

ADVANCED THERAPIES INVESTMENT REPORT 2017

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THE CHALLENGES AND
OPPORTUNITIES OF THE
ADVANCED THERAPY
SECTOR

A GUIDE TO SUCCESSFUL
INVESTMENT

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Many thanks to the following organisations for their expert insight contribution to this report



Abbreviations used

ADA-SCID: Adenosine Deaminase Deficiency Severe Combined Immunodeficiency Disorder

ADV: Adenovirus

ALL: Acute Lymphoblastic Leukaemia

AML: Acute Myeloid Leukaemia

ASC: Adult Stem Cell

ATMP: Advanced Therapy Medicinal Product

AWMSG: All Wales Medicines Strategy Group

BIA: BioIndustry Association

BLA: Biologics License Application

BMS: Bristol Myers-Squibb

BPDCN: Blastic Plasmacytoid Dendritic Cell Neoplasm

CAR-T: Chimeric Antigen Receptor T-Cell

CAT: Committee for Advanced Therapies

CCRM: Centre for Commercialisation of Regenerative Medicines

CDMO: Contract and Development Manufacturing Organisation

CRS: Cytokine Release Syndrome

cGMP: Clinical Good Manufacturing Practice

CHMP: Committee for Medicinal Products for Human Use

CMO: Contract Manufacturing Organisation

CMV: Cytomegalovirus

CQA: Critical Quality Attributes

CRISPR: Clustered regularly interspersed short palindromic repeats (gene editing technology)

CTRM: Cell Therapy and Regenerative Medicine

DbD: Development-by-Design

DLBCL: Diffuse Large B-Cell Lymphoma

DoH: Department of Health

EAMS: Early Access to Medicines Scheme

EMA: European Medicines Agency

ESC: Embryonic Stem Cell

EU: European Commission

FDA: Food and Drug Administration (US)

GAN: Giant Axonal Neuropathy

GMP: Good Manufacturing Practice

GSK: GlaxoSmithKline

GTMP: Gene Therapy Medicinal Product

GvHD: Graft vs Host Disease

HE: Hospital Exemption

HSCT: Haematopoietic Stem Cell Transplant

HTA: Health Technology Appraisal

ICER: Incremental Cost-Effectiveness Ratio

IND: Investigational New Drug

iPSC: Induced Pluripotent Stem Cell

KFDA: Korea Food and Drug Administration

LADD: Live Attenuated Double-Deleted

LPLD: Lipoprotein Lipase Deficiency

MA: Market Authorisation

MAA: Market Authorisation Application

MHRA: Medicines and Healthcare Products Regulatory Agency

MLD: Metachromatic Leukodystrophy

MM: Multiple Myeloma

MPS: Mucopolysaccharidosis

NHL: Non-Hodgkin Lymphoma

NICE: National Institute for Clinical Excellence

NSCLC: Non-Small Cell Lung Cancer

P&R: Pricing and Reimbursement

PAI: Pre-Approval Inspection

PAS: Patient Access Scheme

PIM: Promising Innovative Medicine

PIP: Paediatric Investigation Plan

PRIME: PRiority MEDicines scheme

PSUR: Periodic Safety Update Report

QALY: Quality-Adjusted Life Year

QTPP: Quality Target Product Profile

r/r: Relapsed or Refractory

RAT: Regenerative Advanced Therapy

SCTMP: Somatic Cell Therapy Medicinal Product

SMC: Scottish Medicines Consortium

TCR: T-Cell Receptor

TEP: Tissue Engineered Product

TPP: Target Product Profile

T-regs: T-regulatory cells

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Editor's introduction

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The past 60 years have seen globally significant advances in medical technology which have drastically increased both quality and expectancy of life across the globe. Made possible through advancements in antibiotics, vaccinations, small molecule drugs, and biologics, the developed world now expects to live long and healthy lives. Successes in medical science have suppressed the incidence of predominantly acute external pathologies, altering the clinical landscape to place chronic internal failures of the body firmly in the foreground. 80% of 2012 EU deaths were a result of non-communicable diseases.¹ Despite on-going and partially successful efforts from existing treatment modalities, heart failure and cancer together account for over a million deaths every year in the US, and in the EU, there are an estimated 1.3 million annual deaths from cancer alone.^{2,3} Progress in cancer treatment has been slow; treatment approaches have remained largely unchanged since chemotherapy became commonplace in the 1940s, and often, cancer treatment side effects can be as damaging as the disease itself.

This picture is now developing in innovative and exciting ways. Advances in our basic understanding of disease pathophysiologies, cell biology and cell culture, as well as genetic engineering tools being safer and more precise than ever before, have enabled the development of a new generation of medicinal products promising to offer highly efficacious clinical results. Advanced therapies leverage living cells or genetically active compositions to actuate metabolic, immunologic, or genetic mechanisms of action. The complexity of cell products allows diseases to be treated in novel and disruptive ways including regenerating damaged tissues, precisely targeting cancers, or modulating the immune system, while gene therapies aim to target the fundamental cause of genetic diseases to completely reverse their manifestation. For the first time in interventional treatments, the word 'cure' is increasingly entering the conversation.

The opportunities for investors here are clear. The need for novel therapies in treating intractable disease has, is, and will continue to increase as populations continue to age, while governments globally have a responsibility to facilitate on-going reimbursement for efficacious medicinal products. The high efficacy rates of some advanced therapies command an equally high price point, while the broad application of cutting-edge platform technologies offers real value in some of the largest healthcare markets. Cell and gene therapies are not without their challenges; demanding technical complexity, potentially unaffordable prices, and an immature peripheral industry constitute high levels of risk to technology developers and investors alike, but the rewards for those who can successfully address the challenges inherent to this young and disruptive industry are likely to be tremendous. Many challenges are surmountable through informed strategic decision-making alone, while others require technological advancement, or other multi-stakeholder solutions for their successful resolution.

This report aims to equip investors with the basic knowledge required to understand the risks of investing in cell and gene-based technologies through contextualised and empirical experience, valuable insight from a series of leading industry stakeholders, and market research and analysis. Building on deep understanding of the major risks in commercialising advanced therapies this report offers insightful and pragmatic guidance to maximising return on investments in advanced therapies.

Executive Summary

The advanced therapy sector is a rapidly growing industry which offers substantial opportunities for return on investment (ROI) for those able to understand and overcome the significant challenges to successful commercialisation. Advanced therapy medicinal products (ATMPs) are drug products which leverage living cellular or active genetic materials to offer novel treatment modalities in a range of both acute and chronic diseases. Immuno-oncology is currently a major commercial focus representing almost half of all clinical trials and over \$1.5 billion of public and private investment, but additional target markets are increasingly under consideration. The ATMP industry is characterised predominantly by small, young biotechnology companies developing therapeutic agents and peripheral technologies, supported largely by academic and publicly funded basic and translational research efforts. ATMPs are regulated and authorised for marketing by the European Medicines Agency (EMA) in the EU and the Food and Drug Administration (FDA) in the US, each of which have specific routes to market depending on the product's legal categorisation. Several regulators now offer conditional approval following early efficacy data. Deep understanding of a product's basic biology and mechanism of action is absolutely fundamental to mitigating the complexity of ATMPs, and must be leveraged in the design and optimisation of bioprocess manufacturing, testing and validation, clinical development, supply chain, and market access strategy. Validated functional assays and disease models are central to this effort. Product pricing should be based on value to payer rather than production cost. Health technology appraisal (HTA) methodologies vary nationally but often favour the use of comparator products, and a lack of relevant comparators (common in orphan indications) complicates P&R negotiations. The high efficacy/high price dynamic of many advanced therapies implies that complications to P&R and novel reimbursement models may be required, particularly regarding US private health insurance. The National Institute for Clinical Excellence (NICE) has undertaken a mock CAR-T appraisal in association with an extensive report from the University of York, finding that an exemplar curative CAR-T costing £356,100 would be reimbursed, and that monthly annuity payments and/or performance-linked reimbursement could be viable options. High-priced medicines such as 'curative' gene therapies may be unaffordable to reimbursement funds even when deemed cost-effective. Capturing the true value of therapies offering long-term clinical gains is difficult and requires either long-term clinical trial endpoints and/or extrapolated data, plus in some cases an assessment of indirect healthcare cost savings. Conditional market approval without confirmatory phase III trial data may implicate P&R risks. Solutions to these challenges are either available, under discussion, or in development. Pricing is not the only barrier to market access; ease of use and disruption to standard operating procedure may affect success.

The complexity and sensitivity of ATMPs makes manufacturing and supply chain design high-risk concerns. Difficulties in precisely defining cell-based products mean that manufacturing processes may inform product characterisation; therefore, modifying the manufacturing process may jeopardise regulatory approvals which depend on process-based definitions. Critical to mitigating this risk is designing a scalable and preferably automated manufacturing process in preclinical or early clinical development which requires little modification for commercial-scale supply. Additional challenges include insufficient raw materials supply, high-demand logistics, and shortfall in manufacturing bandwidth. Optimising manufacturing through simplification and automation can substantially decrease operating costs, increase robustness, and enhance quality control. Autologous therapies are particularly demanding as

batch failure or mismanagement can have fatal consequences. Manufacturing may be undertaken centrally or through a distributed network of decentralised facilities, depending on product characteristics, market forces, and supply chain risk structure. Shipping and logistics can be high-risk areas of the supply chain; autologous therapies must be tracked throughout the circular supply chain, and cell-based products can suffer from short shelf-lives. Technology developers are investing in manufacturing ahead of phase I/II trials, but fully automated manufacturing bioprocesses are not yet widely implemented. Some leading companies have sacrificed first-generation product manufacturability, choosing to implement automation for their second-generation products. Several major manufacturing stakeholders now offer services in the ATMP sector providing both bespoke solutions and off-the-shelf instrumentation, while an expanding network of contract development and manufacturing organisations (CDMOs) offer virtual model manufacturing (16 stakeholders identified). Supply chain challenges present an opportunity for ROI by investing in novel scalable manufacturing and other solutions.

Large drug manufacturers are increasingly engaging with the ATMP sector. The first application of advanced cellular and genetic engineering was in developing tissue models, now widely implemented in high-throughput drug screening. The intersection of traditional pharmaceutical organisations with the advanced therapy space is highly collaborative, with extensive research collaborations, licensing deals, and commercialisation rights being agreed between stakeholders. GlaxoSmithKline (GSK) developed and authorised the first *ex vivo* gene therapy (Strimvelis), Novartis are widely expected to launch the first CAR-T product this year, and most other major pharmaceutical organisations are now engaging with advanced therapy products, in immuno-oncology for cell-based therapies and in a narrow range of gene therapy indications. Many deals involve unusually early-stage companies developing highly innovative and valuable platforms whose inherent value is recognised.

Investors approaching the advanced therapy sector are faced with extensive barriers but strategies for risk mitigation are increasingly established. Investors must be equipped with sufficient technical understanding to assess the merit of a therapeutic or platform and understand associated clinical and preclinical data. Platform technologies can share risk and offer achievable revenue goals, while sidestepping the commercialisation barriers inherent to directly developing therapeutics. P&R and manufacturing issues are complex and should be thoroughly understood to mitigate risk and design effective solutions. Increasing interest from biopharmaceutical companies may offer exit opportunities. In the public market some small advanced therapy companies have performed very well despite an overall decline in the biomedical technology sector, but investors must maintain vigilance as more companies than not have yielded negative lifetime performance. Attracting limited partnership (LP) investment to advanced therapy VC funds holds unique but surmountable challenges.

Expert Insight

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Development activity in gene therapy and related fields (gene editing, adoptive cellular immunotherapy) has exploded over the past couple of years, fueled by a handful of clinical successes, abundant access to capital, and a large unmet medical need across an array of therapeutic categories. As the field accelerates up a steep learning curve with accumulating clinical experience and lessons, the opportunity to deliver benefit to patients in need is substantial. However, equally substantial are the challenges that lay ahead. Not only do these represent generally novel platforms (which comes with its own inherent risks to navigate), but the business model is also rather unprecedented in offering long-term therapeutic benefit (or potentially even cures) for what are often ultra-rare diseases.

Focusing first on the opportunity, the ability to genetically modify cells *ex vivo* or *in vivo* is exceptionally powerful. These are the ultimate fruits of the genomics revolution, but also just the beginning as the field's understanding of gene control continues to improve. As genotype/phenotype correlations continue to be elucidated, gene therapy and related therapeutics have almost boundless potential to treat patients with both hereditary and acquired diseases. Ultimately each opportunity is unique in terms of the addressable patient population, the unmet medical need and existing treatment options, pricing potential, and competitive horizon. In some settings, competition within gene therapy and related technologies is already appreciable (such as Hemophilia or CD-19 targeting CAR-T therapeutics). In others, there is only a single lead player (such as Spinal Muscular Atrophy or Parkinson's Disease). Patients, families and caregivers have much to gain from these therapies, and the medical ecosystem has a responsibility to ensure that not only are the products developed both responsibly and swiftly, but also to ensure appropriate dissemination of information and provide access to those who want to benefit.

But just like the opportunities for these therapies cannot be overstated, neither can the risks. On the development side, these are still early days and our understanding of the risk/benefit of each therapy is still being informed. Until we have a broader dataset of experience and exposures to quantify platform-specific and product-specific risks, the risk/benefit equation will have key missing inputs. Some of the diseases being addressed have no prior approved therapies, which require validation of endpoints and often establishment of natural history against which to correlate clinical studies. Regulatory requirements will depend on the nuances of each program and may evolve over time as experience with these therapies grows. Manufacturing at commercial scale will also be an important step along the way and could pose random pitfalls that delay (or even derail) some programs. Beyond that, the 'cures' business model is also not well established, and the experience with Gilead highlights the lack of comfort investors have with this type of therapy. The industry's ability to convince investors in a growth outlook (either via annuity payments or sequential gene therapy approvals) may be an important driver of valuations and ability to drive additional capital into the field to fund new projects.

