



Leading Innovation

The UK's ATMP Landscape



Alliance *for*
Regenerative
Medicine





The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory, and public understanding of, and support for, this expanding field.

www.alliancerm.org



Established over 25 years ago at the infancy of biotechnology, the BioIndustry Association (BIA) is the trade association for innovative enterprises involved in UK bioscience. Members include emerging and more established bioscience companies; pharmaceutical companies; academic, research and philanthropic organisations; and service providers to the bioscience sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and the media. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

www.bioindustry.org

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I am very pleased to have been able to work with the Alliance for Regenerative Medicine on this unique report, setting out the scope of the UK's robust and growing cell and gene therapy sector.

This is an extraordinarily exciting time in medical research, as advances in biology, technology, and data science open up new frontiers in the treatments of disease. New classes of medicines, including cell and gene therapies, have emerged, transforming outcomes for patients. Conditions that until recently were debilitating or life-shortening are now increasingly being effectively treated by new cell and gene therapies.

The UK has already played a major role in the development of these kinds of treatments, staking a claim as a leader in cell and gene therapies. It owes this success in large part to the support of the UK Government, which recognises the value of these innovations both to patients and to the wider economy. The BIA has played its part with an expert Cell and Gene Therapy Advisory Committee (CGTAC) which has been active for a number of years. Our industry has worked in partnership with government through the Advanced Therapies Manufacturing Taskforce (ATMT), the recommendations of which on anchoring commercial scale ATMPs in the UK were accepted in full in the Life Sciences Industrial Strategy.

The UK is 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 many cell and gene therapies needs to be performed by experienced clinicians 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. Working together, they will establish best practice for the safe and effective delivery of cell and gene therapies.

The future for cell and gene therapies in the UK is immensely promising. However, as with any innovation, cell and gene therapies risk out-pacing society's and government's capacity to adopt them. The UK needs the right infrastructure, talent, and regulation in place to continue to lead in cell and gene therapies, so that it can benefit both socially and economically from the advances in the sector. We need 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 who will benefit from them.

I hope you find this report useful in understanding the potential—both future and already realised—of the cell and gene therapy sector in the UK.



A handwritten signature in purple ink, appearing to read 'Steve Bates', written over a light blue circular watermark.

Steve Bates, OBE
CHIEF EXECUTIVE OFFICER
UK BIOINDUSTRY ASSOCIATION

Those of us in the Alliance for Regenerative Medicine are privileged to be a part of the ATMP community just as a new wave of these therapies are reaching patients.

The findings of this report illustrate the amazing success that the UK has had thus far in advancing gene therapies, cell therapies, and tissue-engineered products. The UK, owing to its leadership position in attracting world-class scientific and medical talent, is a global leader of this thriving sector. UK-based companies have raised more than \$440 million so far in 2019 and are sponsoring 27 clinical trials—nearly one third of all ATMP-focused clinical trials currently ongoing in the UK.

Advanced therapy products are already on the market in the UK for some haematological malignancies, as well as certain rare genetic disorders. Going forward, we expect to see cell and gene therapies approved for additional rare diseases and solid tumours, but also for diseases with larger patient populations, including additional cancers, cardiovascular indications, and certain neurodegenerative disorders, such as Alzheimer's and Parkinson's. Thousands of patients in the UK and abroad will benefit from these therapies, many in the very near term.

As the potential patient population for cell and gene therapies increases, there are a number of challenges that the sector must overcome. Our priority is driving the necessary financial and commercial innovation needed to ensure that patients are able to access these therapies. The NHS continues to be a leader in innovation in this area as well, with an emphasis on long-term value provided to the healthcare system and alternative funding frameworks provided through programs like the UK Cancer Drugs Fund and the Accelerated Access Collaborative (AAC). Policymakers are also engaging industry and other stakeholders to address issues in regulation, manufacturing, scale-up, and other potential barriers to patient access.

We have enjoyed enthusiastic collaboration with the BIA on this report as we've highlighted the growth and current state of the sector, as well as the major impact these transformative therapies will likely have in the UK. We look forward to continued engagement with stakeholders as this sector continues to push forward.



A handwritten signature in blue ink, appearing to read 'Janet Lambert', written over a light blue grid background.

Janet Lambert
CHIEF EXECUTIVE OFFICER
ALLIANCE FOR REGENERATIVE MEDICINE

Report Overview

The global ATMP sector is growing rapidly.



900+
THERAPEUTIC DEVELOPERS
active worldwide



These companies are sponsoring
1,060
CLINICAL TRIALS
including **93 Phase 3 trials**,
in fields including oncology,
cardiovascular, central nervous
system, and other indications



14
APPROVED advanced therapy medical products (ATMPs)
in the UK, with the potential
for dozens of additional
approvals in the next decade

Source: Alliance for Regenerative Medicine Q1 2019 Global Sector Report

The UK is a cornerstone in the international life sciences community, and advanced therapy medicinal products (ATMPs) are a fast growing part of the UK economy.

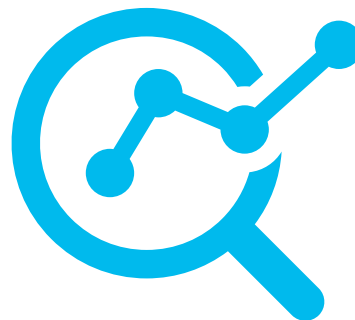
The UK cell and gene therapy industry employs 1,500 people; by 2035, the cell and gene therapy industry could be worth £10B and provide 18,000 jobs.

This report is intended to provide an overview of the current ATMP sector landscape in the UK. The growth in this industry highlights the need for coordinated efforts to promote regulatory pathways for safe and effective products, develop and implement innovative reimbursement options, address challenges in scale-up and manufacturing, and foster international policy convergence to ensure that patients across the globe are able to access these products in a timely manner.*

**Source: Cell and Gene Therapy Catapult 2018 Annual Report*

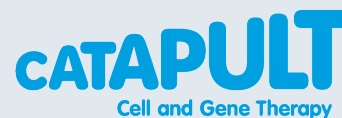
KEY TAKEAWAYS FROM THE REPORT

- 1** The UK is a leading source of innovation in the research and development of advanced therapy medicinal products (ATMPs) in Europe.
- 2** There is strong government support for scientific innovation, capital formation, and patient access to cell and gene therapies in the UK.
- 3** There is significant investment in the UK to support the development of these life-changing therapies.
- 4** The clinical pipeline in the UK, both in terms of UK-based companies and other companies interested in clinical development in the UK, is robust and growing.



