CELL AND GENE THERAPY EXPLAINED

A summarised guide to cell and gene therapy

UK BioIndustry Association

2019

Foreword

The 21st century is proving to be one of the most exciting and prolific periods of innovation in biosciences and healthcare, and UK bioscience companies are at the forefront of this innovation.

These companies are a key part of the UK Bioindustry Association (BIA)'s membership, and we provide a home for them through our Advisory Committees and working groups on antimicrobial resistance, cell and gene therapy, engineering biology and genomics.

We are delighted to publish this short summary of **A guide to cell and gene therapy and UK excellence in the field** as an accompaniment to our Explainer series, within which we describe what these four strategic technologies are all about, and showcase the important contributions being made by some of the UK bioscience firms who make up our dynamic and innovative membership. You can access the full versions of these Explainer documents on our website, or get in touch with us if you would like some hard copies.

We hope you enjoy reading them.

Steve Bates OBE CEO,
UK Bioindustry Association

What is cell and gene therapy?

Many modern medicines are one-size-fits-all: we all take the same pill or injection for a particular condition. Cell and gene therapies are different, and may offer longer lasting effects than traditional medicines. They have the potential to address complex diseases and many rare disorders for which there are currently no effective treatments.

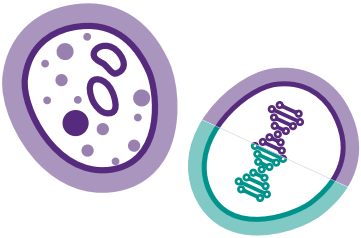
In their simplest form, gene therapies work by replacing a faulty or missing gene that causes an inherited condition. Scientists have developed molecules that can deliver a repaired copy of the faulty gene for the appropriate cells, enabling those cells to function correctly, alleviating some or all of the symptoms of the disease.

Cell-based therapies rely on modifying both genetic material and cells. Some of the most exciting new cell therapies involve extracting and re-programming a patient's own immune cells to equip them to fight disease. In these new medicines, a patients' own T-cells, are genetically re-programmed to make them better at detecting and killing cancerous cells. These modified T-cells are known as CAR-T cells.

For now, cell and gene therapies are highly specialised and are either experimental, or available only to specific patient populations. They are complex to manufacture and administer, and very expensive. UK companies are among those working on new ways to design, manufacture and safely administer cell and gene therapies.

Cell Medica

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 as well as making them 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 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. Cell Medica's ambition is to be a leader in allogeneic (off-the-shelf) CAR-T therapies. Cell Medica raised £60 million in private funding in March 2017.

Immunocore

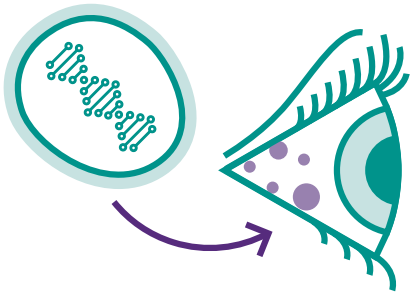
CAR-T cell therapies offer exciting new cancer treatment options, but they also present challenges. Most are expensive, time-consuming to manufacture and face constraints around mode of administration and dose-control. To date, they have shown limited clinical efficacy in solid tumours. Immunocore has 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 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. 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. The company is headquartered in the UK and is privately held by a range of international investors.

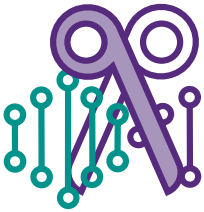
Nightstar Therapeutics

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. Retinal cells in those with choroideremia lack a protein needed to remove waste products from cells, causing the cells to gradually die, leading to vision loss and ultimately blindness in many patients.

Nightstar's lead gene therapy programme, which is in the final stage of clinical testing, inserts a working copy of the gene using a benign virus. The therapy, administered using sub-retinal surgery, has already been shown to limit vision loss among some patients. 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.



Horizon Discovery



Horizon Discovery's technologies and services help scientists better understand genes and gene function. Horizon's suite of gene-editing tools is enhanced by some of the very latest techniques, including CRISPR (clustered regularly interspaced short palindromic repeats). The CRISPR mechanism enables scientists to efficiently and rapidly cut out particular genes or DNA sequences from a cell or organism, like a molecular scissors. 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, helping identify new drug targets.

Horizon can engineer a very special kind of 'master' cell known as an induced pluripotent stem cell (IPSC) which have the ability to turn into any cell type within the body. They offer scientists a way to isolate and study the effects of individual genetic mutations that drive disease, with minimum background genetic variability. 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.

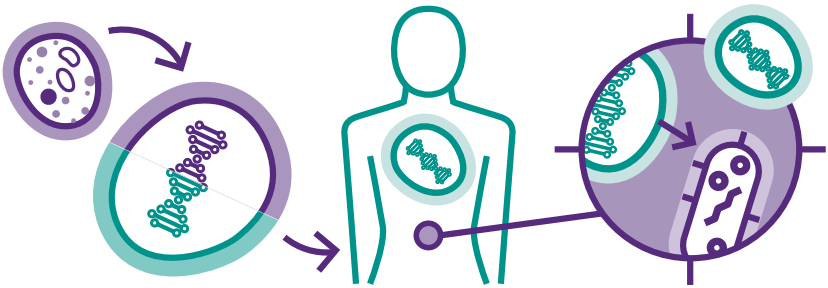
Oxford BioMedica

Oxford BioMedica's gene delivery technology lies at the heart of an emerging class of transformative cell and gene therapies. It is a key component of Novartis' Kymriah™, a pioneering immune cell-based therapy approved for certain aggressive blood cancers and 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 to include only the components necessary for efficient gene delivery and integration, removing pathogenic and other unwanted parts of the viral genome.

Oxford BioMedica's technology is involved in a number of partnered products which 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.

Oxford BioMedica, listed on the London Stock Exchange, has two independent (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.



To access the full version of this report, take a look at our Strategic Technologies page: www.bioindustry.org/policy/strategic-technologies.html

This report would not have been possible without the input and expertise from BIA member companies, who we thank for their contributions. The production of this report was also supported by life sciences specialist writer Melanie Senior, who we also acknowledge and thank for her contribution to the content of this report.

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