All these factors play into valuations, investor sentiment, stock performance and capital-raising. As the industry overall advances, new datapoints will drive valuations of individual companies and also have potential read-throughs to others, which will invariably create meaningful volatility. But at the end of the day, those who innovate successfully and bring value to patients are invariably rewarded for doing so.

OVERVIEW OF ADVANCED THERAPY INDUSTRY

Chapter 1

1.1. Summary of Chapter 1

Advanced therapies are innovative and cutting-edge medicinal products subject to great amounts of clinical academic research and increasing industry engagement. The promise of unusually high efficacy levels has attracted a great deal of attention and investment, and a new generation of drug products are expected to reach the market over the coming years. Advanced therapies are legally categorised depending on their nature and intended function, and may leverage pluripotent stem cells, somatic cells, genetic constructs, or a combination. Immuno-oncology is currently the dominating area of industry engagement, with several well-funded biotechnology companies developing competing products predominantly in liquid blood cancer indications. The scale of initial public offerings (IPOs), which total almost \$1 billion for six chimeric antigen receptor T-cell (CAR-T) companies alone, are testament to the hype CAR-Ts have generated. Advanced therapies are conceptually applicable to a huge diversity of indications and various stakeholders are generating clinical data across a range of indications, most notably in immunological and autoimmune indications, tissue repair, and gene therapies for blood clotting and haemophilia disorders.

1.2. Introduction to advanced therapies

Advanced therapy medicinal products (ATMPs) represent a broad category of innovative medicines which leverage cell and gene-based approaches to treat disease. ATMPs are distinct from traditional small molecules and biopharmaceuticals as they contain active cells or genetic constructs which exert a metabolic, immunologic, genetic or other non-pharmaceutical mechanism of action. ATMPs are technically demanding to design and manufacture, and to date have met very limited commercial success, but the industry is rapidly evolving to meet these challenges and develop efficacious new treatments across a range of indications. Two US or EU market authorisations for CAR-T products are expected this year, and a diverse range of additional products are following closely behind.

Academia has been the major force for the technological development that has driven value in the ATMP industry, and continues to represent the core driver of disruptive innovation. This is reflected by the growing number of research alliances and industry-academia collaborations characteristic of the ATMP space, and the value of such partnerships is evidenced by the successful development and (anticipated) authorisation of several such projects.

The promise of 'curative' cell and gene therapy treatments and ground-breaking early clinical trials has attracted a great deal of investor attention, with venture capital investment in the CAR-T space reaching over \$600 million as of 1st September 2016 and many companies achieving record IPOs.⁴ The field holds potential for substantial returns for those backing the right technologies, but *clinical success does not guarantee commercial success*. The novelty of highly efficacious but highly complex and expensive advanced therapy products is disrupting every element of the route to commercial success including supply chain needs, reimbursement models, and more. Achieving ROI in the advanced therapy sector demands business models and strategies as innovative as the products themselves.

1.3. Defining advanced therapies

The European Medicines Agency (EMA) divides ATMPs into four main categories: Tissue engineered products (TEPs), somatic cell therapy medicinal products (SCTMPs), gene therapy medicinal products (GTMPs), and combined ATMPs (Table 1). TEPs are generally regenerative approaches involving the application of stem-type cells for the long-term regeneration and/or

replacement of damaged tissue such as heart, cartilage, bone, or nervous tissue repair. SCTMPs involve cells engineered to enact a different purpose to their original function, often exerting a short-term interventionalist effect on patient physiology to intercept disease pathology (e.g. oncology indications). GTMPs do not contain active cells but leverage genetic engineering tools to modify the genetic composition of (a subset of) a patient's cells through active recombinant nucleic acids. Combinational products constitute a medical device combined with an active cellular substance, e.g. where live cells are encapsulated within an artificial capsule.

Cell therapies can be either autologous or allogeneic. Autologous therapies are derived from the treated patient and manufactured through a defined protocol before re-administration. Autologous therapies offer the advantage of immunological compatibility but generally demand a more complex supply chain. Allogeneic therapies are derived from donor cells and through the construction of master and working cell banks are produced on a large scale that allows off-the-shelf distribution and application.

Subject	Legal definition wording
Advanced Therapy Medicinal Product (ATMP)	<ul style="list-style-type: none"> a) a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, b) a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, c) a tissue engineered product as defined in Article 2.1 (b) Regulation (EC) No 1394/2007
Tissue Engineered Product (TEP)	<ul style="list-style-type: none"> a) contains or consists of engineered cells or tissues, and b) is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
Somatic cell therapy medicinal product (SCTMP)	<ul style="list-style-type: none"> a) Contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant to for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor; b) Is presented as having properties for, or is used in or administered to human beings, with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
Gene Therapy Medicinal Product (GTMP)	<ul style="list-style-type: none"> a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.
Combined Advanced Therapy Medicinal Product (combined ATMP)	<ul style="list-style-type: none"> a) must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and b) its cellular or tissue part must contain viable cells or tissues, or c) its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

Table 1: Legal wording of key definitions, according to Article 2.1 Regulation (EC) No 1394/2007

1.3.1. Stem cell therapies

'Stem cells' is a catch-all term used to refer to a multitude of cell types, but broadly defined are cells capable of both self-renewing and differentiating into a range of more mature downstream cell types. Embryonic stem cells (ESCs) are present in embryos of around 4-8 days old and are pluripotent, i.e. can differentiate into any cell type found in the adult body. Adult stem cells (ASCs) are tissue-specific multipotent cells whose main function is to replenish the somatic cell population of its respective tissue type; for example, cardiac progenitor cells are multipotent heart muscle cells that can both differentiate into mature cardiomyocytes and self-renew their own population. The self-renewing capability of ASCs, yet close relation to highly functional somatic tissue types makes them amenable to producing effective therapies through large-scale manufacture.

The development of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka *et al.* in 2006 completely changed the stem cell therapy treatment paradigm. iPSCs are a stem cell type that can be formed by reprogramming mature cell types back to a pluripotent state through the action of four key reprogramming factors, usually in the form of retrovirally inserted genes. The technology enables the creation of patient-specific stem cells capable of differentiating into any desired cell type, paving the way for personalised regenerative treatments. The clinical application of iPSCs is currently limited by high production costs and technical safety issues but several early-stage clinical trials are underway. iPSCs are currently widely used in developing healthy and disease-state tissue models for both basic research and drug screening, with several large pharmaceutical companies integrating iPSC-derived tissue models into their low-throughput screening processes.

1.3.1. Gene therapies

Gene therapies can be applied either in combination with cell products and through an *ex vivo* treatment mode (e.g. Strimvelis), or directly administered *in vitro* (e.g. Glybera). Several vectors present clinically relevant options, including adenovirus (AV), adeno-associated virus (AAV), and lentivirus. Adenovirus was responsible for the infamous death of Jessie Gelsinger in 1999, but after advances in genetic engineering and extensive R&D, Celgene are now applying AV vector in the clinic. Lentiviral vectors are more broadly used owing to their more favourable integration profile, which favours gene loci rather than promotor or transcriptional control sites, limiting the potential for oncogenesis.^{5,6}

Forecasts for gene therapy market value in 2025 range from \$4.3 billion to \$10 billion, but to many, there is little doubt of the role gene therapies will play in the future of medicine.^{7,8} This growth has been enabled largely by advances in genetic understandings of disease, and by innovation in genetic engineering tools such as TALEN, RNAi, and CRISPR/Cas9. In the EU and US, Glybera (2012) and Strimvelis (2016) are the only two approved gene therapies to date, developed by UniQure and GSK respectively. However, Glybera will not have its marketing authorisation renewed when it expires in October 2017, primarily due to poor market performance.⁹ Today, there are over 60 companies developing therapeutic genetic technologies worldwide, and over 1,000 clinical trials, the vast majority within academia.

1.4. Major therapeutic areas of interest

Immuno-oncology currently dominates the advanced therapy sector, accounting for around half of all clinical trials in 2016.¹⁰ CAR-Ts are the major driving force behind this and the CAR-T market is forecast to value \$8.5 billion by 2028.¹¹ Growth in the sector has been largely driven by developing understandings of the role of genetics in oncology, in synergy with the validation of lentiviral vector safety and cutting-edge genetic engineering tools such as CRISPR/Cas9. As opposed to the traditional chemotherapy and radiotherapy cancer treatment paradigm of non-specific cell ablation, which can destroy the immune system and have other devastating side effects, immuno-oncology approaches aim to leverage and augment the natural immune response to precisely target cancers. There are several approaches by which cellular therapies can be applied to oncology: the first major cell based approach was haematopoietic stem cell transplants following chemotherapy and/or radiation treatment, but more specific approaches have emerged since, including dendritic cell vaccines, T-cell receptor (TCR) engineering, and chimeric antigen receptor T-cells. CAR-Ts involve the genetic engineering of T-cell receptors to specific tumour antigens, resulting in T-cells which both directly attack tumour cells and initiate a broader immune response. CAR-Ts are now the leading technology type in the ATMP space, with over 100 clinical trials underway in 2016, a 250% rise over 2015 and almost \$600 million in venture capital equity

Indications of advanced therapy trials

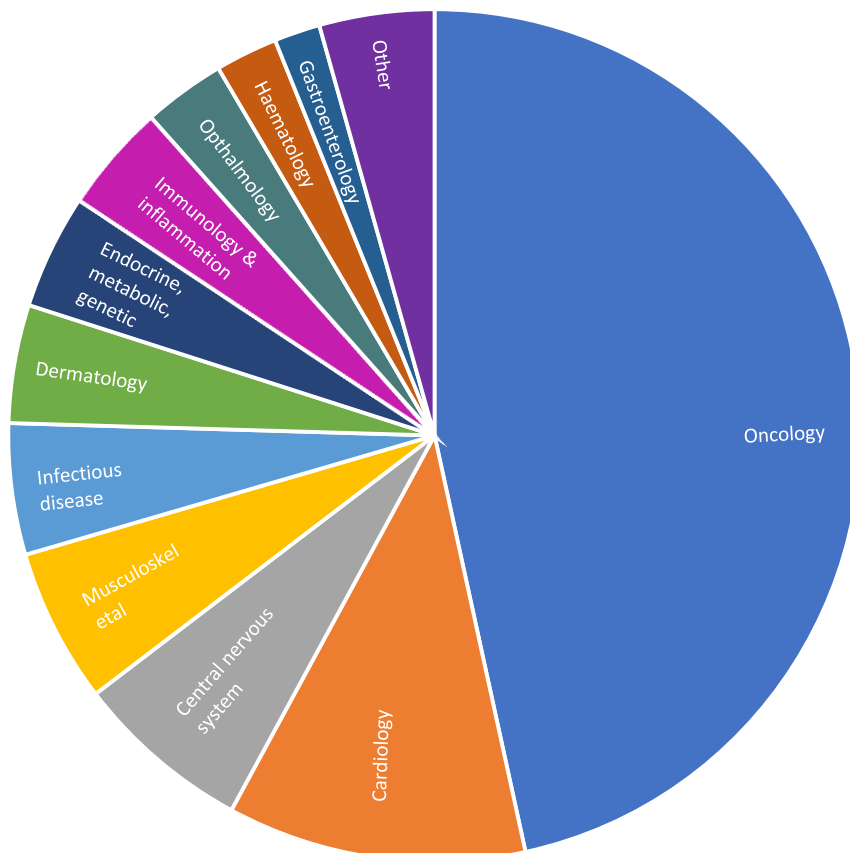


Figure 1: Disease indications of past and current clinical trials as of 31st December 2016. Oncology CAR-T products dominate the field, with regenerative somatic cell therapies comprising a major fraction of trials. Source: Alliance for Regenerative Medicine Data Report 2016.

(Table 2).¹² Equally, the public market has reflected this interest, with the six leading advanced therapy companies (the majority of which are developing CAR-T products) raising nearly \$1 billion in their IPOs (Table 3). Malignant lymphomas, the major indication category for CAR-Ts, represents 3.37% of all malignancy worldwide.¹³ In the US in 2017, there will be an estimated 174,000 cases of leukaemia, lymphoma, non-Hodgkin lymphoma, and myeloma, the major blood cancers pursued by CAR-T products.¹⁴ With limited and mixed data in solid tumours, there is concern that CAR-Ts will quickly saturate a rather limited market.¹⁵⁻¹⁷ Many companies are recognising this and developing additional CAR-Ts against alternative cell surface markers to expand their potential market.

Company	Venture capital (\$ millions)	Date	CAR-T approach
Kite Pharma	15	March 2011	Autologous
Kite Pharma	20	May 2013	Autologous
Kite Pharma	20	April 2014	Autologous
Juno	176	April 2014	Autologous
Juno	143	August 2014	Autologous
Bellicum	55	August 2014	Autologous
Autolus	45	January 2015	Autologous
Poseida	23	December 2015	Allogeneic
CARsgen	30	January 2016	Autologous
Autolus	57	March 2016	Autologous
Total	584		

Table 2: Adapted from Cell & Gene Therapy Insights. Includes only venture capital funding for companies involved in CAR-T program(s) at the time of investment. For example, venture capital funding of Bluebird Bio occurred prior to their CAR-T programs, while the company had only a gene therapy focus. These investments are not included. Source: Company press releases.

Company	IPO (\$ millions)	IPO date	CAR-T approach
Bluebird bio	101	June 2013	Autologous
Kite	128	June 2014	Autologous
Bellicum	140	December 2014	Autologous
Juno	265	December 2014	Autologous
Collectis	228	March 2015	Allogeneic
Ceylad	100	May 2015	Allogeneic and autologous
Total	962		

Table 3: Adapted from Cell & Gene Therapy Insights. IPO value of CAR-T companies. Only includes IPOs where the company had a CAR-T focus at the time of going public. Source: Company press releases.