These therapies are already positively impacting thousands of patients worldwide. In order to ensure that patients in the UK and globally can continue to access these transformative therapies, ***it is imperative that stakeholders from across the sector continue to promote a positive environment to support the research, development, approval, and commercialisation of ATMPs.***

The Cell and Gene Therapy Ecosystem in the UK



In 2019 there are more than 70 companies developing ATMPs in the UK, 25 manufacturing facilities, and three unicorn companies that have each reached over \$1B in value. The number of clinical trials ongoing in the UK has grown by 37% compared to 2018, with an increasing number of trials sponsored by commercial organisations. Additionally, the UK has seen 10 newly formed cell and gene therapy spinouts formed in the last year alone. This is a credit to the supportive ecosystem in the UK for the development, manufacture, and adoption of cell and gene therapies.

This rapid growth contrasts starkly with 2012, when there were only 22 cell and gene therapy companies in the UK. A handful of therapies were being developed in academic laboratories and in a few pioneering firms, CMOs were hesitant about committing to building large facilities, and most small biotechs struggled to get a foot in the door with investors, let alone receive investment.

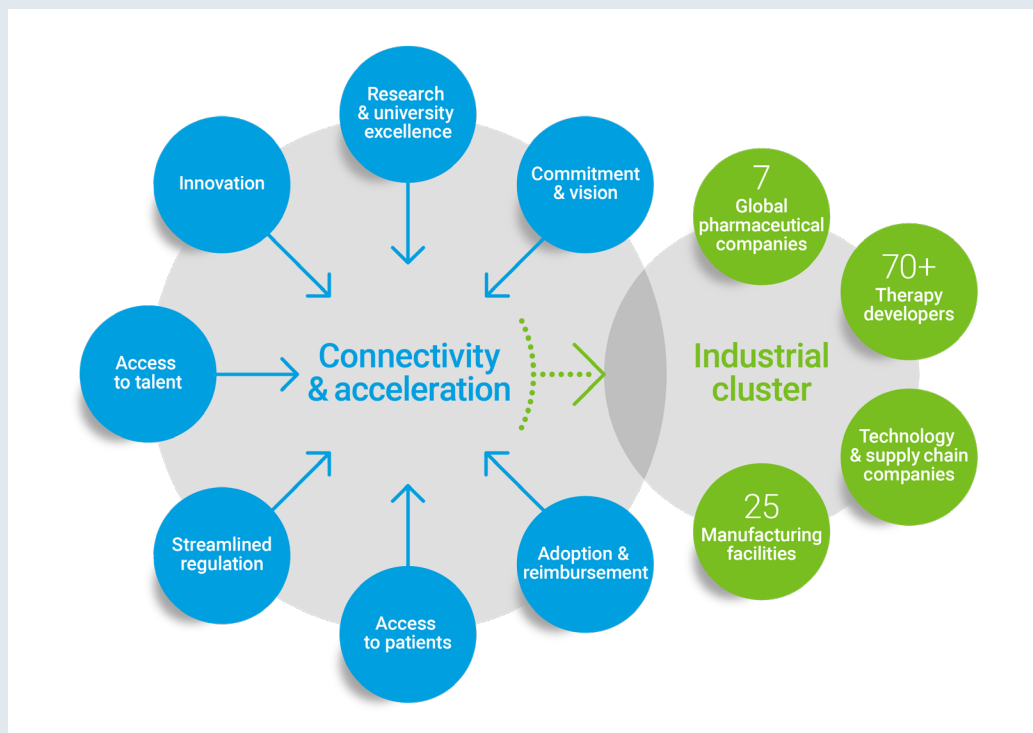
The UK recognises the potential of cell and gene therapies to address significant and growing unmet healthcare needs and has developed a uniquely supportive ecosystem, allowing companies at all stages to develop cell and gene therapies through to commercialisation. The cell and gene therapy ecosystem in the UK encompasses a number of

government and privately supported organisations working together to support the industry, overcoming barriers in order to accelerate their growth.

The ecosystem has developed to support the Government's long-term industrial vision, with commitment from the UK Government itself and collaborative work with private companies. Organisations such as BEIS, UKRI, Innovate UK, BIA, NICE, NHS, and initiatives such as the Government's industrial strategy, the setup of the MHRA's one stop shop, the Cell and Gene Therapy (CGT) Catapult manufacturing centre, the ATTC Network, and MMIP are examples of the commitment of the UK to innovation and to this field. CGT Catapult works to connect these organisations, accelerating industry growth. The UK provides research excellence through world leading universities and access to talent, and also through ATMP-specific apprenticeship programs with the industrial cluster providing industry expertise, services, and support.

The CGT Catapult represents one of the unique UK assets which has already had a strong impact in facilitating the growth of the UK ecosystem. With the core purpose of overcoming industry challenges which prevent the growth of the field, the CGT Catapult is helping address:

- › Process development challenges through collaborations with industry and academia at its development laboratories.
- › Large scale manufacturing challenges through its manufacturing centre, which provides a collaborative environment to enable companies to develop their manufacturing processes at scale.
- › Skills shortages through the Advanced Therapies Apprenticeship Community.
- › Clinical adoption challenges through the coordination of the ATTC Network, a world-first, UK system of Advanced Therapy Treatment Centres (ATTC) operating within the NHS framework.





“The UK’s advanced therapies ecosystem is flourishing, and the UK is the go-to place for cell and gene therapy development. This is evidenced by the growth in the number of companies in the UK compared to the 64 companies reported in July 2018 and also the number of international companies who have chosen to expand or relocate to the UK.”

