and minimises the likelihood that treatment enters the circulation or tissues outside the eye. Furthermore, retinal cells don't turnover and regenerate in the way the body's other cells do. As a consequence, once the corrected DNA enters a given cell, its effects should endure. Nightstar reports that its experimental therapy has helped some patients to maintain their vision for up to five years.

The choroideremia gene therapy, known as NSR-REP1, has been granted Regenerative Medicine Advanced Therapy (RMAT) designation by the US regulator, the FDA. This programme accelerates the review process for regenerative medicines addressing serious conditions with few or no therapy options.

There are dozens of other under-treated (and under-diagnosed) inherited retinal diseases that gene therapy might help address. Nightstar is tackling some of them. Its second product candidate is in a Phase I/II safety/efficacy trial for patients with X-linked retinitis pigmentosa, which also affects the light-sensitive photoreceptor cells in the retina.

Nightstar's programmes are based on pioneering work by Professor Robert MacLaren of the Nuffield Laboratory of Ophthalmology at the University of Oxford. The company was spun out of the University of Oxford with support from UK life sciences investment company Syncona, which originated from the Wellcome Trust. Syncona maintains a 42% equity stake in Nightstar, which has been listed on the US Nasdaq since 2017.

Tools, manufacturing and scale

Horizon Discovery and Oxford Biomedica are offering technologies and services that are fundamental to the development and delivery of cell and gene therapies. Horizon Discovery's offerings enable scientists to better understand genes and gene function. The gene delivery technology offered by Oxford Biomedica underpins an emerging class of transformative cell and gene therapies.

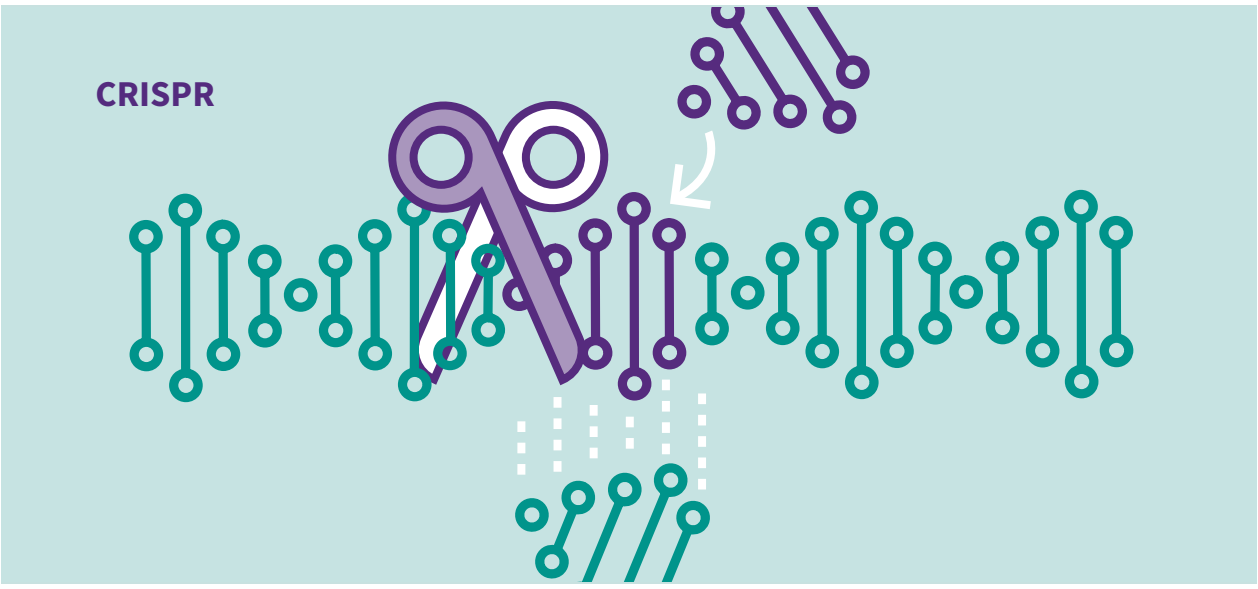
Horizon Discovery

Horizon Discovery's technologies and services help scientists better understand genes and gene function. This in turn enables and accelerates drug discovery, through more rapid, effective identification of promising molecular targets and drug candidates.