1.4.1. Non-oncological immunology

Advanced therapies are under development for a range of additional immunologically relevant indications outside of oncology, including graft versus host disease (GvHD), diabetes, and other autoimmune indications. Major cell types are mesenchymal stromal cells (MSCs)* and T-regulatory cells. MSCs are widely evidenced to have immunomodulatory effects, generally understood to actuate their function through a paracrine mechanism of action, and are currently undergoing over 250 clinical trials across a vast range of indications.¹⁸ Despite

* A note on terminology: MSCs are a heterogenous population of cells generally defined as per the 2006 position paper published by the International Society for Cellular Therapy (Dominici *et al* 2006). Originally termed mesenchymal stem cells, their functional disparity from true stem cells has led to the widespread substitution of 'stem' for 'stromal'. However, MSCs are often still referred to as mesenchymal stem cells.

widespread early-stage clinical trials many leaders in the field remain sceptical of their true efficacy, with only 7% of listed trials in phase 3. Phase 3 indications include GvHD, stroke and other cardiovascular diseases, spinal cord repair, Crohn's disease, bone diseases, and cerebral palsy. Commercial interest in MSCs is currently limited in response to the lack of robust clinical data.

Cytotoxic T-cells have applications outside oncology, primarily in reducing viral infection following haematopoietic stem cell transplant (HSCT). 20% to 35% of patients undergoing allogeneic HSCT develop cytomegalovirus (CMV) infection.^{19,20} Supporting HSCT with CMV or adenovirus (ADV)-specific CD8⁺ T-cells has been shown to reduce the risk of infection, and several companies are developing allogeneic products to deliver on this need (e.g. Cell Medica, London, UK).

Regulatory T-cells (T-regs) are potent suppressors of the immune system, endogenously functioning to maintain immunological homeostasis. T-regs provide a counterbalance to the stimulatory nature of cytotoxic T-cells, maintain tolerance to self-antigens, and prevent autoimmune disease in healthy individuals. Approximately 60 clinical studies are currently ongoing, all in early testing stages.¹⁸ Despite a relative lack of clinical data to date T-regs are widely expected to enter commercial development over the coming years.²¹

1.4.2. Tissue engineering and regenerative medicines

A significant proportion of cell-based advanced therapies employ a 'regeneration' treatment modality, and can be loosely defined as tissue engineered or regenerative medicines. Such products generally fall within the EMA definition of a TEP, in contrast to SCTMPs which tend to act transiently and do not necessarily implicate long-term tissue repair. TERM products often involve progenitor cell types. Examples are HeartCel for cardiac repair (Cell Therapy Ltd), CTX for stroke and critical limb ischemia (ReNeuron), MACI for cartilage repair (Vericel), and a host of cellular dermal repair products indicated for burns or diabetic skin ulcers (e.g. Dermagraft, Epicel, AmnioExcel). Applications for EMA guidance on ATMP classification in 2016 showed a substantial rise in the number of TEPs over any previous year (Figure 2).

Outcome of guidance applications on classification of ATMPs

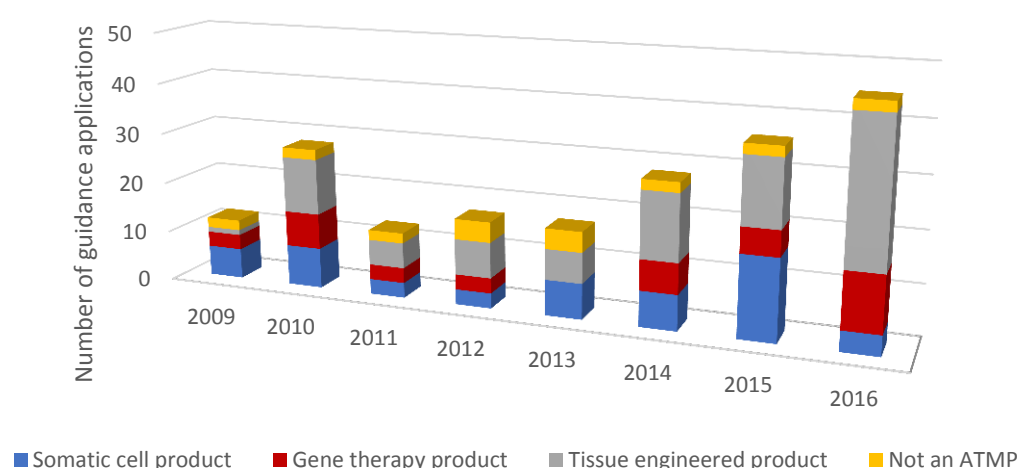


Figure 2: Number of applications for guidance on classification of ATMPs from the EMA. Representative of the number of products in development within each classification. Source: European Medicines Agency.

1.4.3. Gene therapies

Gene therapies have previously focused on orphan indications owing to the favourable financial, regulatory and market incentives. Orphan status permits for higher reimbursable pricing points which can justify higher development costs, augmented by up to 12-year market exclusivity rights. Gene therapies are increasingly looking to enter larger and more competitive markets as product development infrastructures mature. Haemophilia A and B are currently major indications for gene therapy products with high competition between several late-clinical-stage companies. Spark Therapeutics, Pfizer, Bayer, Sangamo, Freeline Therapeutics, UniQure, and Shire are all developing gene therapy products for haemophilia. Other companies operating in the gene therapy space include, Nightstar, CRISPR Therapeutics, Editas, Bluebird, Celgene, Intellia, Pfizer, and Precision Biosciences.

1.5. Platform and supportive technologies

A healthy industry of peripheral technologies is emerging around advanced therapies, and these constitute an essential element to the success of the industry. Platform technologies such as proprietary cell lines or gene vectors are the primary means by which a single product can be expanded into a robust portfolio of candidates; for example, Immunicum have three platforms across gene editing, CAR-T cell expansion, and T-cell primers, enabling the company to advance a series of immuno-oncology candidates including a lead CAR-T platform and follow-up dendritic cell neoantigen presentation technology. Immunicum aim to leverage the natural allo-immune response to enhance the anti-tumour response.

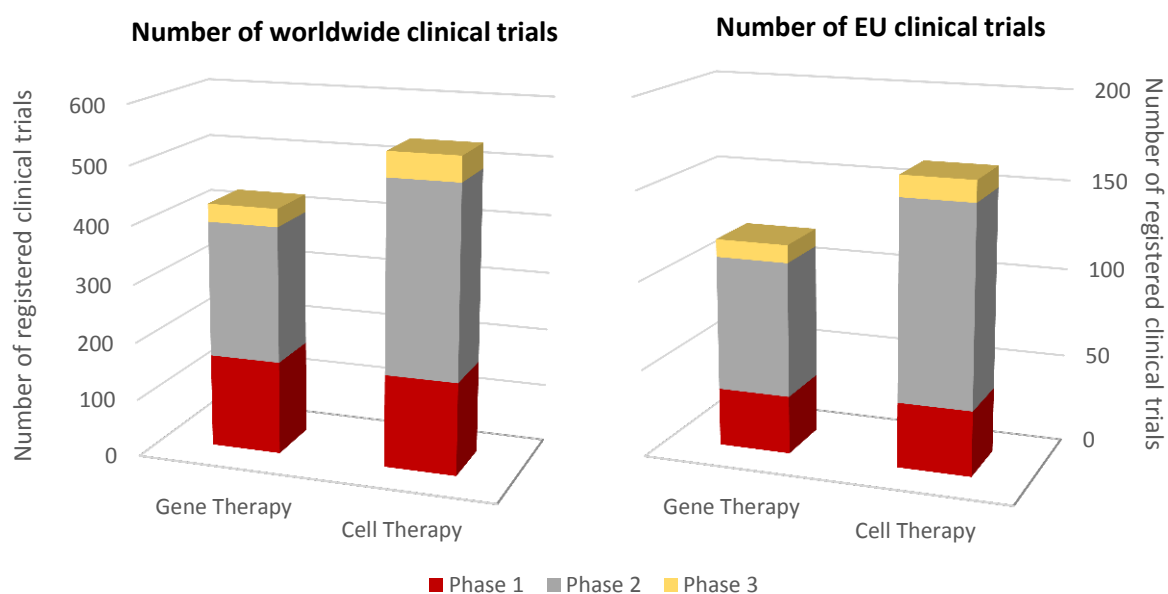


Figure 3: Number of advanced therapy clinical trials worldwide and within EU, stratified by phase. Ethical restrictions prevent advanced therapies from undergoing phase I testing in healthy volunteers. Because early-phase trial subjects are patients, most pilot trials include efficacy endpoints, and are thus categorised as phase I/II trials. The classification of pilot trials as phase II explains the relatively high number of phase II trials compared to phase I. Few advanced therapies have yet reached phase III. Source: Alliance for Regenerative Medicine Data Report 2016.

Platform technologies offer lower risk investments as they may be leveraged not only in expanding a growing portfolio of candidates, but through out-licensing or co-development

agreements, support the development of partnership programmes. MaxCyte provides a key example. Through a cutting-edge proprietary cell engineering platform, the company now has over 40 high-value cell therapy partnership programmes within immune-oncology, regenerative medicine and gene editing, including 15 clinical-stage programmes. After launching an IPO on AIM in March 2016 for 70p per share, MaxCyte (LON:MXCT) now trades at 288p. Immunicum is a clinical-stage Swedish company with a T-cell activation and immune-priming platform 'COMBIG', a CAR-T cell expansion platform, and a next-generation AV vector to gene edit immune cells. Immunicum are looking to develop an allogeneic dendritic cell *in vivo* vaccine for the treatment of solid tumours, leveraging histological immunogenicity to raise an immune reaction against the tumour.

Supportive technologies such as medical devices or cell-support structures supplement the function of ATMPs by providing favourable environmental cues or by enhancing or enabling the therapy's treatment mode in other ways. Two major examples are cell encapsulation systems and tissue scaffolds.

Expert Insight

Alex Karlsson-Parra

Chief Scientific Officer, Immunicum



The strong allogeneic response to donor major histocompatibility complex (MHC) molecules in transplantation and the normally weak response to tumor antigens represent two important and divergent but potentially interactive immune responses.

It is well established that unprimed T lymphocytes from one individual react directly and with unusual strength against MHC antigens expressed on metabolically active dendritic cells (DCs) from other members of the same species —a phenomenon called alloaggression.

An early demonstration of this phenomenon was the intense *in vitro* T-cell proliferation observed when mixing peripheral blood mononuclear cells and dendritic cells (DCs) from unrelated individuals. Moreover, a plethora of immune-cell recruiting chemokines and immune-cell activating cytokines are generated during this alloaggressive response.¹¹⁴

Alloaggression has therefore obvious implication for the generation of an immunostimulatory environment; if strategically located by intratumoral administration of allogeneic proinflammatory DCs, it might create a potent immunostimulatory environment leading to recruitment and activation of endogenous "bystander" DCs subsequently favouring the development of desirable T-cell responses to tumor antigens.

Since this cell-based concept of immune activation doesn't require MHC-compatibility between injected cells and the patient, it introduces the possibility of using pre-produced and freeze-stored DCs from healthy blood donors as an off- the-shelf immune enhancer.

Cell encapsulation systems allow allogeneic or xenogeneic transplantation without immune-rejection, and can be macro-encapsulated or micro-encapsulated, predominantly alginate-calcium based systems. ViaCyte is a macro-encapsulation platform currently under development for the treatment of diabetes, through the encapsulation of healthy ESC-derived β -islet cells and subdermal device implantation.²² Alginate-based micro-encapsulation systems such as NovaMatrix can be applied to treating acute liver failure, diabetes, and more.²³⁻²⁵ Encapsulation membranes permeable to factors under approximately 200kDa

allows for normal cellular metabolic function while providing a physical barrier to cell migration and immunologic contact.

Tissue scaffolds applied predominantly in regenerative medicines or tissue engineering products, with particular application to bone repair.²⁶⁻²⁸ Synthetic scaffolds are composed of a wide range of materials with varying properties and applications, while natural scaffolds are generally derived from decellularised tissues. Videregen is a clinical-stage company with a tissue engineered trachea product. Their manufacturing process involves decellularising deceased donor tracheas to leave just the extracellular matrix scaffold, before re-seeding the scaffold with a patient's own cells. Once fully expanded and matured, the re-cellularised trachea is transplanted back into the patient. The advantage of natural matrices is their inherently optimal structure in supporting and encouraging cell growth for their specific tissue type, but synthetic scaffolds have greater design flexibility and present ideal patenting opportunities.

1.6. Typical biotech early-stage development

Advanced therapies frequently experience long development timelines due to the significant preclinical product development and clinical testing needs. Early stage biotechs tend to start small to reduce cash burn through early development, expanding throughout clinical development as products are de-risked and brought closer to market. The vast majority of products and technology platforms are originally developed in academia, and public funds are therefore predominantly responsible for early stage innovation and development. Funding sources such as the Innovate UK Developmental Pathway Funding Scheme (DPFS) are often leveraged for early-stage and translational research. In the US, billions of dollars of public money go into biotechnology research, a significant proportion of which are for gene and stem cell therapies.

Attracting greater levels of investment on the scale of venture capital can be problematic due to the inherently high barriers to entry, level of uncertainty, and scale of challenges requiring significant early capital.

Expert Insight

Ayal Ronen

Vice President, FreeMind Group



Every year, the National Institutes of Health (NIH), Department of Defense (DOD), and other US Federal agencies such as the Biomedical Advanced Research and Development Authority (BARDA), National Science Foundation (NSF), etc., award billions of dollars in grant money to fund the research and development of a highly diverse portfolio covering literally any area of scientific interest. Of these, hundreds of millions are dedicated specifically to Gene Therapy and over \$1.5B to Stem Cell research covering projects at an early exploratory stage, through pre-clinical activities as well as clinical stage programs.

Diversity in the Cell and Gene Therapy space is exemplified by the number of Federal Institutes and Centers open to funding research and development projects containing such solutions to unmet medical needs. For example, the National Cancer Institute (NCI) is actively funding applications directed at advancing immuno-oncology, whereas the National Institute of Neurological Disorders and Stroke (NINDS) is employing Stem Cells to address the most pressing matters in Neuroscience.

In summary, depending on the area of interest, securing non-dilutive funding to further Cell and Gene Therapy programs is a key component in any diverse funding strategy. Keys to success are in the execution of a well-orchestrated long-term multi-submission granting strategy.