— Keith Thompson, CEO, CGT Catapult

RESEARCH HOTSPOTS THROUGHOUT THE UK



DISTRIBUTION OF MHRA LICENCED GMP FACILITIES



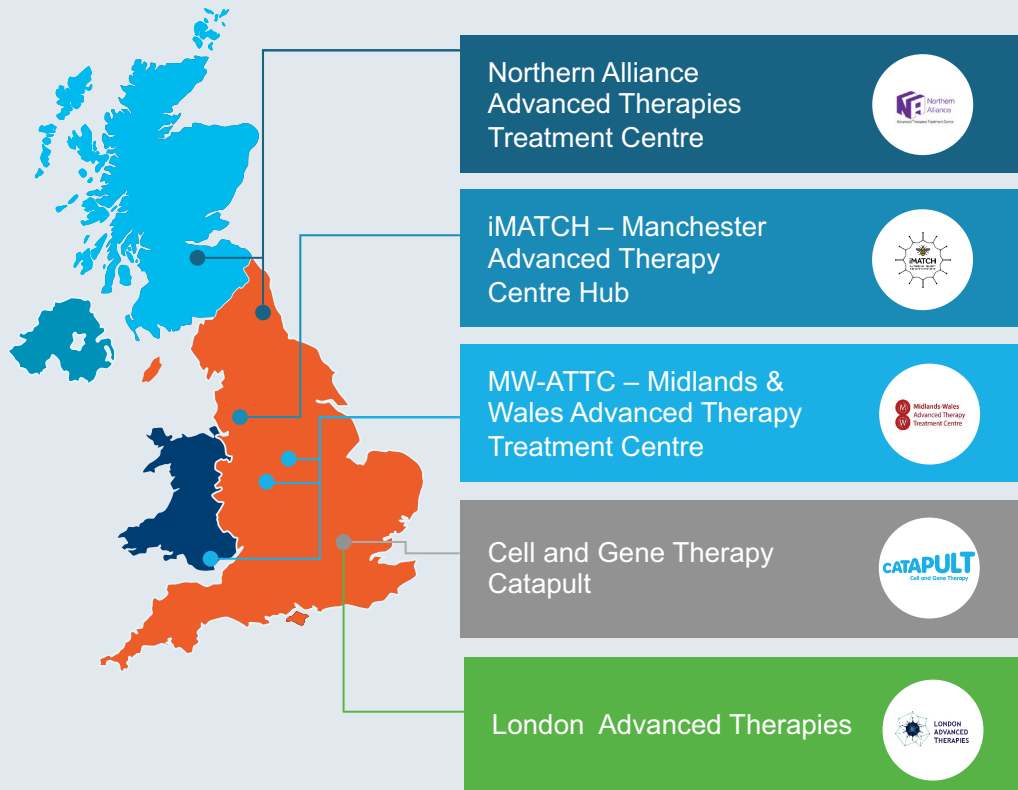


**INDUSTRIAL
STRATEGY**

UK Research
and Innovation

Advanced Therapy Treatment Centre Network

The ATTC Network Programme is a world-first, UK system of Advanced Therapy Treatment Centres (ATTC) operating within the NHS framework and coordinated by the Cell and Gene Therapy Catapult, that will address the unique and complex challenges of bringing pioneering advanced therapy medicinal products (ATMPs) to patients. This project has been funded by the Industrial Strategy Challenge Fund, part of the government's modern Industrial Strategy. The fund is delivered by UK Research and Innovation.



Sector Insights and History

The UK is the leading source of innovation and development of ATMPs in Europe. These products, which include gene therapies, cell therapies, and tissue-engineered products, are intended to augment, repair, replace, or regenerate organs, tissues, cells, genes, and metabolic processes within the body. These therapies have the potential to provide **profound and durable responses**—often with just a single treatment—for patients with a diverse array of serious diseases and disorders.

Today, the impact of this transformative field of medicine is being increasingly felt by patients in the UK and across the globe as increasing numbers of life-changing therapies enter the clinic and come to market.

56 Total ATMP developers headquartered in the UK, with **70+ total companies active in the UK**, including gene therapy, cell therapy, and tissue engineering therapeutic developers