Horizon's suite of gene-editing tools is enhanced by some of the very latest techniques, including CRISPR (clustered regularly interspaced short palindromic repeats). CRISPR is based on a natural gene editing system used by bacteria as a defence against viruses. The CRISPR mechanism, along with a scissor-like protein, enables scientists to efficiently and rapidly cut out particular genes or DNA sequences from a cell or organism. This helps them probe the specific function of those genes.

For example, knocking out certain genes and observing the downstream effects can help to elucidate which genes are responsible for a particular disease. Horizon also offers CRISPR-based approaches that allow scientists to reduce, rather than completely shut off, the expression of particular genes. They can also amplify gene expression, or indeed add in new DNA sequences to understand gene function.

These manipulations can help identify viable drug targets and drug candidates. For instance, they might uncover which genes contribute to drug toxicity, or to



increased resistance or sensitivity to particular experimental therapies. Horizon's gene-editing technologies can alter an increasingly wide range of gene sequences within human cells and several different species of mammalian cells.

Horizon also offers a wide range of engineered cell lines. These families of identical cells, designed with particular genetic characteristics, are another important tool for gene- and cell-based therapy discovery. Cell lines provide a platform on which to study the effect of particular gene-edits, including those made using CRISPR. They are also powerful *in vitro* models for genetically-based diseases, allowing scientists to uncover, for instance, how particular mutations impact drug activity, drug resistance, and patient responsiveness. Finally, cell lines also enable more accurate predictions about which particular patients are likely to respond to current and future treatments, furthering progress toward personalised medicine.

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Horizon can engineer a very special kind of 'master' cell known as an induced pluripotent stem cell (IPSC). These cells have the ability to turn into any cell type within the body, such as liver cells, heart cells or neurons. They offer scientists a way to isolate and study the effects of individual genetic mutations that drive disease, with minimum background genetic variability. The IPSC platform is particularly useful in the development of new therapies.

The company is also applying its gene editing and cell line engineering expertise to improve the efficiency of biopharmaceutical production. Many biopharmaceuticals (including antibody drugs) are made using Chinese hamster ovary (CHO) cells in large, stainless steel fermenter tanks. The process is expensive, and relatively low-yield. Horizon is using CRISPR-based gene editing to boost CHO yields. This may one day allow more rapid, lower-cost production of this growing class of medicines.

Horizon Discovery is based at the UK Cambridge Research Park, with offices in the US. Its customers include biopharma and diagnostics companies, research institutes and contract manufacturing organisations.

Oxford BioMedica

Oxford BioMedica's gene delivery technology lies at the heart of an emerging class of transformative gene and cell therapies. It is a key component of Novartis' Kymriah™, a pioneering immune cell-based therapy approved for certain aggressive blood cancers. It is also central to efforts to develop gene therapies for Parkinson's disease, ocular diseases, immunological diseases and cystic fibrosis.

Safe and accurate gene delivery is one of the key challenges of cell and gene therapies. Oxford BioMedica's technology exploits mechanisms used by certain kinds of viruses, called lentiviruses, to integrate their DNA into that of a host cell. The company has adapted and fine-tuned lentiviruses (the best known of which is the HIV virus) to include only the components necessary for efficient gene delivery and integration, removing pathogenic and other unwanted parts of the viral genome. Oxford BioMedica was the first to administer lentiviral vectors directly into patients in 2008 for the treatment of Parkinson's disease.

Kymriah™ involves extracting and reprogramming patients' immune cells to make them better at detecting and killing cancer. Oxford BioMedica's *LentiVector*™ platform, based around work that began at Oxford University, is used to deliver the appropriate genes into the extracted immune cells, known as T cells. Kymriah™ was the first approved advanced therapy in the US using *LentiVector*™-enabled technology.