1.7. Role of academia in ATMP ecosystem

The basic and applied research necessary to develop novel technologies and advance technical ability sufficiently to validate effective novel treatments is labour, time and resource intensive, and possible almost exclusively within an academic framework. Academia is responsible for pioneering all commercially leading technology platforms to date, most notably CAR-Ts largely within the University of Pennsylvania, CRISPR-Cas9 at UC Berkley/Broad Institute, iPSC technology at the RIKEN centre, and GSK's *ex vivo* gene therapy pipeline at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget).²⁹⁻³² Academic research is often hampered by clinical testing resource availability and is not necessarily incentivised to consider the commercial potential of their research, but academic/commercial partnerships as an exception to this generalisation have often proven successful, provided sufficient investment can be found. Often this involves stakeholders with long-term financial perspectives such as charitable funding (e.g. Wellcome Trust Syncona Partners/Royal Free Hospital partnership in London) or robust pharmaceutical companies with the resources to accommodate long-term investment (e.g. GSK/SR-Tiget partnership).

Expert Insight

Ferran Prat

*Vice President, Strategic Industry Ventures,
MD Anderson Cancer Center*



When it comes to advanced therapies, translating opportunities out of academia is inherently difficult. These are not opportunities that can be easily out-licensed to Pharmaceutical Companies, which pushes this type of opportunities towards the NewCo pathway. However, it is also inherently difficult to create NewCo's around Advanced Therapies due to the fact that these entities need high-caliber management and substantial funding to have a fighting chance to be successful. It is theoretically possible to develop a conventional small molecule "on a budget". Not so with cell therapy or gene therapy. Only the strongest VC's that have experience and a track-record in company building (i.e., not just tagging along in a syndicate), working together with top-tier academic institutions can survive in this environment.

Expert Insight

Uta Griesenbach

President, British Society for Gene and Cell Therapy



Academia has been a major force in developing advanced therapy investigational medicinal products (ATIMPs) to date and continues to be so. The growing number of academic-industrial research collaborations in this field is testament to the close relationship between academia and industry.

It is certainly our view that the academic pipeline of innovation is essential for the growth of this sector and it is, therefore, imperative that any major investments in the field (e.g. via the UK Industrial Strategy Challenge Fund) considers the needs of academics to keep this essential pipeline open.

Academics are calling for suitable support and infrastructure to conduct pre-clinical research and academic-led early phase clinical trials. More specifically this includes access to affordable non-GLP and GLP ATIMP manufacturing sites, access to suitably trained staff (specifically pharmacists and nurses to conduct the trials) and access to grant funding to cover the generally high costs of ATIMP pre-clinical and clinical research.

UNDERSTANDING CELL & GENE THERAPY PIPELINES

Chapter 2

2.1. Summary of Chapter 2

In the EU, the European Medicines Agency (EMA) authorises advanced therapies for market sale through the centralised authorisation procedure. Developers must submit formal evidence of their product's safety and efficacy through a market authorisation application (MAA). Conditional approval mechanisms pioneered in the Asia-Pacific have now been adopted by EU and US regulators. In the EU, conditional MA is available in specific circumstances, and requires post-authorisation confirmation studies or real-world data generation as specified on a case by case basis. Conditional authorisation schemes including authorisation under exceptional circumstances, adaptive licensing, priority medicines (PRIME) scheme, and early access to medicines scheme (EAMS) provide supportive regulatory environments to enable expedited market access and regulatory support. Hospital exemption (HE) and the 'specials' scheme offer unlicensed product use in exceptional cases. Accelerated market access can provide cash flow opportunities but may complicate market access and reimbursement negotiations. Advanced therapies are a diverse population of medicines with divergent needs, but generally involve substantial product development and four key milestones.

Advanced therapies can be difficult to define, particularly cell-based products, and this has implications on both clinical development and manufacturing. Fully elucidating a product's mechanism of action mitigates many development risks, and contributes to efforts in characterising the product, including through the development of disease models or other functional assays. Valid product definition assays should be developed at preclinical stage and later optimised, as full characterisation also informs the clinical development strategy. Clinical trials should in turn be optimised to de-risk regulatory proceedings, optimise healthcare economics, and expand market access.

2.1. Typical stages of cell therapy development

The high level of diversity in advanced therapy design means that no two development pathways will experience the same overall process or set of specific challenges. There are however underlying principles and themes, broadly separated into four key value inflections: licensing or identification of the technology and initial fundraising round; submission of phase I regulatory application (e.g. IND); good manufacturing practice (GMP) validation and initial manufacture for clinical trials; and pre-approval inspection for a license to manufacture the product to supply the market.

Expert Insight

Thomas Heathman MEng, Ph.D.

*Business Leader, Technology Development,
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PCT Cell Therapy Services, LLC

A Hitachi Group Company

In general, the typical process for developing a cell therapy includes the following steps and key milestones:

- Identification of target disease and new cell-based therapy method of treatment
- Scientific discovery and early research and development (including pre-clinical animal studies and first in man studies)
- Milestone #1: Licensing of technology and initial round of funding for product development
- Establishment of clinical partners, supply chain and logistics to begin clinical development

- Manufacturing development to prepare for Phase I (establish Quality Target Product Profile (QTPP), Critical-to-quality Attributes (CQAs) and apply Development-by-Design (DbD) methodology as roadmap for future manufacturing development)
 - Process Development to establish a robust and compliant process
 - Analytical Development to establish compliant quality assays for QTPP and CQAs
- Technology transfer of development process into clinical manufacturing under full GMP conditions
 - Establish documentation (SOPs, batch records, etc.)
 - Complete Personnel Training (Quality control, quality assurance and operations)
 - Qualification of the equipment, process and analytics
 - Stability and shipping studies for ensure successful and compliant logistics
- Milestone #2: Submission of regulatory documentation for Phase I (e.g. IND in the US)
- Milestone #3: GMP manufacture for Phase I and first patient treatment
- Further manufacturing development for the next clinical phase. The pathway depends on the nature of the therapy and the regulatory territory (e.g. US, EU or Japan).
- Once sufficient safety and efficacy data has been obtained during the phased clinical trials, file for Biological License Application (BLA) (US only)
- Milestone #4: Pre-Approval Inspection (PAI) to enable commercial manufacturing and distribution of the cell therapy product.

2.2. EU regulatory route to market

In the EU Directive 2001/83/EC1, as implemented nationally, requires that ATMPs are authorised by the EMA before they can be marketed. The centralised authorisation procedure is the mandatory mechanism for ATMPs, through which products are authorised for sale within all EU member states simultaneously. Application is assessed is made on the merit of a MAA, a large document submitted by the technology developer, which provides evidence of a product's characteristics, intended use, and safety and efficacy profile as evidenced through clinical trial. Upon submission to the EMA, the Committee for Medicinal Products for Human Use (CHMP) assess the document through their relevant working parties, undertaking a risk/benefit analysis of the data presented to form an 'Scientific Opinion'. The CHMP decision can be either positive, negative, conditionally positive with obligations, or positive under exceptional circumstances.³³ The CHMP scientific opinion is passed to the European Commission (EC), who then have 67 days to consider the opinion and either issue an authorisation or rejection accordingly.

In the case of a refusal for market authorisation feedback is usually provided to the applicant whereupon they may modify and resubmit their MAA. Authorisations by the EMA generally take longer than by the FDA due to the 'stop clock' period at day 120 of the review process, allowing the applicant time to prepare answers to any questions raised by the EMA. The entire approval process can take up to 277 days. Granted MAs are valid for 5 years when unconditional and 1 year when conditional, after which they must be renewed. The EMA provides extensive guidance on the MAA procedure, available on their website (<http://www.ema.europa.eu>).

2.2.1. Conditional approval

EU, US, Japanese and South Korean regulatory authorities may offer conditional approvals for advanced therapies (subject to their specific definitions) in specific circumstances. South Korea was the first country to offer conditional approvals in 2001, although not specifically for advanced therapies. The Korea Food and Drug Administration (KFDA) has authorised 18

cell products since 2001, and most of them conditionally.³⁴ Japan was the second country to adopt conditional approval legislation, with the 2013 Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMDA).³⁵ Through the Japanese system, medicines which have proven safety and probable efficacy could be authorised following phase II-type efficacy data, therefore bypassing large-scale phase III efficacy confirmation studies. Developers would instead be mandated to gather real-world patient efficacy data to satisfy the conditions of approval, the exact details and demands of which vary on a case-by-case basis. Although this was not the first conditional approval law in place, the move generated substantial attention and conflict, with some commentators critical of Japan 'lowering the bar' for market approval and thereby jeopardising patient safety.³⁶ The move was deemed innovative and pioneering by many more, giving greater precedence for conditional approvals systems, and the EU and US have since followed suit.^{37,38}

Conditional MAs are not available for every therapeutic. In the EU, a product must meet the following conditions to be eligible:³⁹

1. The benefit/risk balance is positive
2. It is likely that comprehensive clinical data will be provided following authorisation
3. Unmet medical needs will be fulfilled
4. Benefit to public health of immediate availability outweighs risks that additional data are still required

Successful applicants may be obliged to specific activities following authorisation, including the completion of any ongoing or planned studies to a satisfactory quality and within a reasonable timeframe, and a demonstration of the feasibility and quality of any necessary additional studies to be performed.⁴⁰ The nature of the approval, any conditions, and their timeframe, become publicly available information, and financial penalties can be imposed in the case of infringement of any specific obligations. Conditional MAs are valid for 1 year and may be renewed through re-application, at which point the EMA will review the evidence of benefit/risk and the status of any specific obligations. The applicant is obliged to provide an interim status report of any specific obligations upon renewal, including relevant data, and the status or outcome of any other data submitted since conditional MA. Where specific obligations do not require comparable data, a periodic safety update report (PSUR) should be submitted. The CHMP will then assess the renewal application within 90 days and confirm the benefit/risk balance, or recommend regulatory actions such as modifications of the authorisation conditions. Upon fulfilment of all specific obligations, the conditional MA may be converted to a full MA.

There were 30 successful conditional MAs and 22 unsuccessful applications to the EMA between January 2006 and June 2016 across all therapy types.⁴¹ 11 of the successful 30 were later converted into full ('standard') market authorisations, 2 were withdrawn for commercial reasons, and 17 are still conditionally approved. Approved therapies were mostly indicated for oncology, infectious disease, neurology, and ophthalmology, with unsuccessful applications indicated for a broader range of conditions. 14 of the 30 (47%) applications were approved as originally proposed by the applicant, without modification by the EMA.

2.2.2. MA under Exceptional Circumstances

Applicants who are unable to provide comprehensive clinical data on their medicine because of the rarity of the disease, the present limitations of scientific knowledge, or ethical restraints, may be authorised under 'Exceptional Circumstances' (as opined by the CHMP).⁴² This mechanism is a form of conditional authorisation and is subject to the same specific

post-authorisation procedures or obligations as any other conditional authorisation, with a focus on safety studies. A granted license is valid for 5 years and renewable annually through a reassessment of the benefit-risk balance conducted by the CHMP.

2.2.3. Adaptive licensing

The adaptive licensing pathway offered by the EMA is designed for treatments in high medical need areas where collection of data via traditional routes is difficult and where large clinical trials would expose patients who are unlikely to benefit from the medicine to unnecessary risk. The pathway allows treatments to be licensed for a restricted patient population, and through the collection of real-world data to supplement clinical trials, gradually expanded to fulfil the needs of both regulators and HTA bodies to justify treatment in additional populations. Its key feature is multi-stakeholder engagement to provide feedback on a prospectively planned real-world data collection strategies, involving multiple regulatory bodies, HTA authorities, and patient representatives. Payers may also be involved on an ad-hoc basis to facilitate HTAs. Technology developers wishing to engage with adaptive licensing protocols should engage with the EMA at least by first-in-man stage to ensure the design of clinical studies optimally addresses regulatory and HTA needs.

2.2.4. Priority Medicines (PRIME) scheme

The PRIME scheme was launched by the EMA to expedite access to promising medicines where a major public health interest presents significant unmet medical need. Through enhanced scientific and regulatory support, the voluntary scheme aims to optimise the generation of robust clinical data and accelerate authorisation application assessments. Major benefits of PRIME registration are:

- The EMA appoints a rapporteur from the Committee for Advanced Therapies (CAT) or CHMP who becomes the contact point for the developer, responsible for coordinating all regulatory support offered throughout the scheme
- A 'kick-off meeting' is organised between the technology developer and EMA representatives, including the rapporteur, a multidisciplinary expert group from relevant committees, CHMP working parties, and other EMA staff. The meeting provides preliminary guidance on the overall development plan, discusses key development steps of future advice, and opens the discussion on the recommended regulatory strategy
- Scientific advice is provided on the overall development plan, at major milestones, and on key issues, with the possibility to involve additional stakeholders
- The potential for accelerated assessment at the time of MAA is confirmed

Application to PRIME requires the identification of the unmet medical need and an assessment of its magnitude, clinical evidence of the product's ability to deliver on that need, plus an assessment of clinical outcome relevance. Eight ATMPs have received PRIME designation to date (Table 5), evidencing its value. PRIME has some characteristics in common with adaptive licensing but differs in its intention and specific requirements (Table 4)

	PRIME	Adaptive pathways
Conceptual framework	Early and enhanced scientific and regulatory support to medicine developers to optimise the generation of robust data and enable accelerated assessment.	Scientific concept of medicines development and data generation with lifespan approach, which relies on the targeted development of a medicine in a restricted patient population as an initial step and the progressive gathering of evidence through real-life data and prospectively planned clinical trials with the view to expand the patient population in which the medicine can be used. Level of evidence addresses not only the needs of regulators, but of HTA bodies as well.
Which medicines are eligible	Accelerated assessment criteria, i.e. Medicinal products of a major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation (unmet medical need).	Medicines (primarily intended for unmet medical need), with: <ul style="list-style-type: none"> • An iterative development plan (either gradual expansion of the target population or progressive reduction of uncertainty after initial authorisation); • An iterative development plan (either gradual expansion of the target population or progressive reduction of uncertainty after initial authorisation); • Ability to engage HTA bodies and other stakeholders; • Use of real-world data to supplement clinical trials
Which medicines are not eligible	Medicines which are already authorised. Medicines which are not addressing an unmet medical need.	Medicines that do not fulfil the criteria above
Key features	Identify potential for accelerated assessment earlier in development. Early Rapporteur appointment. Reinforced scientific and regulatory support from the SAWP/ CHMP and EMA. Dedicated contact point within EMA	Early multi-stakeholder dialogue with feedback on suitability of a prospectively planned, adaptive approach and strategic collection and use of real-world data.
Who is involved (stakeholders)	Multidisciplinary expertise from regulators. Relevant stakeholder involvement (eg HTA, patients) will be considered on a case by case basis, depending on the specific needs of the development.	Multidisciplinary expertise from regulators, HTA, patients. Potential involvement of payers on an ad-hoc basis.
Post-authorisation implications	On a case by case basis, depending on the authorisation route and development plan followed	Yes, in view of real-world data acquisition requirement.
How to apply	Submit request supported by justification on the claim that the medicinal product addresses to a significant extent the unmet medical needs.	Applicants are invited to contact EMA for advice on the content and suitability of their request to be considered.
Most appropriate time to request	At least first in man. During the development, based on preliminary clinical evidence (proof of concept). Exceptionally earlier access to SMEs and academia (proof of principle).	At least first in man. Early stages of development offer the highest opportunity for a meaningful dialogue and input from regulators, HTAs and patients.