24
Gene
Therapy



33
Cell
Therapy



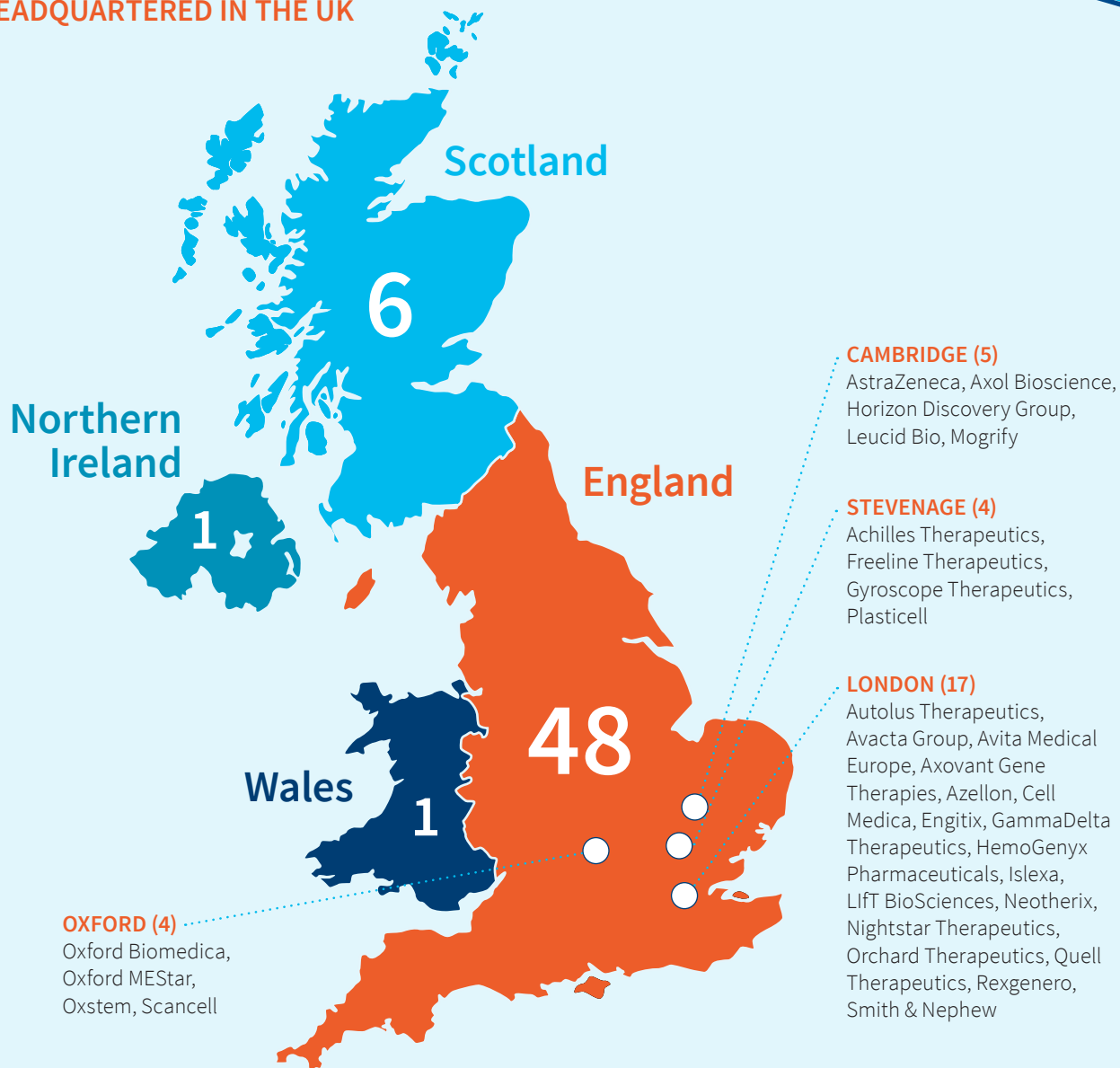
11
Tissue
Engineering

**Some developers may be active in more than one technology platform.*



24% of ATMP developers in Europe are headquartered in the UK.

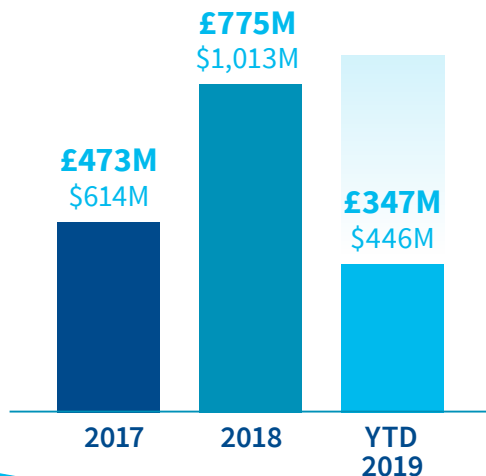
ATMP DEVELOPERS HEADQUARTERED IN THE UK



Access to Capital and Investor Interest

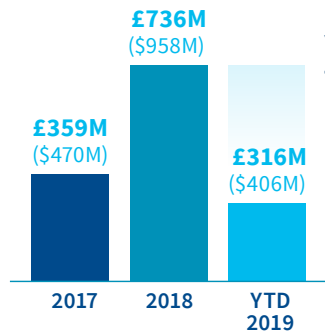
TOTAL YTD 2019 UK FINANCINGS

YTD financings are **45% of full-year 2018**



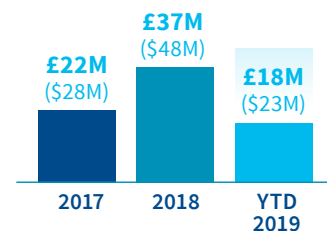
Gene and Gene-Modified Cell Therapy

YTD financings are **43% of full-year 2018**



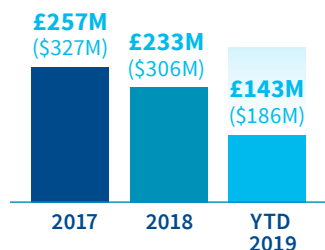
Tissue Engineering

YTD financings are **49% of full-year 2018**



Cell Therapy

YTD financings are **61% of full-year 2018**



EXAMPLES OF RECENT KEY FINANCINGS IN THE UK

Public Offerings

- Orchard Therapeutics raises **£100M** (\$128M) in public offering **3 JUNE 2019**
- Autolus Therapeutics raises **£91M** (\$116M) in public offering **15 APRIL 2019**
- Axovant raises **£31M** (\$40M) in public offering **13 MARCH 2019**

Other Financings

- Oxford Biomedica raises **£53M** (\$68M) in private placement **28 MAY 2019**
- Quell Therapeutics launches with **£35M** (\$44M) Series A **20 MAY 2019**
- AVITA Medical raises **£11M** (\$14M) in equity financing **7 FEBRUARY 2019**
- Transgene signs **£8M** (\$10M) upfront option agreement with AstraZeneca to co-develop five oncolytic virus candidates **2 MAY 2019**

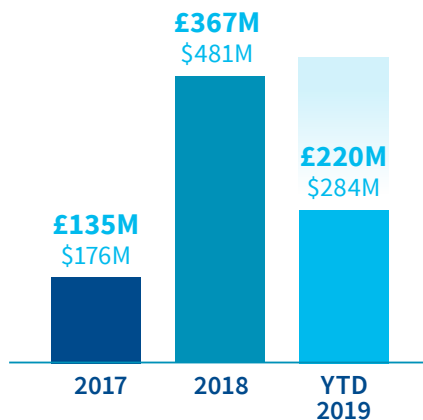
M&A Activity

- Biogen acquires Nightstar Therapeutics for **£688M** (\$877M) upfront **7 JUNE 2019**
- Smith & Nephew acquires Osiris Therapeutics for **£518M** (\$660M) **17 APRIL 2019**

TOTAL UK FINANCINGS BY TYPE, BY YEAR

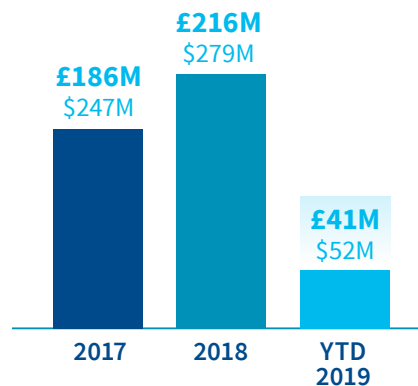
Public Offerings

YTD 2019 financings are **60% of full-year 2018**



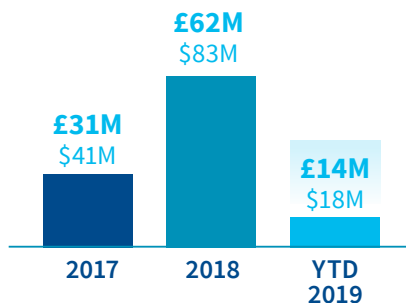
Venture Capital

YTD 2019 financings are **19% of full-year 2018**



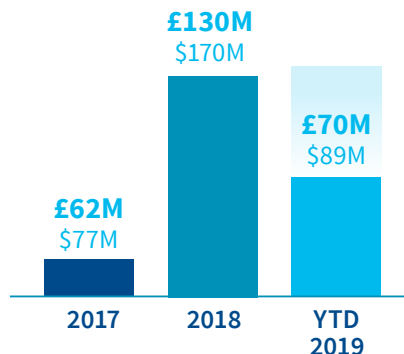
Corporate Partnerships (upfront payments)