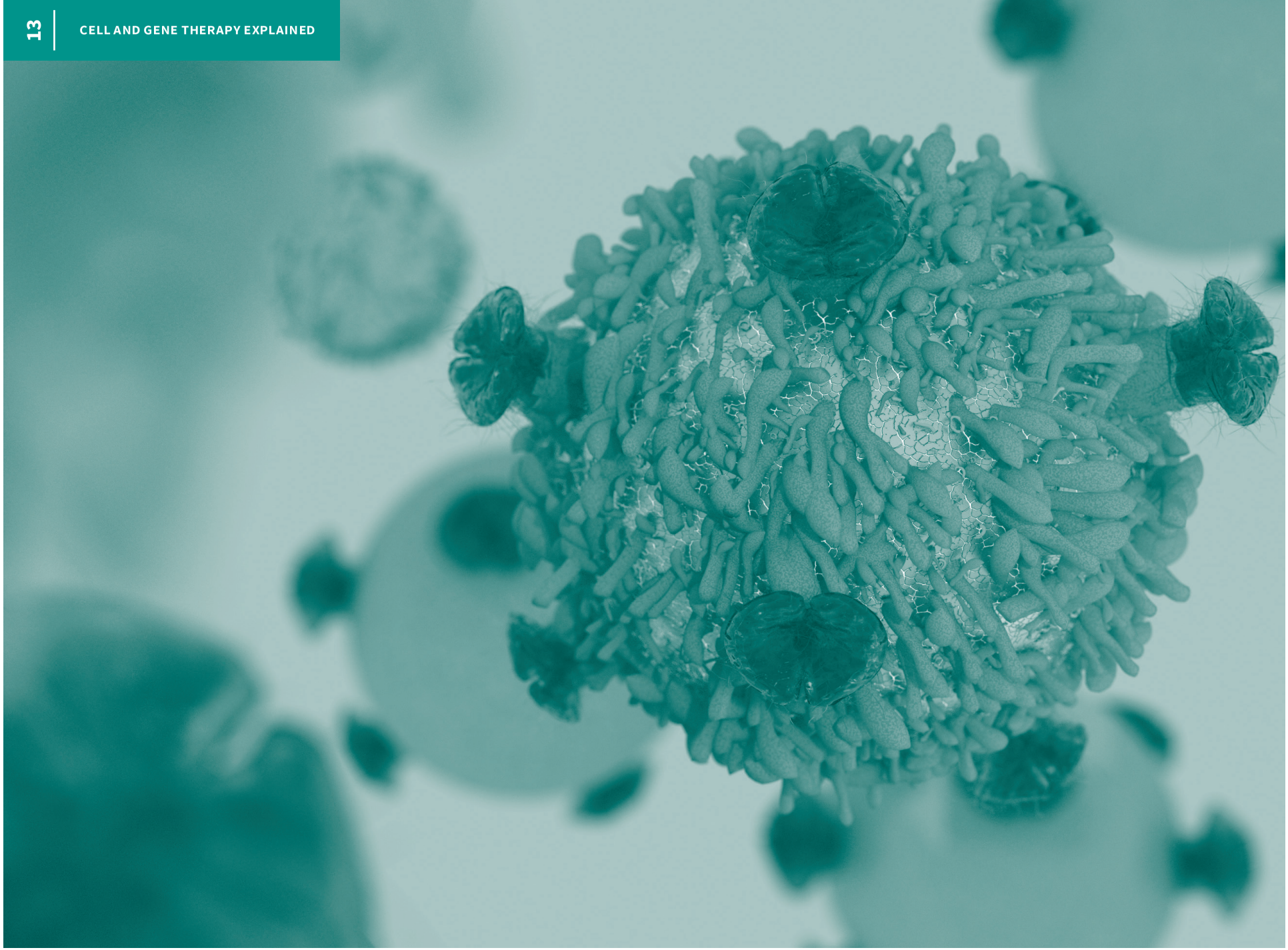
Lentiviral-based gene carriers offer some advantages over other virus-based systems. They can carry relatively large, complex pieces of DNA, and they integrate fully into the host genome, leading to long-term gene expression and the possibility of an equally long-term therapeutic effect. And typically there are no pre-existing immune responses to lentiviral vectors in patients, explains Kyriacos Mitrophanous, Oxford Biomedica's Chief Scientific Officer.

Kymriah™ involves extracting and reprogramming patients' immune cells to make them better at detecting and killing cancer."