Table 4: Key differences between PRIME and adaptive pathways in the EU. Source: Daniel Rabbie, Regulatory Affairs Manager, Cell and Gene Therapy Catapult.

One of the most common reasons for application failure is a lack of paediatric investigation plan (PIP), as described in Regulation (EC) No 1901/2006. The PIP is a necessary part of PRIME application and ensures the proper consideration of medicine suitability for patients between 0-18 years. Meeting the data requirements of a PIP may require modification to clinical trial design.

Company	Product	Indication	Date granted
Kite Pharma	KTE-C19 CAR-T	DLBCL	1 st June 2016
BioMarin	BMN270 gene therapy	Haemophilia A	1 st February 2017
UniQure	AMT-060 gene therapy	Haemophilia B	25 th April 2017
Spark/Pfizer	SPK-9001 gene therapy	Haemophilia B	2 nd March 2017
bluebird bio	LentiGlobin gene therapy	β -thalassaemia	21 st September 2016
AveXis	AVXS-101 gene therapy	Spinal muscular atrophy type 1	31 st January 2017
Adaptimmune	SPEAR TCR therapy	Synovial sarcoma	28 th July 2016
Juno/Celgene	JCAR017 CAR-T	r/r DLBCL	20 th December 2016

Table 5: Companies and ATMPs which have been accepted into the PRIME scheme. Source: Company press releases.

2.2.5. Early Access to Medicines Scheme (EAMS)

National level acceleration schemes also exist for early patient access. Similarly to PRIME but UK-specific, EAMS aims to deliver on urgent unmet medical need by offering early access to unauthorised medicines. Unlike PRIME, it is aimed at later stage medicines, and does not contribute an equivalent level of regulatory support. The scheme is intended for medicines that have completed phase III trials (possibly extending to phase II medicines in exceptional circumstances) that have promising innovative medicine (PIM) designation. PIM designation requires the following criteria:

1. The indication has high unmet need, and is a life threatening or seriously debilitating condition
2. The product is likely to offer significant advantages over methods already available in the UK
3. Positive benefit/risk ratio
4. The product is manufactured to GMP standards

Upon successful application to EAMS, medicinal products are provided to the NHS free of charge until marketing authorisation is granted. Following authorisation, reimbursement will be subject to the same HTA appraisal process as non-EAMS products. The scheme is not widely used as developers are not permitted to charge for the product through EAMS.

2.2.6. Hospital Exemption and Specials scheme

Hospital Exemption (HE) provides a legal mechanism by which unlicensed medicinal products may be provided to individual patients on a non-routine basis following a specific request from the attending physician and when the product meets GMP quality, pharmacovigilance, and traceability requirements. The legislation came into force in August 2010 under Article 3(7) of Directive 2001/83/EC. In 2012, there were 18 ATMPs authorised for manufacture and supply under HE, the majority through academia.⁴³

The UK 'Specials' scheme, under Article 5 (1) of Directive 2001/83/EC, encompasses similar situations as to HE, but is legally distinct and has fundamental differences (Table 6). The UK Specials scheme permits doctors and certain other prescribers to commission an unlicensed medicinal product to meet the special needs of an individual patient.⁴⁴ National level regulators (the MHRA in the UK) are the responsible authorities for both schemes. MHRA

guidance on differentiating between the two schemes is available at <https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing>.

The HE and Specials schemes provide an opportunity for advanced therapies to demonstrate clinical proof-of-concept before undergoing formal trials. Early development in clinical academic centres may offer a particularly good opportunity for application through HE, Specials, or other similar schemes.

Hospital exemption	Specials scheme
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a "non- routine basis"	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product)
The ATMP must be used in a hospital	There is no stipulation as to location

Table 6: Summary of the main differences in scope between the HE scheme and Specials scheme.
Source: 'Guidance on the UK's arrangements under the hospital exemption scheme' (MHRA).

2.3. US regulatory route to market

The FDA regulates all testing, manufacture, and marketing of advanced therapies intended to treat human disease under the Federal Food, Drug, and Cosmetic Act (FDCA).⁴⁵ Biological products are also regulated under the Public Health Service Act (PHSA), and depending on the manufacturing techniques used, intended application, and primary mode of action, human tissue and cell-based products (HTCPs) may also meet the definition of a drug product, medical device, combination drug/device, or biological product/device.

Biological products are licensed for marketing based on the submission of a BLA, a dossier of all clinical data generated to support the application similar to the EMA MAA. Most advanced therapies are also classified as drugs, as per the definition in 21 U.S.C. § 321(g)(1): "(a) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and (b) articles (other than food) intended to affect the structure or any function of the body of man or other animals". This requires the filing of an investigational new drug (IND) application prior to clinical trial initiation, and the subsequent manufacture of the drug according to cGMP practices.

A second legislative route to market exists for HTCPs deemed 'low risk'. Products that fall under section 361 of the PHSA (often referred to as 'section 361 products') are subject only to registration, donor screening and testing, and good tissue practice requirements, excluding the host of legislative demands associated with medicinal products falling under the FDCA, including the need for a BLA. To qualify for this designation, HTCPs must fall within specific legal definitions, as set out at 21 CFR § 1271.10 and defined below:

- The HTCP is minimally manipulated;
- The HTCP is intended for homologous use only (that is, only for the replacement or supplementation of a recipient's cells or tissues with an HTCP that performs the same basic function or functions in the recipient as in the donor), as reflected by the labelling, advertising, or other indications of the manufacturer's objective intent;

- The manufacture of the HTCP does not involve the combination of the cell or tissue component with a drug or a device, except for a sterilising, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the HTCP; **and**
- **either** the HTCP does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function;
- **or** the HTCP has a systemic effect or is dependent on the metabolic activity of living cells for its primary function; **and**:
 - is for autologous use, or
 - is for allogeneic use in a first-degree or second-degree blood relative, or
 - is for reproductive use

The entire HTCP regulatory scheme is codified at 21 CFR Part 1271. Regulation solely under Section 361 involves substantially less demanding regulatory requirements, but manufacturers are restricted in their liberty to advertise medicinal effect claims which have not been substantiated through formal clinical trials. Despite lower regulatory barriers, section 361 regulation are limited in their marketability and therefore may face higher barriers to commercial success.

2.3.1. 21st Century Cures Act

The US 21st Century Cures Act was enacted in December 2016, and amongst other legislative changes, allows companies to apply to the FDA to delegate their products as a 'regenerative advanced therapy' (RAT), a classification bringing several regulatory incentives.⁴⁶ According to H.R.34 - 21st Century Cures Act Section 3033, RATs must meet the following definition for eligibility:

- a) Is a regenerative medicine therapy (cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products);
- b) Is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
- c) Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

According to the definitions of the Act, cellular immunotherapies such as CAR-Ts can fall within RAT designation, despite the therapies not being strictly regenerative in nature.⁴⁷ Products regulated solely under section 361 of the PHSA are explicitly excluded. Upon designation, RAT status offers:⁴⁸

- Greater interaction with the FDA to expedite development and review, as with breakthrough designation therapies
- Early discussions with the FDA on the validity of potential surrogate or intermediate endpoint to support accelerated approval
- Possible eligibility for priority review
- Possible eligibility for accelerated approval as agreed upon during development, and pending agreement on:
 - The design of surrogate or intermediary endpoints likely to predict long-term clinical benefit
 - Reliance on data obtained from a meaningful number of sites, including through expansion to additional sites

Accelerated approval may be granted conditionally, following which one or more of the following requirements may require fulfilment:

- Post-approval clinical studies
- The submission of clinical evidence, clinical studies, patient registries, or other sources of real world evidence such as electronic health records
- The collection of larger confirmatory data sets as agreed upon during product development
- Post-approval monitoring of all patients treated with such therapy prior to approval of the therapy

The Act allows for conditional market approval for RAT products based on intermediate or surrogate trial endpoints that predict long-term clinical benefit from shorter-term clinical data. This does not undermine the need for phase III trials, but may mean that authorisation is possible from smaller and/or shorter clinical trials. Despite potentially lowering development risk, this process may present complications to market access and pricing and reimbursement (P&R) as explored in Section 2.4 'Implications of conditional market approval on ROI'.

In the US, four programs exist to expedite drug access in cases of serious unmet need in the treatment of serious or life-threatening conditions.⁴⁹ A therapy may be eligible for more than one pathway. For guidance on differentiating between programs, including a description of qualifying criteria, see FDA 'Guidance for Industry: *Expedited Programs for Serious Conditions- Drugs and Biologics*' (2014).

2.3.2. Breakthrough Therapy designation

Company	Product	Indication	Date awarded
Novartis	CTL019 CAR-T	r/r DLBCL	18 th April 2017
UniQure	AMT-060 gene therapy	Haemophilia B	30 th January 2017
Juno	JCAR017 CAR-T	r/r DLBCL	20 th December 2016
Kite Pharma	KTE-C19 CAR-T	NHL	7 th December 2016
Gamida	NiCord HSCT support	Haematological malignancies	11 th October 2016
AveXis	AVXS-101 gene therapy	Spinal muscular atrophy	20 th July 2016
ATARA Biotherapeutics	Cytotoxic T lymphocytes	CMV infection	2 nd March 2015
bluebird bio	LentiGlobin gene therapy	B-thalassemia	2 nd February 2015
Novartis	CTL019 CAR-T	r/r ALL	7 th July 2014
TiGenix	ChondroCelect	Cartilage repair	June 2012

Table 7: Non-exhaustive list of advanced therapies with breakthrough status. DLBCL= Diffuse large B-cell lymphoma; NHL= Non-Hodgkin lymphoma; r/r= relapsed/refractory; ALL= Acute lymphoblastic leukaemia; CMV= Cytomegalovirus. Source: Company press releases.

The FDA Safety and Innovation Act was signed in July 2012 and provides a pathway by which medicines deemed 'breakthrough therapies' can benefit from expedited development, with BLA application review in 60 days or less. Breakthrough therapies can also be licensed for marketing based on preliminary clinical evidence of safety and efficacy, with ongoing

'rolling review' to confirm predicted efficacy data. The FDA offers support in the design of any additional clinical trials required for market authorisation. The program is widely used by advanced therapy developers (Table 7) as it allows for relatively accessible early sales and accelerated cash flow.

2.3.3. Fast Track designation

Fast track designation offers supportive meetings with the FDA in preparation for IND filing, designed to discuss phase I and phase II clinical trial design, dose-response concerns, biomarker use, and other issues as appropriate. The designation also allows the FDA to review materials of a MA before submission of the complete application. The program is designed to support and expedite clinical development for promising therapies. To date, the majority of advanced therapies using Fast Track designation have been gene therapies (Table 8).

Company	Product	Indication	Date
Caladrius	CLBS03 T-reg therapy	Type 1 Diabetes	July 2016
Aboena	ABO-102 gene therapy	Sanfillipo Syndrome Type A	October 2016
Angionetics	Generx gene therapy	Chronic angina	February 2017
VM BioPharma	VM202 gene therapy	Amyotrophic lateral sclerosis	May 2016
Sangamo	SB-FIX gene therapy	Haemophilia B	May 2017
Catabasis Pharma	CAT-1004 gene therapy	Duchenne muscular dystrophy	July 2015
XyloCor Therapeutics	XC001 gene therapy	Chronic angina	May 2017

Table 8: Non-exhaustive list of advanced therapy products with fast track designation. Source: Company press releases.

2.3.4. Accelerated Approval

The accelerated approval pathway is designed specifically to deliver upon serious or life threatening unmet need, and is comparable to the EMA conditional approval mechanism. Therapeutics may undergo accelerated approval where surrogate endpoints are reasonably likely to predict clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the lack of alternative treatments. The accelerated approval pathway is used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. Therapies within this program are subject to post-authorisation confirmatory trials to verify and further describe the anticipated clinical benefit of the drug, as specified in Section 506(c)(2)(A) of the FDCA. The pathway is similar to that of breakthrough therapy designation but refers specifically to the legal status of market authorisation, and accounts for predictive and surrogate clinical data.

2.3.5. Priority Review

Priority review accelerates the review period for BLA or NDA applications to within 60 days of submission, with a shorter clock for review of marketing authorisation applications (6 months compared to 10 months for standard review). Drugs which treat serious conditions and if approved would provide a significant improvement in safety or efficacy are eligible for priority review. Generally speaking, any drugs eligible for accelerated approval, breakthrough therapy status, or fast track designation, are also applicable for priority review.