YTD 2019 financings are **23% of full-year 2018**



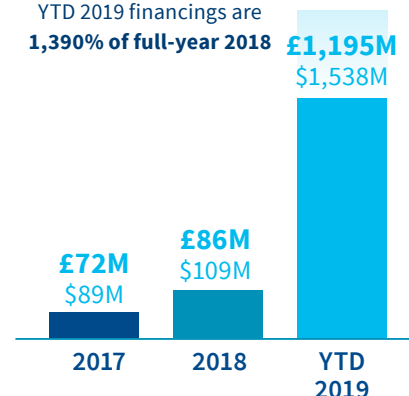
Private Placement / PIPES

YTD 2019 financings are **54% of full-year 2018**



Mergers and Acquisitions (upfront payments)

YTD 2019 financings are **1,390% of full-year 2018**



*Total amount raised represents sector-wide figures; please note that some companies utilise technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.

**In addition to the deal categories included above, the total financings figure also includes private equity financings equivalent to £2M in YTD 2019 and £59M in 2017.

***Figures do not include M&A transaction totals.

****YTD 2019 figures calculated as of 19 June 2019.

Clinical Trials by Phase and Technology Type

27 ATMP-focused clinical trials sponsored by UK-BASED COMPANIES

**Approximately 1/3 of all ATMP-focused clinical trials in the UK are sponsored by UK-based developers*

BY PHASE

9 Phase 1 **16** Phase 2 **2** Phase 3

BY TECHNOLOGY TYPE



10

Gene Therapy



13

Gene-Modified Cell Therapy



3

Cell Therapy



1

Tissue Engineering

93 TOTAL ONGOING ATMP-focused clinical trials in the UK

BY PHASE

21 Phase 1 **45** Phase 2 **27** Phase 3

BY TECHNOLOGY TYPE



48

Gene Therapy



25

Gene-Modified Cell Therapy



16

Cell Therapy



4

Tissue Engineering

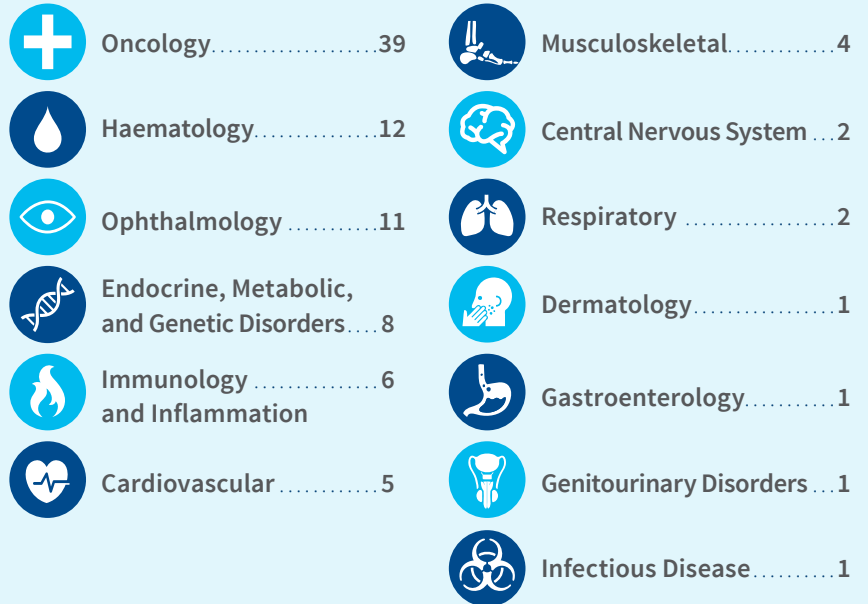
**All 27 clinical trials sponsored by companies headquartered in the UK have trial locations in the UK; 10 also have additional trial locations outside of the UK.*

Clinical Trials by Indication

TRIALS SPONSORED BY UK-BASED COMPANIES



ALL CLINICAL TRIALS ONGOING IN THE UK



63% of trials sponsored by UK-based developers and 42% of all current clinical trials in the UK are in oncology, including leukaemia, lymphoma, and cancers of the brain, head, neck, lungs, and skin, among others.



Select Significant Clinical Data Readouts



CELL-BASED IMMUNO-ONCOLOGY

- Adaptimmune announced positive data in patients with synovial sarcoma treated with ADP-A2M4, antitumour activity in other solid tumours. [6 MAY 2019](#)
 - » The data showed partial responses in four out of five synovial sarcoma patients treated with ~10 billion cells in the ADP-A2M4 pilot study, and tumour shrinkage seen in nearly all assessed synovial sarcoma patients.
- Cell Medica collaborators presented positive early patient data from a CAR-NKT trial in neuroblastoma. [30 APRIL 2019](#)
 - » There was also strong radiological evidence of extensive tumour regression at four weeks post infusion in one patient, with further regression observed at eight weeks. No significant treatment associated toxicities, including cytokine release syndrome or neurotoxicity, were observed.
- Adaptimmune presented safety data with evidence of tumour necrosis in one patient with advanced hepatocellular carcinoma in ADP-A2AFP study. [2 APRIL 2019](#)
 - » There was no evidence of clinically significant hepatotoxicity, off-target toxicity, or alloreactivity, and no protocol-defined dose limiting toxicities were observed.
- Autolus Therapeutics announced initial results from their ALLCAR19 Phase 1/2 trial in adult acute lymphoblastic leukaemia. [1 APRIL 2019](#)
 - » At a median follow up of five months, six of 10 patients are alive and continue to be in molecular remission.
- Autolus Therapeutics announced updated results from the ongoing CARPALL trial in pediatric acute lymphoblastic leukaemia. [19 FEBRUARY 2019](#)
 - » Twelve of 14 patients achieved a complete response. The median duration of remission in responding patients was 7.3 months with a median follow-up of 14 months. Five of 14 patients remain in complete remission with ongoing persistence of CAR T cells and associated B cell aplasia.