Oxford BioMedica's technology is involved in a number of partnered products, including several in the clinic. These generate development milestones and potential royalty payments. In mid-2018, US-based Axovant paid $30 million up front and promised over $800 million in potential development milestones for worldwide rights to Oxford BioMedica's Parkinson's disease programme. The candidate, now known as AXO-Lenti-PD, delivers genes that switch on the production of dopamine, a neurotransmitter whose levels are depleted in Parkinson's patients. An earlier version of the therapy was tested in a Phase I/II study and found that a single administration of the gene therapy could improve patients' motor functions for many years. If the therapy makes it to market, Axovant will pay Oxford BioMedica 7–10% tiered royalties on net sales.

The company is also developing gene therapies for eye diseases. Partner Sanofi is pursuing clinical trials begun by Oxford BioMedica with two of these, for Stargardt disease and Usher Syndrome type 1B. Both conditions involve retinal degeneration. The UK company is also applying its lentiviral development and manufacturing expertise in an international collaboration with the Cystic Fibrosis Gene Therapy Consortium and Imperial Innovations. Cystic fibrosis patients require new copies of the CFTR gene, which are faulty in patients with this condition.

Oxford BioMedica, listed on the London Stock Exchange, has two independent good manufacturing practice (GMP) approved bioprocessing facilities and state of the art research facilities. Licensing partners for its *LentiVector*™ platform, production facilities and expertise include Sanofi, Novartis, Bioverativ (part of the Sanofi group), Boehringer Ingelheim/UK Cystic Fibrosis Gene Therapy Consortium and Orchard Therapeutics.



What next?

As with all areas of scientific innovation, there is a risk that the exciting science underpinning cell and gene therapies will out-pace society's ability and willingness to adopt its outputs. The UK must ensure it has the right infrastructure, systems and people in place to remain internationally competitive in the field, and subsequently fully reap the economic and societal benefits of a thriving cell and gene therapy industry.

The previous section demonstrated the UK's capabilities in manufacturing for advanced therapies, however, additional capacity is required. Traditional medicines are usually produced using a common manufacturing process or platform, meaning multiple products can be made at one site and in batches large enough to meet anticipated demand. This is not the case for cell and gene therapies. These treatments are far more varied in terms of their format and how they are administered, and they are often manufactured in response to an individual patient's need. This results in many different manufacturing and logistical processes, making it challenging to manufacture cell and gene therapies at scale. As a growing number of companies approach late stage clinical trials and commercial supply, there is a risk that the manufacturing supply chain in the UK could become a bottleneck.

In addition, issues around manufacturing capacity in the UK could be exacerbated by a shortage in skills. While this challenge is not unique to the cell and gene therapy sector – in fact it is common across all STEM fields – the projected growth of the industry suggests the problem could be particularly acute. In 2016 a joint industry-government taskforce was established to consider what measures are needed to make the UK the go to destination for international investment in advanced therapies manufacturing. As part of this the taskforce developed an end-to-end talent plan for the sector, which is now being implemented with financial support from Innovate UK.