2.4. Implications of conditional market approval on ROI

Conditional market authorisations such as through RAT designation in the US, or PRIME, EAMS, or adaptive licensing schemes in the EU represent an opportunity to both de-risk and accelerate the route to market, providing investors with the chance to expedite cash flow and ROI. However, investors should be cautious of reaching the market prematurely and without a robust body of clinical data upon which to enter reimbursement negotiations. Regulatory authorisation is not the sole element of achieving market access goals; arguably more demanding is successfully mitigating P&R risk. Negotiating a sufficiently high price point to recover development costs within the investment horizon is crucial to achieving ROI, and in the case of high-price/high-reward therapies (e.g. 'curative' gene therapies), reimbursement infrastructure may not be appropriately structured to reimburse the therapy. See Section 3.6 'Unique reimbursement challenges of conditionally approved medicines' for further exploration of this issue.

Conditional approval usually mandates that every treated patient is followed up sufficiently to monitor long-term treatment effects. How long this period is depends on the product and its likely persistence in the body; for example, MSCs are generally perceived to clear relatively quickly from the body, with around 1% persistence after 7 days.^{50,51} In this case, patient follow-up is usually for around 1 year. Gene therapies permanently alter the genome of a subset of patient's cells and are likely to require much more substantial follow-up, perhaps in some cases even for the lifetime of the patient. This would create huge demands for the technology developer if they were to administer gene therapies on a conditional market authorisation.

Expert Insight

Dr. Tim Farries

Director of Regulatory Affairs, Gene and Cell Therapies at ERA Consulting



Although it is too early to see impact from the latest initiatives, there is enough evidence from existing schemes that there will be a positive benefit for commercialisation of cell and gene therapy. The first conditional approvals for regenerative medicines have been issued under the PMD Act and, with the high reimbursement received, this is also drawing Western developers to prioritise Japan for market access. Developers of advanced therapies that have received the US breakthrough and the EU PRIME designations have reported that a particular value is the support in the design of registration studies that would be acceptable to the authorities for registration.

Currently, within the EU, most of the advanced therapy products on the market are available only locally through various national provisions, such as hospital exemption. It is widely perceived that the regulatory system needs to do more to encourage EU-wide market authorisations. In this context, it is notable that the first gene therapy (Glybera) was approved under exceptional circumstances, and the first approved stem-cell containing product (Holoclar) was granted conditional marketing authorization (as was Zalmoxis). Accelerated approval could therefore be a major factor for supporting more widespread commercialisation.

P&R negotiations must be undertaken from a position of maximum possible strength to justify a sufficiently high pricing point for commercial success. The data requirements for successful pricing an advanced therapy may be substantially higher than for achieving market

authorisation. Entering P&R negotiations with minimal clinical data that does not capture the true value of the therapy can result in a price point lower than that which may be otherwise achieved. There is therefore a strategic decision to be made around whether conditional approval is right for any one product, or whether extended and more comprehensive direct pre-authorisation clinical data would be advantageous.

2.5. Understanding and characterising cellular products

Characterising advanced therapies through extensive basic research, and developing a deep biological understanding of a product's MoA, is crucial to commercial success. The degree of understanding around the biology of the product either directly or indirectly informs every other risk factor along the path to commercial success, from supply chain management, to clinical trial design, to P&R and market access. Dedicating resources to developing this understanding and undertaking subsequent early-stage product development can substantially de-risk many of the late-stage barriers which would otherwise demand potentially insurmountable levels of time and capital.

Expert Insight

Dr. Mark Lowdell

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The complexity of ATMPs and the corresponding challenges in defining the underlying biological mechanisms of action often provide tempting reasons to develop them as medicines without dissecting their mode of action to the degree of conventional pharmaceuticals or biologics.

This facilitates early entry into trials, especially by academic investigators, but creates challenges downstream when the critical characteristics of the product are needed to form the product description. Understanding how the product works allows the developer to create in-process and release tests which define the product and this definition can be independent of the product manufacturing process – i.e. the process no longer defines the product. This allows process development, scale-up or scale-out and technology transfer to other manufacturing sites during the product lifetime without bridging studies. Most importantly it allows the rapid transfer from a small-scale process fit for early clinical trials into one fit for phase III and marketing authorisation application.

Finally, understanding the mode of action allows informed discussions with regulatory agencies about likely risk factors and thus facilitates development of these complex and expensive therapies into lower risk disease group than those treated in phase I and II trials and even moves into new diseases – increasing the ability to determine the likely potential of the new therapy.

In contrast to small molecules and biologics which can be defined by their atomic, chemical or amino acid composition, the complexity of cell therapies make them particularly difficult to accurately characterise. Cell populations are traditionally defined by surface markers and adherence properties, but a number of different modalities including gene expression, morphology, viability, biomass, and functional characteristics such as metabolic or immunologic properties may represent applicable additions in supporting a product TPP. Testing is often direct, e.g. through flow cytometry/FACS and gene expression microarrays but may also be inferential, e.g. cell culture monitoring glucose levels to indicate cell count or

measuring pH to infer metabolic function. Factors deemed critical to the quality of an advanced therapy constitute the critical quality attributes (CQAs). Some of these parameters may be shared with the TPP, which specifies additional characteristics including that of a product's intended application, market, and other elements of design or usage.

2.5.1. Disease modelling

Developing valid and accurate disease models at an early stage has a crucial and often overlooked role in de-risking advanced therapy development. Representative disease models enable direct and empirical understandings of a therapeutics expected MoA, safety, efficacy, and potency profiles, which in turn inform a valid CQA profile and enhance product development and optimisation. These processes may also contribute to a battery of functional assays which can be leveraged in comparability studies and/or batch release. The EMA, FDA and national level regulators can provide guidance on the most appropriate disease model, or where there is no relevant option, assist in the development of a novel solution.⁵²⁻⁵⁴ Technology developers must engage directly with regulators to agree upon the best model to fulfil regulatory requirements through a two-way discussion.

Several disease model options may exist and varying model types can have differing niche applications. 'Gold standard' models are those most widely-used and well characterised within the research community and are generally pre-validated by regulators. Due to the limitations of comparing animal with human physiology some indications do not have a gold standard, particularly in neuronal diseases such as Alzheimer's and Parkinson's, or in sparsely studied indications. In such a case, technology developers must work with support from regulatory authorities to develop new models. These may be animal models (murine, canine, ovine, porcine, and primate are most widely used, each with significantly differing cost requirements) but in some cases may be *in vitro* tissue models. Regulators are increasingly encouraging the use of *in vitro* models in an effort to reduce the number of animals used in research, and this modality is generally cheaper, more flexible, amenable to higher throughput, and easier to genetically modify. *In silico* modelling can also play a role in modelling and even product design; Massachusetts Eye and Ear, the world's largest vision and hearing research centre, used *in silico* methods to design a series of synthetic AAV vectors for gene therapy.⁵⁵ *In silico* product development requires deep quantitative understanding and sufficiently scaled data sets, and often a combination of complementary models is optimal to fulfil various testing and development needs, reflecting the diversity of product characteristics that require testing and limited applications of each individual modelling methodology.

2.5.2. Optimising preclinical research

According to FDA guidance on preclinical assessment of investigational advanced therapies, the overall goals of preclinical research include:^{56,57}

1. Establishment of biological plausibility.
2. Identification of biologically active dose levels.
3. Selection of potential starting dose level, dose-escalation schedule, and dosing regimen for clinical trials.
4. Establishment of feasibility and reasonable safety of the investigational product's proposed clinical route of administration.
5. Support of patient eligibility criteria.
6. Identification of physiologic parameters that can guide clinical monitoring.

7. Identification of potential public health risks (e.g., to the general public, caregivers, family members, close contacts (for example co-workers), and intimate contacts).

For advanced therapies, in particular cell-based therapies, preclinical development also offers an opportunity to mitigate downstream uncertainty through optimising and validating a scalable manufacturing process. The significant demands of time and capital expenditure required to undertake process modifications and the associated comparability studies in late clinical development may necessitate investing in extended preclinical or early clinical bioprocess optimisation. Developing a comprehensive understanding of the product's intrinsic biology and MoA is an essential early stage priority in this pursuit; understandings generated through preclinical development inform the design of critical process parameters (CPPs), the accurate and comprehensive specification of which are critical to a robust manufacturing system and supply chain.

In the US, preclinical research also informs the design of IND application. Legislation around IND filing and associated preclinical research requirements can be found in IND Regulations 21 CFR Part 312.

2.6. Clinical trial design in advanced therapies

Small molecules and similar therapeutic agents typically adhere to the traditional three-phase clinical testing process. This begins with small-scale trials testing a range of dosages in healthy volunteers to establish the highest tolerated dose (phase I), before moving into early efficacy studies for dose-response testing and optimisation (phase II), and finally, undergoing larger clinical trials designed to confirm and fully characterise product efficacy (phase III). Phase III trials provide the basis for cost-effectiveness analysis and subsequent market authorisation, but phase II and I data may be included. Cell and gene therapies do not fit precisely into this framework, and novel clinical development pipelines are often necessary. Because of the possibility for long-term persistence of cell and gene therapies and possible related toxicities, their risk profile in phase I stage makes testing in healthy volunteers unjustifiable. Early-stage clinical trials are therefore usually in a similar patient population as that intended to be the eventual target market, and trials often incorporate efficacy within secondary endpoints, resulting in phase I/II classification. The diversity of advanced therapies means there is no one-size-fits-all approach; this blurring of traditional trial phases complicates the clinical development process and requires that technology developers engage with regulators to ratify their clinical development rationale and design relevant and validated clinical trials.

The rarity of the disease, degree of benefit predicted, and anticipated safety profile will affect the number of participants and other design aspects of each trial. While small molecule drugs offering incremental gains to large markets regularly recruit hundreds of patients across several trials of all phases prior to MAA submission, this may be drastically different for 'curative' therapies in small markets. Glybera (an orphan status gene therapy) was approved following two clinical trials totalling only 19 subjects (plus a retrospective trial on 17 of the previous subjects).⁵⁸

2.6.1. Understanding clinical data

Critically assessing clinical data is essential when navigating the advanced therapy field. Product developers, especially when publicly traded, will spin clinical results to appear as successful as possible in order to support investment and/or stock value. Company stock often fluctuates following major clinical data announcements and the direction of movement

is not always clear cut; at the start of December 2015, Juno Therapeutics (a major CAR-T company) announced a series of positive clinical data results, yet company stock fell by 60% over the following two months. Investors were anticipating this data and its value was therefore likely to already be factored in to the stock price. What was not expected, and likely caused the slide in stock price, was evidence of significant side effects.

Understanding the science behind a product can represent significant opportunities for private equity investors. Through a single investment of \$8 million by Oxford Bioscience Partners, SQZ Biotech (an MIT spinout lead by Robert Langer) attracted a \$500 million deal from Roche and consolidated itself as a major player in antigen presentation platform technologies without generating any clinical data.⁵⁹ Understanding the data behind company valuation is crucial to making investment decisions in both private and public arenas.

2.6.1. Optimising clinical trial design for regulation and market access

The specific design of clinical trials can have a substantial impact on clinical development risk and market potential, and can therefore heavily implicate ROI. Medicinal products are granted a market license only for the precise patient population described by the inclusion and exclusion criteria of pivotal clinical trials upon which the licensing decision is made. Other markets may be later expanded into through additional clinical studies.

An optimal strategy for clinical trial design may be to structure early-stage clinical trials to maximise the chance of trial success, while loosening inclusion criteria for expanded patient populations in pivotal late-stage trials. A balance must be struck between designing sufficiently broad criteria so as to maximise market potential, while not unnecessarily exposing the trial to risk by including patients most unlikely to recover. The ethical implications of clinical trial design are unavoidable; excluding the most unwell patients may be the lowest risk course of action for the company, but is at the potentially deadly cost of those individuals most in need of greater therapeutic options. The wording of patient population inclusion criteria can also affect how clinical trials are perceived by the regulators when it comes to considering a MAA, particularly where clinical gains are only marginal and there is no clear-cut evidence of substantial gains in clinical effectiveness over the comparator.

Many advanced therapies involve complex administration protocols which may require specialist training. Implementing a therapy into clinical practice within any one site can be demanding and potentially prohibitive to market access. Technology developers may therefore wish to undertake clinical trials in sites which later go on to become specialist centres of administration once the product receives marketing authorisation. Strimvelis provides a good example of this strategy, where GSK's investigation sites in Milan and Jerusalem became specific administration centres to which patients must travel to receive the therapy.

BUILDING VALUE FOR CELL AND GENE THERAPIES AND ESTABLISHING MARKET ACCESS PATHWAYS

Chapter 3

3.1. Summary of Chapter 3

Cost, price and value are key principles to understand in pricing advanced therapies. Pricing should predominantly consider healthcare economics, and in some cases integrate elements of cost. Pricing and reimbursement (P&R) are major challenges for advanced therapies owing to their high cost/high reward profile which can present difficulties to buyers. Drug pricing must be negotiated on a national level and public healthcare authorities have differing decision-making frameworks. Many countries also offer autonomy on a regional level for the implementation of new drugs. In the UK P&R assessments are undertaken by NICE, considering cost-effectiveness as a function of quality-adjusted gain to life expectancy associated with therapy administration, preferably in the context of a relevant comparator. Long-term clinical data and indirect healthcare cost requirement analysis is key to fully capturing the value of 'curative' treatments, in turn essential to justify the high price required to recover development costs. Direct data is considered of the highest quality but often technology developers opt for extrapolated models based on shorter term data. Reimbursement appraisals take into consideration the risk of a therapeutic failing to function as intended, based on the robustness of clinical data. Even therapies proven to be cost-effective and technically eligible for reimbursement may not be bought as high prices could present a barrier to adoption and (due to their structure) reimbursement funds may not be able to afford or effectively reimburse clinicians for unusually expensive products. Novel reimbursement mechanisms have been widely considered but so far not adopted, with buyers previously expressing preference for traditional upfront payments. Gene therapies particularly exemplify this dynamic. The private insurance reimbursement framework in the US presents additional complications.