GENE THERAPY

- › Axovant announced six-month follow-up data from the first cohort of their Sunrise-PD Phase 2 trial of AXO-Lenti-PD. [6 JUNE 2019](#)
 - » On average, the patients experienced an improvement from baseline of ON time without dyskinesia of 2.7 hours, a reduction of 2.4 hours in ON time with non-troublesome dyskinesias, a reduction of ON time with troublesome dyskinesias of 1.5 hours, and an increase in OFF time of 0.9 hours.
- › Orchard Therapeutics announced clinical proof-of-concept data for gene therapy OTL-300 demonstrating efficacy in transfusion-dependent beta-thalassemia. [29 APRIL 2019](#)
 - » Of the six pediatric patients treated, four achieved transfusion independence and one showed a reduction in transfusion requirement.
- › Axovant announced positive data from clinical trial of AXO-AAV-GM2 in GM2 gangliosidosis (Tay Sachs disease). [29 MARCH 2019](#)
 - » There was an approximately 25% decrease in GM2 ganglioside in the cerebral spinal fluid observed at end of three-month period in the first child dosed with AXO-AAV-GM2.



CELL THERAPY

- › ReNeuron presented positive data from its Phase I/II trial of its hRPC cell therapy candidate for the treatment of retinitis pigmentosa. [20 FEBRUARY 2019](#)
 - » All three of the first cohort of subjects in the Phase II part of the trial have reported a significant improvement in vision, on average equivalent to reading an additional three lines of five letters on the ETDRS eye chart.
 - » At the most recent follow-up, subjects in the study showed a mean improvement from baseline in visual acuity of + 23 letters in the treated eye. [26 APRIL 2019](#)

Autolus

Autolus Therapeutics (Nasdaq: AUTL) is at the forefront of a revolution in cancer treatment. Autolus is a clinical-stage biopharmaceutical company developing next-generation programmed T cell therapies for the treatment of cancer. Spun out from University College London in 2014, Autolus is headquartered in London with state-of-the-art facilities in White City, and today employs more than 250 people.

TECHNOLOGY OVERVIEW

Using its broad suite of proprietary and modular T cell programming technologies, Autolus is focused on the development of precisely targeted, controlled, and highly active T cell therapies that have the potential to offer cancer patients substantial benefits over the existing standard of care, including the potential for cure in some patients. In addition, Autolus has developed their own proprietary viral vector and semi-automated cell manufacturing processes and this year initiated manufacturing for clinical studies at the Cell and Gene Therapy Manufacturing Centre, Stevenage. Additional expansion will take place with further facilities planned in Enfield in the UK.



FOCUS AREAS

Autolus has a clinical-stage portfolio of product candidates in development in five indications for the treatment of haematological malignancies and solid tumours and is constantly innovating with next-generation products also in development, with a similar number of projects at an advanced stage in the preclinical pipeline. The Company is focusing on areas of high unmet need, with the lead programmes targeting:

- Adult Acute Lymphoblastic Leukaemia (aALL)
- Pediatric ALL
- Diffuse Large B-Cell Lymphoma (DLBCL)
- T-cell Lymphoma
- Multiple Myeloma (MM)





Oxford Biomedica is a leading gene and cell therapy company whose work delivers life-changing treatments to patients. The Company has a broad clinical and commercial track record in the gene therapy field, spanning 22 years. Data demonstrates more than six years of stable, dose-dependent gene expression in patients after a single direct administration. Its LentiVector® platform, the first commercially approved lentiviral based gene delivery system, has delivered the first FDA and EMA approved CAR-T cell therapy, Kymriah® and several hundreds of patients have now received treatment with therapies that use its lentiviral vectors.

Lentiviral vectors are advantageous for a number of reasons:

- They can deliver large therapeutic payloads (up to 10kb) into target cells
- Permanent modification of dividing and non-dividing cells is achieved through gene integration to achieve long-term expression
- Their lack of pre-existing immunity makes them safer to use

FROM CLINIC TO THE MARKET

Oxford Biomedica’s manufacturing process has been validated for commercial supply; this means that use of its proprietary process to make clinical trial material enables the Company to move rapidly to pivotal trials and commercial production without the need for tech-transfer, expensive process change and scale-up.

Oxford Biomedica proprietary products (to be spun-out or out-licensed)

OXB-202	Ophthalmology (corneal graft rejection)	Phase I/II trial preparation
OXB-302	Cancer (Multiple)	Pre-Clinical complete
OXB-201	Ophthalmology (Wet AMD)	Phase I complete
OXB-204	Ophthalmology (LCA10)	Pre-Clinical
OXB-208	Ophthalmology (RP1)	Pre-Clinical
OXB-103	CNS (ALS)	Pre-Clinical

BROAD APPLICABILITY

Oxford Biomedica has manufactured lentiviral vector products for both *in vivo* and *ex vivo* gene therapy applications, including CAR-T cell programs, CD34+ haematopoietic stem cell programs and direct injection into, for example, the brain.

WORKING WITH PARTNERS

We continue to invest in the development of a proprietary pipeline of innovative gene therapies to treat diseases with unmet medical needs, for future out-licensing or spin-out.

Rare blood cancers

Oxford Biomedica is the sole commercial manufacturer of lentiviral vector for Kymriah®, a groundbreaking CAR-T cell therapy from Novartis targeting rare blood cancers.

CAR-T therapy involves extracting a patient's T cells—a type of white blood cell—and genetically modifying them with a lentiviral vector to express artificial T-cell receptors (making them CAR-T cells) that enable them to selectively recognise and then kill cancer cells.

The patient's T cells are expanded until the population numbers hundreds of millions and then reinfused back into the patient where, guided by the engineered receptors, they recognise and kill the cancerous cells. This highly promising approach has led to dramatic response rates.

Kymriah® was approved by the European Commission in August 2018 and a commercial deal with NHS England was approved less than 10 days later, representing one of the fastest funding approvals in the 70-year history of the NHS.

Parkinson's Disease

AXO-Lenti-PD is an investigational therapy for Parkinson's disease that delivers three genes to the brain via a single lentiviral vector, enabling the production of the three critical enzymes required for dopamine synthesis with the goal of restoring steady levels of dopamine in the brain. It was originally developed by Oxford Biomedica and subsequently outlicensed to Axovant in 2018. A clinical study is being ongoing at two sites in the UK: the Institute of Neurology at University College London and the Centre for Brain Repair in Cambridge.