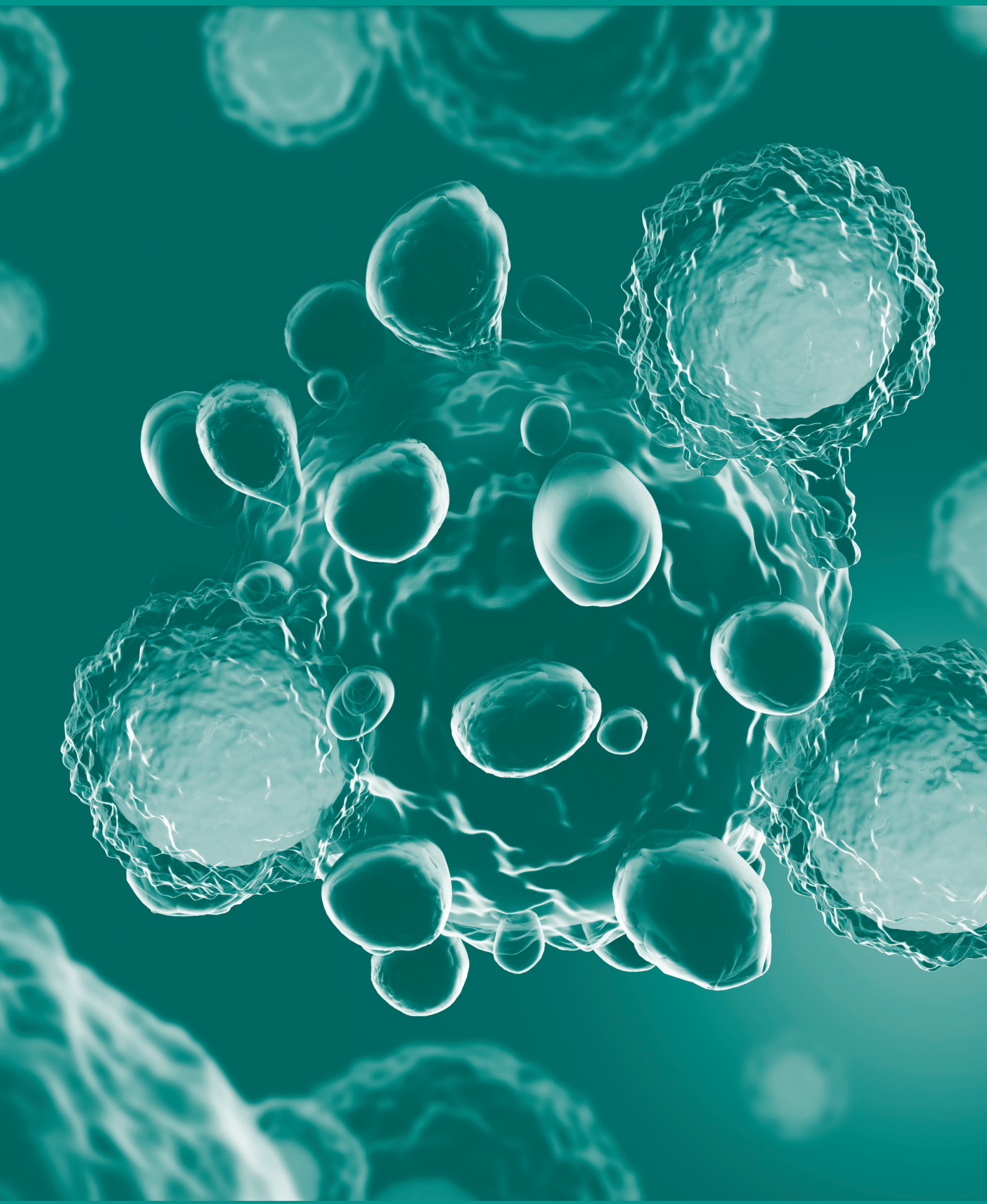
To retain its competitive edge the UK should not only address its capacity to develop and manufacture cell and gene therapies, it should also ensure there is a viable and extensive market for them in the NHS.

The previous section explained how a national network of Advanced Therapy Treatment Centres will develop the systems and processes required for clinicians to treat patients however, questions around how the NHS will pay for these treatments remain.

Cell and gene therapies present particular difficulties for health technology assessment bodies (HTAs), such as the National Institute for Health and Care Excellence (NICE), which are responsible for assessing the value of medicines and whether they should be made routinely available to patients. Due to the personalised nature of cell and gene therapies they are generally expensive to manufacture and administer and there may be a lack of data available to assess their cost and clinical effectiveness because of small patient populations. In addition, cell and gene therapies tend to be one-off treatments but they have the potential to deliver substantial long-term health gains, meaning large up-front costs for the NHS. This is very different to how the NHS currently pays for medicines. New payment models will therefore be needed to ensure patients can access these treatments.

In March 2016, NICE conducted a mock assessment for a CAR-T cell product and concluded that their appraisal methods could be applied to cell and gene therapies. Nonetheless, industry still has concerns, especially given NICE's increasing reliance on cost-effectiveness thresholds. It was really positive to see the deal announced between NHS England and Novartis to grant young patients access to the CAR-T treatment Kymriah. However as therapies continue to come to market, NHS England, NICE and industry will need to continue to work together and remain flexible to ensure NHS patients do not miss out.

Despite these challenges the future for cell and gene therapies in the UK looks promising. What is clear from the issues discussed here, and in the previous section, is the commitment from all parts of the ecosystem to address potential barriers to the growth of the industry and to ensure that these treatments reach patients quickly and are administered safely and effectively.



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