Conditionally approved medicines can access the market faster but the relatively lower volume of clinical data associated with conditional approval may undermine market pricing. Price points justifiable by the level of data required for conditional MA may not reflect the true value of the product, and elevating prices may frustrate market penetration efforts. Various opportunities exist to mitigate this risk, including cost reduction strategies, achieving orphan status designation, engaging with buyers to develop novel reimbursement models, negotiating lower discount ratings, leveraging patient access schemes (PASs), and entering markets with low levels of competition. The National Institute for Clinical Excellence (NICE) have published a mock appraisal for a fictitious CAR-T product, which can serve as a reference point for stakeholders developing such products with similar pricing dynamics. Further to P&R, successful market access requires consideration of ease of use, degree of change to standard operating procedure, and subjective user perceptions.

3.2. Cost, price and value

The meanings of cost, price and value are subtle but important to differentiate. In the context of P&R: cost is the amount required to manufacture and deliver the therapy; price is the amount reimbursed for the product; and value is what the healthcare provider perceives as the worth of the therapy. These factors are to some extent positively correlated but price and cost should be largely divorced.

Cost can be divided into operational cost and development cost. Operational cost is dependent on manufacturing, supply chain, delivery, and ongoing expenses such as staff salaries, while development costs refer to expenses incurred throughout product development and include R&D, clinical testing, and regulatory filings. Operational costs

continuously accrue while development costs may fluctuate depending on product development stage, access to infrastructure, and other needs.

Price should depend primarily on external forces such as market value, orphan status, clinical value (relative to competitors), and other health economics calculations. Cost may be a factor in pricing evaluation but should not be a primary driver.

Value is what the buyer perceives the product to be worth. In the case of medicinal products this is measured as cost-effectiveness, and largely depends on the clinical safety and efficacy data gathered through clinical trials. Clinical evidence can be thought of as the core driver of product value.

The price of several market-stage ATMPs is given below (Table 9). Despite the broad expectation that autologous therapies will be generally more expensive than allogeneic due to their higher manufacturing cost, pricing points to date have not reflected this, evidencing the disparity between cost and price. ChondroCelect and Cartistem are autologous and allogeneic products respectively both indicated for chondrocyte repair; their similar pricing points (\$24,000 and \$20,000-\$40,000) evidences this value-focused pricing approach where the value to the patient and healthcare provider of using the therapy is reflected by the price. Similarly, 'curative' gene therapies have been unusually expensive as they aim to offer a lifetime cure with relatively lower manufacturing costs than autologous cell therapies.

Therapy	Product type	List price	Geography
Strimvelis	<i>Ex vivo</i> gene therapy	\$665,000	EU
Glybera	<i>In vivo</i> gene therapy	€1.1-1.4 million	EU
ChondroCelect	Autologous chondrocyte cell therapy	\$24,000	EU, US
Provenge	Autologous dendritic cell cancer vaccine	\$93,000	US
Hearticellgram	Autologous MSCs for AMI	\$19,000	South Korea
Temcell	Allogeneic GvHD adjuvant	\$115,000-170,000	Japan
Cartistem	Allogeneic MSC chondrocyte repair	\$20,000-\$40,000	South Korea
Prochymal	Allogeneic MSCs for GvHD	\$200,000	Canada

Table 9: List price of market-authorised ATMPs. Source: <http://celltrials.info/2016/09/06/pricing/>

3.3. Pricing and reimbursement decisions in advanced therapies

Advanced therapies are substantially more expensive to develop and manufacture than small molecules and molecular biologics, and aim to deliver high clinical benefit in areas of significant unmet need. High pricing points are therefore likely, as evidenced to date. Several complex and largely unresolved issues exist around how to optimise reimbursement, and this presents risk to their commercial success. Crucial to mitigating these risks is firstly to explore and fully understand perceptions and incentives across the issue, and secondly to engage with the relevant stakeholders early in the product development cycle for their discussion and resolution. Engaging with reimbursement bodies through industry groups such as the BioIndustry Association (BIA) can be an approachable and informative first step.

In England, the Department of Health (DoH) makes the final decision on pricing, based on assessments formed by the English HTA authority, the National Institute for Health and Care Excellence (NICE). In Scotland, the HTA body is the Scottish Medicines Consortium (SMC),

and in Wales, the All Wales Medicines Strategy Group (AWMSG), and these bodies maintain autonomy, conduct separate assessments and may decide differently on a therapy's adoption. Commissioning decisions made by NHS England do have some influence on those made by NHS Northern Ireland, NHS Scotland and NHS Wales.

3.4. How pricing decisions are made

The gold standard for drug pricing is through comparability studies with existing products, often the standard of care, but P&R strategies vary nationally across the EU and globally. Jørgensen and Kefalas (2015) provides an excellent summary of ATMP reimbursement considerations across major European markets.⁶⁰ In England, NICE assesses the merit of a novel medicine through an assessment of its cost-utility. The gain in quality-adjusted life year (QALY), which refers to both the duration and quality of life extension, is factored in with treatment cost to produce an incremental cost-effectiveness ratio (ICER) value. The ICER is calculated as:

$$ICER = \frac{\text{Cost of treatment B} - \text{Cost of treatment A}}{\text{QALY of treatment B} - \text{QALY of treatment A}}$$

Medicines with an ICER value below £20,000 are always recommended by NICE, while values between £20,000 and £30,000 are assessed on a case-by-case basis with increasing detail as the ICER value rises. Factors contributing to such an assessment are the degree of certainty around the data, the adequacy of quality of life benefit, the innovative nature of the technology, whether the technology is considered to be a 'life-extending treatment at the end of life', and aspects that relate to the non-health objectives of the NHS.

In December 2015, Prof. Stephen Palmer and colleagues at the University of York published an extensive assessment of regenerative medicine product technology appraisals in response to the Regenerative Medicine Expert Group, in turn established by a House of Lords' formal inquiry into regenerative medicine.⁴ The 296-page York report is considered the most extensive analysis of regenerative medicine healthcare technology assessment and appraisal issues across the EU to date. The report finds that regenerative medicine products did not present any unique challenges to the technology appraisal process, and that existing NICE infrastructure is suitable to the task. Major challenges associated with reimbursement appraisal were evidential in nature, and a consequence not of the nature of ATMPs, but rather, the potential for the significant magnitude of efficacy uncommon in medicinal products. The promise of high efficacy implicates the potential for equally significant failure to deliver, and the report goes on to highlight the need for risk-sharing reimbursement models where clinical evidence does not sufficiently mitigate this risk.

The York report finds that the major challenges associated with successful appraisal were evidential, and a consequence not of the nature of the technology but rather of the potential for substantial efficacy not common in medicinal products.

3.4.1. Investor-led pricing

A major contributor to advanced therapy pricing is the mode of their development and associated cost-timeline relationships. Small molecules and biopharmaceuticals are predominantly developed within large pharmaceutical organisations who have integrated much of the R&D, clinical development and manufacturing pipeline, and therefore have well-precedented and closely controlled cost understandings for each of these aspects. Large biopharmaceutical organisations typically have secure revenues from a diversity of sources and are unlikely to rely on any one product for their financial security, thus are (to a limited

extent) comfortable with pricing points unlikely to recover development costs if the product achieves corporate or other strategic goals. Strimvelis is an optimal example; GSK expect to make only 10-12 sales per year in the EU at an overall loss following development costs, but the product's success demonstrates proof of feasibility that de-risks the development of downstream gene therapy candidates more likely to be profitable. In contrast, advanced therapies developed and manufactured by young and independent companies funded by private equity investors may need to (at least partly) recover development costs through drug pricing, potentially jeopardising the price-value relationship. Any complications or delays to product development which incur additional costs may exacerbate this, reinforcing the need for comprehensive and de-risked product development strategies.

3.5. Challenges in pricing and reimbursement

3.5.1. Extended clinical benefit and HTAs

Central to HTAs is the availability of comparative clinical data. The chosen comparator treatment should reflect the standard of care for an indication but ideally would be similar in nature to the tested product. Comparator identification may require input from HTA bodies. Most advanced therapy approvals in the EU and US have occurred within the last 7 years and there are relatively few relevant products through which to compare new ATMPs, complicating HTA calculations. This effect is compounded where ATMPs pursue rare indications with few or no existing treatment options, further reducing the pool of potential comparators. A 2015 correspondence in *Nature Biotechnology* identified organ transplantation as the preferred comparator for gene therapies owing to the homology of their perceived patient benefits.⁶³ This is in contrast from the conventional wisdom that ongoing enzyme replacement costs might be a relevant comparator.

Direct head-to-head comparisons are the gold standard, but in some cases indirect comparisons are increasingly used. This is usually in situations where patient recruitment and ethical considerations present challenges with the inclusion of comparator arms in clinical trials, such as in small patient populations or sub-populations, in terminal or high-risk patients, or in particular the combination of both. In cases where the clinical and economic outcomes associated with SOC are not well documented, generation of comparative evidence may also be necessary to demonstrate incremental benefit of new treatments. NICE refused to recommend reimbursement for Provenge in 2014, stating that “[it] was shown to prolong overall survival compared with a placebo treatment, but there were uncertainties in the evidence about how well [it] works compared with some other existing treatments.”

Advanced therapies may require novel surgical or non-surgical administration devices or protocols, and these may in some cases require a separate HTA assessment before the medicinal product itself can be appraised. This could delay reimbursement negotiations and present additional complications. The healthcare economics contribution of peripheral devices should be considered within appraisal of the therapeutic itself.

3.5.2. Capturing the value of curative treatments

The clinical benefit of ATMPs can extend over a longer horizon than is often supported by direct clinical trial data, and capturing this extended value in some form or another is crucial to capturing the total worth of a therapy. The need for high-quality and long-term clinical data to negotiate a commercially sustainable pricing point is clear; however, long-term patient follow up is in itself a financially demanding process, requiring extensive clinical and administrative coordination. Direct long-term follow-up may also be incompatible with

clinical development timelines. Manufacturers should therefore consider the relative benefit of directly capturing long-term clinical data compared to indicative or surrogate long-term data generation, a combination of both, or incorporating pricing discounts or annuity payment models dependent on the subsequent generation of clinical data.

Extrapolating long-term clinical benefit from short-term trial data is a common solution. This usually involves multiple parametric and non-parametric models which are validated through statistical considerations and clinical expert opinion on biological plausibility. Across major European countries only NICE provides clear formal guidance on how long-term claims can be substantiated through extrapolation, and the relevance of extrapolated data will need to be clarified on a case-by-case national level. Extrapolated data and indirect observations are considered weaker evidence than direct clinical observation and their utility in reimbursement negotiations is reflected as such. However, in the US, the 21st Century Cures Act (Section 2.3.1) specifically allows for accelerated approval based on surrogate or intermediate clinical trial endpoints.

The focus of HTA analyses are typically on the healthcare budget specifically, therefore exclude implications on social care or other peripheral costs. Including these parameters into clinical trials may provide an opportunity to support healthcare economics calculations, and several early-stage advanced therapy biotechs are expected to incorporate such data points.

3.5.3. Regionality

Clinical practice (and therefore ideal trial comparator) and reimbursement and pricing assessment methods can differ between countries. For countries that prefer an alternative comparator to that used in clinical trials, indirect comparisons to the preferred comparator must be made. Indirect comparisons are often less robust than direct comparisons, and although statistical regression analyses can be used to control imbalances to some extent, negotiation outcomes are generally impacted.

Across the Big5EU (UK, France, Germany, Spain, Italy) there is diversity in how HTAs are undertaken, with the additional complication of regional-level product implementation and pricing decision-making; regions within each nation generally have autonomy over the implementation of medicines and the power to renegotiate pricing with the manufacturer. For a description of HTA appraisal methodologies across Big5EU countries with reference to ATMPs, readers are directed towards Jørgensen and Kefalas (2015).⁶⁰

3.5.4. Pricing clarity and uncertainty

To enable HTA authorities to make informed and valid decisions in support of higher pricing points, the cost to the healthcare provider of not only the therapy itself but associated healthcare needs should be fully elucidated. In case of Provenge, NICE cited a lack of clarity about what additional costs the treatment might incur and how these might be paid for in its reasons to refuse reimbursement recommendation. The novelty of the treatment mode further compounded the issue as NICE had no similar therapeutics from which to model a reimbursement strategy. Non-clinical factors can make a significant difference where trial data shows only marginal gains- these include sociocultural and other external factors such as contact with the biopharmaceutical industry, charity support, patient advocacy groups, and patient testimonies.

3.5.5. Extended and hidden treatment costs

ATMPs are often associated with higher logistical demands for their administration, particularly for autologous therapies, where patients will need two appointments (one for cell

harvest and another for administration). This reduces the ease of implementing the product within a clinical setting, and as a result, autologous therapies may be restricted to specifically trained clinical establishments with a service-type experience more analogous to IVF treatment than a drug prescription. The need for such costs, which are often hidden, can dramatically affect the cost-utility analysis. Overlooking the need for hidden costs can present market access issues, whereby clinical centres are faced with additional treatment costs not factored in to the healthcare economics of product use.

3.5.6. Reimbursement for gene therapies

Gene therapies are likely to face complex challenges in P&R. Payers are accustomed to long-term low-cost treatment approaches designed to manage diseases largely through incremental clinical gains, and the high price/high reward paradigm of curative gene therapy treatments may require original pricing strategies despite little precedence at present.⁶⁴ Prior market-stage gene therapies have opted for single upfront payments despite their developers being open to annuity or performance-based models, and concurrently, buyers have expressed preference for this model as it better fits the siloed structure of reimbursement funds.⁶³

GSK priced Strimvelis at \$665,000, taking steps to de-risk purchase and encourage prescription through a money-back guarantee. Glybera was the first approved gene therapy, indicated for the treatment of lipoprotein lipase deficiency (LPLD), a rare inherited disorder which can cause severe pancreatitis. Owing to high development costs and the rarity of the indication Glybera was priced at a record-breaking \$1.2 million. Despite offering a potentially curative treatment that was technically cost effective, the high price of the drug proved a major obstacle to purchase, and was only bought once. In April 2017 UniQure announced it would not be renewing its market authorisation upon expiry in October.⁹

3.6. Unique reimbursement challenges of conditionally approved medicines

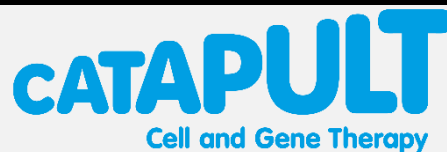
An increasing number of advanced therapies are approved on conditional market authorisations. While conditional approval has clear incentives around shorter development timeline and earlier cash flow, the strategy may present issues in convincing healthcare providers to reimburse the treatment. Conditional market authorisations rely on post-market surveillance to generate efficacy data, but this can only occur if the product is successfully bought, and the uncontrolled nature of market patient population treatment may result in poorer observed efficacy rates than through a controlled-environment clinical trial. Foregoing the conditional authorisation mechanism for formal late-stage efficacy data may therefore be advantageous to commercial success.