IN-HOUSE DEVELOPMENT

Oxford Biomedica continues to invest in the development of a proprietary pipeline of innovative gene therapies to treat diseases with unmet medical needs, for future out-licensing or spin-out.

OXB-302: Gene-based immunotherapy targeting a range of cancers

OXB-302 is a gene-based cancer immunotherapy targeting a wide range of tumours and a number of haematological malignancies. This cell therapy uses the LentiVector® platform to engineer patients' harvested T-cells to express chimeric antigen receptors (CAR) against the 5T4 antigen, which is expressed on the cell surface in many common cancers. These, now CAR –T cells are then infused back into the patient, and subsequently recognise the 5T4 tumour antigen and initiate cell killing immune mechanisms.

OXB-302 is in preclinical development, delivering encouraging efficacy in an industry standard *in vivo* tumour challenge model. Following the successful completion of preclinical development, planning for clinical programme is underway.

Preclinical pipeline

Oxford Biomedica is also working on three additional proprietary assets to advance from research through pre-clinical development. OXB-204 and OXB-208 target inherited retinal diseases, where the Company has extensive experience from its early focus on ophthalmology indications. OXB-103 is in development for the treatment of amyotrophic lateral sclerosis (ALS), a group of rare, progressive neurological diseases.

DEVELOPING EXPERTISE

OXB is committed to supporting the development of early careers in gene and cell therapy to ensure the sustainability of the UK's leading position. The company is a member of the Advanced Therapies Apprenticeship Community (ATAC), which was established to develop the first apprenticeship programme designed specifically to train and upskill individuals to develop, manufacture, and deliver these innovative therapies at scale. The company also supports undergraduate students through industrial placement schemes with institutions such as University College London, where students of Biochemical, Chemical, or Process Engineering spend year 4 of their course in industry. Shaping the academic curriculum and nurturing the talent pool ensures that the future generations of gene and cell therapy specialists are industry-ready.



VISION

Orchard's vision is to build a self-sustaining business that leverages a common technology platform and commercial infrastructure to treat a series of rare genetic diseases globally for the benefit of patients. The therapies Orchard is working on have the potential to transform the lives of people with devastating, often-fatal genetic disorders, many of which affect young children—and they aim to do it in a single administration.

ORCHARD THERAPEUTICS OVERVIEW

Orchard Therapeutics is a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through *ex vivo* autologous gene therapies. Orchard's gene therapy approach seeks to transform a patient's own, or autologous, haematopoietic stem cells (HSCs) into a gene-modified drug product to treat the patient's disease through a single administration. Orchard achieves this outcome by utilising a viral vector to introduce a functional copy of a missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process, resulting in a drug product that can then be administered to the patient at the bedside.

Orchard's approach of using lentiviral vectors to genetically modify HSCs has wide-ranging applicability to a large number of indications. The ability of HSCs to differentiate into multiple cell types allows Orchard to deliver gene-modified cells to multiple physiological systems, including the central nervous system, immune system, and red blood cell lineage, thereby potentially enabling the correction of a wide range of diseases. By leveraging the innate self-renewing capability of HSCs that are engrafted in the bone marrow as well as the ability of lentiviral vectors to achieve stable integration of a modified gene into the chromosomes of HSCs, Orchard's gene therapies have the potential to provide a durable effect following a single administration.

CASE STUDY

In a preclinical study conducted by one of Orchard's scientific advisors and published in Proceedings of the National Academy of Sciences of the United States of America, or PNAS, a subpopulation of gene-modified HSCs have demonstrated the potential to cross the blood-brain barrier, engraft in the brain as microglia, and



express genes and proteins within the central nervous system. The study showcases the potential for HSCs to potentially address a range of diseases that affect the central nervous system. Orchard's OTL-200 program for metachromatic leukodystrophy (MLD) leverages this same mechanism of action to deliver gene-modified HSCs through the blood-brain barrier and deliver a therapeutic gene that can prevent neuronal degeneration.

FOCUS AREAS

Orchard is initially focusing its *ex vivo* autologous gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders, and haemoglobinopathies.

Orchard's portfolio includes Strimvelis®, a gammaretroviral vector-based gene therapy and the first such treatment approved by the European Medicines Agency for severe combined immune deficiency due to adenosine deaminase deficiency (ADA-SCID). Additional programs for neurometabolic disorders, primary immune deficiencies, and haemoglobinopathies are all based on lentiviral vector-based gene modification of autologous HSCs and include three advanced registrational studies for metachromatic leukodystrophy (MLD), ADA-SCID and Wiskott-Aldrich syndrome (WAS), clinical programs for X-linked chronic granulomatous disease (X-CGD), transfusion-dependent beta-thalassemia (TDT), and mucopolysaccharidosis Type I (MPS-I), as well as an extensive preclinical pipeline.

To date, more than 150 patients have been treated with Orchard's commercial product and clinical-stage product candidates across six different diseases, with follow-up periods of up to eight years or more following a single administration.

PARTNERS

Orchard is partnered with academic institutions that are pioneers in *ex vivo* autologous HSC gene therapy and has obtained exclusive licences to extensive preclinical data, clinical data, and know-how to build their portfolio of *ex vivo* autologous HSC gene therapies. These partnerships with leading institutions such as The University of California Los Angeles, Boston Children's Hospital, and the United States National Institutes of Health in the United States, and University College London, Great Ormond Street Hospital, Telethon Institute of Gene Therapy, San Raffaele Hospital, The University of Manchester, the Manchester Foundation Trust, and

	Preclinical	Clinical proof of concept	Registration trial	Commercialisation	Designations
Neurometabolic disorders					
OTL-200	MLD (metachromatic leukodystrophy)				RPD
OTL-203	MPS-1 (Mucopolysaccharidosis type 1)				
OTL-201	MPS-1 (Sanfilippo type A)				RPD
OTL-202	MPS-1 (Sanfilippo type B)				
Primary immune deficiencies					
Strimvelis®	ADA-SCID (adenosine deaminase severe combined immunodeficiency)				RPD
OTL-101	ADA-SCID (adenosine deaminase severe combined immunodeficiency)				RPD; BKT
OTL-103	WAS (Wiskott-Aldrich syndrome)				RPD
OTL-102	MLD (metachromatic leukodystrophy)				
Haemoglobinopathies					
OTL-300	TDT (transfusion-dependent beta-thalassemia)				PRIME

Several additional research and preclinical programs under development

RPD Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher **BKT** Breakthrough Therapy Designation **PRIME** Priority Medicine (PRIME) Designation

Généthon in Europe, are a core part of their research engine through which they are advancing their lead clinical-stage programs and working to identify other opportunities with comparably high probabilities of success. Orchard plans to leverage their internal expertise combined with their relationships with leading academic institutions to transition their lead clinical-stage product candidates from the academic setting to commercial-ready production and further expand their pipeline.

BACKGROUND

Recent technology advancements have enabled significant progress in the efficiency, efficacy, and safety of gene- and cell-based medicines for a multitude of genetic disorders. In particular, these advancements have improved gene delivery to disease-affected cell types. This means that product developers now must improve the gene expression cassette payload in response to the emerging importance of tight, targeted, and robust gene regulation.

SYSTEMATIC IMPROVEMENT OF GENE CONTROL

Synpromics has developed a technology platform, PROMPT®, and a proprietary machine learning methodology to create libraries of promoter candidates that are designed and developed according to a discreet set of specifications, such as the size of the promoter; the tissue, cell, or multiple cell type selectivity of the promoter; the strength of the promoter; and whether the promoter is constitutively expressed in the target cell type(s) or is regulated or inducible in the cell. These promoters can be designed for both *in vivo* or *ex vivo* applications. New promoters are required to drive efficient, yet finely tuned, gene expression so that the therapeutic effect is safe, directed, and durable and to minimise long-term immune responses to the therapeutic cassette.

LIVER GENE THERAPY – A SUCCESSFUL COLLABORATION WITH UNIQUIRE

In 2015, Synpromics embarked on a collaboration with uniQure, the first company to bring a gene therapy into the marketplace, to develop highly potent, liver selective promoters for gene therapy applications. uniQure had developed AAV5 as a tool to deliver gene payloads to the liver and is using it in a number of its clinical programs. However, they recognised that a collaboration with Synpromics would allow them to improve transcriptional targeting of hepatocytes through incorporating Synpromics promoter technology into their AAV5 platform, resulting in an improved safety and efficacy profile.

SHORT POTENT LIVER PROMOTERS – INCORPORATION OF SYNPROMICS TECHNOLOGY INTO CLINICAL CANDIDATES

In the eight-month period following the initiation of the collaboration with uniQure in 2015, the team at Synpromics had designed and screened libraries of liver-selective promoter candidates that showed remarkable strength and passed them onto the uniQure team.

The remit was to create promoters that could mediate liver-selective gene expression five times more effective than the promoter that uniQure was using in its current gene therapies; initial testing in mice showed that the Synpromics lead promoter candidate was closer to 50 times more active than the previous industry standard (Figure 1).

Figure 1. Transfection vs Transduction vs *in vivo*



Figure Legend: The graph shows that the Synpromics promoter (D) is more than eight times stronger than uniQure's previous liver selective promoter (A), when expressing the Super9™ gene in non-human primates.

uniQure's new gene therapy aims to treat all patients with haemophilia A, one of the two main types of haemophilia. Haemophilia A is caused by missing or defective Factor VIII, a protein essential for clotting. Approximately 30 percent of patients with severe haemophilia A will develop an inhibitor that neutralises the infused Factor VIII (FVIII) activity. This patient population has, in the past, been excluded from gene therapy approaches in clinical development; however, uniQure's new candidate has been demonstrated in preclinical studies to circumvent inhibitors to FVIII.

This data shows that the candidate may lead to durable expression in haemophilia A patients and may provide long-term prevention of bleeds. The promoter, developed by Synpromics, is a key component of this new candidate.

uniQure have continued to work on the other Synpromics promoters and, in April 2019, they presented data from their Fabry's disease program, announcing the use of another Synpromics promoter in its preclinical pipeline. The collaboration between the two companies continues to flourish and uniQure remains engaged as the two companies look to combine their respective platforms to improve genetic medicine in other disease indications.

Figure 2. Therapeutic transgene validation in NHP

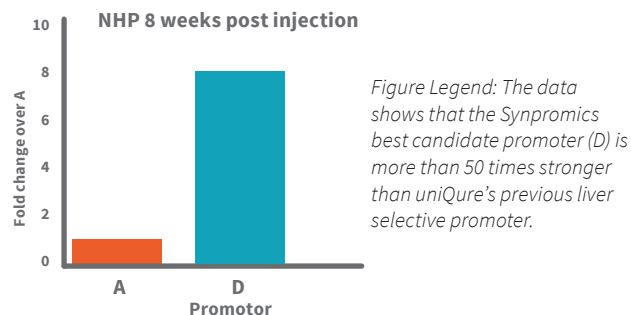


Figure Legend: The data shows that the Synpromics best candidate promoter (D) is more than 50 times stronger than uniQure's previous liver selective promoter.

Recommendations and Conclusion



The UK's ATMP sector is strong and growing. These therapies have the potential to help patients in the UK and worldwide who are suffering from an array of serious diseases and disorders. In order to ensure the continued advancement of this transformational field of medical science, it is imperative that policymakers and other stakeholders promote a positive scientific, regulatory, and reimbursement environment.

The realisation of the immense therapeutic potential will require stakeholders to:

- 1** Support scientific research to develop and advance both cell and gene therapies and ancillary processes, including manufacturing and scale up.
- 2** Foster economic development and the creation of a skilled workforce to promote the continued growth of this industry in the UK.
- 3** Cultivate a positive regulatory environment for the research and development of cell and gene therapies, including fostering accelerated pathways to ensure that patients are able to access safe and effective therapies in a timely manner.
- 4** Develop the necessary infrastructures within NICE and its counterparts in Scotland, Wales, and Northern Ireland to ensure health technology assessments are able to address the long-term value provided by cell and gene therapies.
- 5** Collaborate with the NHS and other public and private payers in the UK to develop innovative financing models to ensure patients can access approved therapies in an efficient manner.

The Alliance for Regenerative Medicine (ARM) and the UK BioIndustry Association (BIA) support the continued collaboration of industry, policymakers, payers, patient advocates, and other sector stakeholders to drive innovation in this sector, ultimately improving the lives of patients in the UK and globally.



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