ATMPs with full market authorisations are not exempt from these issues. Uncertainty about the long-term clinical response was cited as a contributory factor for the refusal of NICE to recommend reimbursement for Provenge in 2014, and this paradigm remains a high-risk concern for products authorised on limited clinical data. To overcome this challenge, technology developers should engage with health insurers and other buyers at an early clinical development stage to ensure clinical trials are designed to maximise the chance of successful reimbursement, to optimise non-clinical elements of the appraisal process, and to begin early negotiations for a mutually agreeable reimbursement strategy.

Expert Insight

Panos Kefalas

*Head of Health Economics and Market Access,
Cell & Gene Therapy Catapult*



The increasing number of early access programmes introduced by regulators across major geographies provide the opportunity for earlier launch of innovative therapies, especially in therapy areas of significant unmet need, but unfortunately such programmes do not secure reimbursement and therapy adoption. The key challenge is the underlying uncertainty in the supporting evidence partly due to the accelerated development. Performance-based managed entry agreements can provide a solution to this challenge, however the challenges associated with the implementation of such agreements would need to be overcome, ideally through joint efforts by healthcare systems and manufacturers.

3.7. Unique challenges of pricing and reimbursement in the US

The US has a buyer ecosystem incomparable to that of most EU countries, with private health insurers providing reimbursement to individuals' healthcare costs. The majority of US citizens are covered by healthcare plans provided by their employer, and it is common for the insurance provider of an employer and thus its employees to change approximately every 2-3 years. This dynamic complicates efforts to develop annuity reimbursement models because of the need to transfer annuity payment contracts between insurers, something not deemed possible without an associated provision of service.⁶³

3.8. Opportunities in pricing and reimbursement

HTA bodies, buyers, and insurance companies are increasingly addressing the raft of issues faced by P&R solutions in advanced therapies. In the face of both existing and future potential clinical value, multiple stakeholders are coming together to develop novel solutions. The Centre for Commercialization of Regenerative Medicine (CCRM) in Canada is one of many translational centres globally working to bring stakeholders together to address these issues.

Expert Insight

Patrick Bedford MBHL RAC

Manager, Clinical Translation and Regulatory Affairs, CCRM



Many exciting scientific discoveries in regenerative medicine have been made in Canada, but even the best scientific discoveries do not automatically translate into clinical treatments that are accessible to patients. Without more efficient product development and/or innovative approaches to reduce development and manufacturing costs, the health care economics of this field will remain a challenge due to high pricing and elusive reimbursement approvals.

A few groups like Toronto-based CCRM are evolving to address the challenges directly impacting cell therapy health economics. Through its Centre for Advanced Therapeutic Cell Technologies, CCRM is developing advanced manufacturing solutions to reduce manufacturing costs, find systemic efficiencies, and encourage novel approaches; however,

even with these efforts, prices for regenerative medicines may remain high because of the (anticipated) value of exponential benefits over existing treatments. For this reason, each respective jurisdiction will need to decide how best to address pricing and reimbursement given their unique context.

In Canada, the following pricing and reimbursement features currently exist:

- Canada has a publicly funded health care system that covers medically necessary hospital care and drugs that are included on provincially administered formularies. It can take over 400 days to decide whether to reimburse a drug that has been authorized for sale by the regulator in Canada;
- Canada conducts national health technology assessments, upon request, for member groups including most provincial governments: The Canadian Agency for Drugs and Technologies in Health or “CADTH” has a newly revised approach to recommending product reimbursement for new drugs that go through its Common Drug Review process;
- Canada has a Patented Medicine Pricing Review Board to restrict the price of emerging products in Canada. This group has the authority to better consider the following when making its decisions:
 - the prices at which the medicine has been sold in the relevant market
 - the prices at which other medicines in the same therapeutic class have been sold in the relevant market
 - the prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada
 - changes in the Consumer Price Index
 - any other factors that may be set out in regulations
- Canadian regulators, public payors and health technology assessment bodies appear to be open to considering more collaborative, comprehensive and earlier engagements.

There is an atmosphere of change in Canada. Novel and exciting initiatives are being considered, and some can already be accessed by regenerative medicine developers. For example, an innovative approach to planning clinical trials has been used by the MaRS Excellence in Clinical Innovation Technology Evaluation (EXCITE) program to de-risk clinical trial investments by facilitating pre-commercialization negotiations with the Ontario provincial government that, once criteria are agreed and met, guarantee reimbursement.

Pricing and reimbursement are issues that affect the global regenerative medicine industry and must be addressed early to be effective. By reducing the development and manufacturing costs of cell therapies, and providing regulatory and reimbursement support, groups like CCRM are playing an essential role in this crucial area that will benefit the global market.

3.8.1. Reducing manufacturing costs

Automated manufacturing solutions present a real opportunity to mitigate manufacturing costs in both autologous and allogeneic supply chains. Labour-intensive manufacturing protocols are not scalable, rarely produce a cost-effective therapy, and are prone to human error causing batch failure. By reducing the number of human operators- the largest cost in ATMP manufacture- a supply chain can become significantly cheaper and more reliable, robust, and consistent. Automation also enables scalability, and designing a quality automated system from early clinical stage significantly de-risks the scale-up process, allowing seamless expansion into late-stage clinical and market scale manufacturing. Allogeneic supply chains

can be substantially de-costed through economy of scale, but autologous therapies must be scaled out rather than up with multiple manufacturing processes running in parallel, limiting the savings of upscaling. Automation is therefore much more important in autologous bioprocessing if manufacturing costs are to be reduced.

3.8.2. Orphan status

Orphan indications are attractive markets for advanced therapy developers owing to their regulatory, financial and market incentives. To be eligible for orphan status in the EU a drug must be indicated for a condition with an incidence not more than 5 in 10,000, or it must be unlikely that the marketing of the product would generate sufficient returns to justify the investment needed for its development. In the US, the disease indication must occur in under 200,000 individuals across the country to qualify for orphan status.

When the first to market, orphan status drugs qualify for a 10-year market exclusivity period (extendable by 2 years with a PIP) in the EU or 7 years in the US. Additional benefits of orphan status are reduced regulatory fees and enhanced regulatory guidance, the latter widely considered to be particularly valuable engagements by many technology developers. Market penetration is likely to be faster and higher overall where market exclusivity is awarded. Given their high price orphan drugs are unlikely to provide value for money according to traditional HTA methodologies, but additional criteria are used to inform reimbursement decisions for orphan status drugs in many countries, including the seriousness of the disease, the availability of other therapies, and the cost to the patient if the medicine is not reimbursed. The maximum price that a healthcare payer is willing to reimburse for a drug could therefore be higher for orphan status drugs to which society attaches a high social value.⁶⁵ Orphan status legislation for the EU is codified by Regulation (EC) No 141/2000, and in the US, by 21 CFR Part 316.

3.8.3. Novel reimbursement models

The traditional drug reimbursement model is a lump sum upfront payment at administration, which can be repeated throughout the treatment course or as required. However, the combination of high cost and short treatment time typical of advanced therapies (gene therapies in particular) means that this reimbursement strategy may not be optimal. Several alternative models have been proposed, including annuity payments over several months or years, either with or without a clinical outcome-dependent component.^{60,64,66} Italy already uses risk-sharing reimbursement approaches relatively frequently, where discounts and rebates are delivered in response to certain clinical milestones.

Original reimbursement methods may offer a potential solution, but they face several challenges. Firstly, identifying valid endpoints by which clinical response can be effectively quantified is not always feasible.⁶⁴ Secondly, healthcare industries such as the US where health insurance providers can be readily and easily changed may complicate long annuity timeframes. Thirdly, there are currently no procurement codes for cell and gene therapies and this complicates payments across different insurers. Finally, the siloed structure of reimbursement funds means that their inherent structural framework can present barriers to reimbursing costly therapies that are likely to straddle the remit of two or more individual funds.

Accordingly, a review of 29 buyers across Western Europe and the US found that due primarily to the structure of existing healthcare reimbursement frameworks, the current preference would be for single upfront payments.⁶³ This was despite a theoretical preference for capped annuity reimbursement in the hypothetical situation of no health system

constraints. In line with these findings, the two currently authorised gene therapies Glybera and Strimvelis are reimbursable only through single upfront payments.

3.8.4. Discount rating

HTA authorities use a discount percentage in their price appraisal calculations. In England, NICE typically use 3.5%. The discount rating accounts for the relatively higher value of clinical outcomes in the present over those in the future. Treatments which restore people who would otherwise die or have a very severely impaired life to full or near full health, in other words curative treatments, are extremely sensitive to the discount rate used owing to the extended nature of clinical benefit. There is provision within the NICE appraisal process (section 6.2.19 of the NICE Guide to the Methods of Technology Appraisal, 2013) for the discount rate to be lowered to 1.5% for 'curative' treatments. However, this is dependent upon the presence of clinical data demonstrating such a response, and follow-up times of 10 months were deemed insufficient by NICE.⁶⁷ This further highlights the need for long-term clinical trials to generate evidence of clinical benefit over several years post-administration.

3.8.5. Patient access scheme (PAS)

Where products are deemed to offer marginally unfavourable cost-utility, PASs can be pursued by the manufacturer, where a lower price is negotiated with the DoH to improve the cost-utility of the therapy.⁶⁸ PASs can either utilise price discounts, or outcome-based reimbursement such as a pay-per-performance risk sharing agreement. Discounts through PASs are kept confidential for the benefit of the manufacturer, so as not to undermine potential pricing in other geographies.

3.8.6. Lack of competition as a pricing opportunity

The market for advanced therapies is currently limited and there is essentially no direct competition for those which are currently authorised. The lack of competition allows developers to independently price advanced therapies based on healthcare economics, market size, and development costs, without the need to consider competitor pricing.⁶⁹ Products that reach the market first have a distinct competitive advantage in their freedom from competitive pricing forces as well as driving up barriers to success for subsequent competitors, which in order to displace an existing treatment option must demonstrate superiority to the existing treatment. This paradigm is a major driver behind the observed focus on orphan indications.

3.9. Case study: NICE appraisal of CAR-T therapy

In March 2016, NICE published a report in response to the 2015 York paper and with support from its authors, undertaken by a special NICE study and expert panel.^{62,67} Entitled 'Exploring the assessment and appraisal of regenerative medicines and cell therapy products', the report was undertaken in partnership with the Cell and Gene Therapy Catapult, and drew on the York paper findings alongside analytical input from a NICE expert panel experienced in technology appraisal. The NICE report summarises a project designed to test whether the NICE HTA methods and processes are fit for purpose for regenerative medicines and cell therapies, and confirmed the York report's findings that existing technology appraisal systems were sufficient.

The NICE report also included a mock HTA case study of a CAR-T therapy for the treatment of relapsed or refractory B-cell acute lymphoblastic leukaemia in children and young adults. The report includes an assessment of three different clinical data efficacy profiles (minimal, moderate, mature) and two treatment modes, one curative and the other a bridge to HSCT.

The clinical data profiles are representative of phase III trial data packages and their differentiation refers to the degree of data generated rather than the magnitude of clinical gain. The three evidence sets were as follows:

- Minimum case scenario: 60-80 patient trial with median follow-up of 10 months
- Intermediate case scenario: 60-80 patients, follow-up up to 5 years
- More mature case scenario: 120-140 patients, maximum follow-up of 5 years

Six situations are therefore described (Table 10). All scenarios assumed historical control.

	Reimbursement model	Reimbursement	Decision
Bridge to transplant	Upfront payment	£356,100	No
		£320,490	Borderline
	Monthly payments until death	£2,765	No
	Monthly payments when in remission*	£2,765	Yes
Curative	Upfront payment	£528,600	No
		£475,740	Borderline/No
		£356,100	Yes
	Monthly payments until death	£3,283	No
		£2,955	Borderline/Yes
	Monthly payments when in remission +	£3,283	Borderline/No

Table 10: Likely NICE reimbursement opinion where minimal clinical data is given (60-80 patient trial with median follow-up of 10 months). All data from NICE 'Exploring the assessment and appraisal of regenerative medicines and cell therapy products' report. Discount rate of 3.5% applied. *Estimated to result in a 35% overall cost reduction. +Estimated to result in a 10% cost reduction.

In the absence of an authorised product with no pricing point, the report calculated a theoretical maximum price cap for a given clinical outcome. For a CAR-T product intending to offer curative treatment that gives a 10.07 QALY gain (representing a 10-year life extension of full health), the price cap was given at £528,600. When the product was intended to bridge to HSCT transplant, giving an eventual QALY gain of 7.46, the pricing cap was £356,100. These were theoretical examples; actual CAR-T clinical outcomes and therefore pricing points may differ dramatically.

The report stated that the NICE panel showed considerable interest in the lifetime leasing method (monthly payments), expressing the view that such a model should be further developed to facilitate reimbursement. In this case, the asset considered for lease is not the therapy itself but patient health, against which monthly payments would be made until patient death or cancer relapse. The panel considered that practical, workable payment methodologies based on the lifetime leasing method could be very important in managing decision uncertainty and facilitating early patient access while the evidence was immature.

The pricing caps given by the report offer a useful quantitative forecast on the CAR-T reimbursement landscape. However, the report also identifies uncertainty around the clinical outcomes assumed by the model as a substantial complication.

The report finds that where there is a combination of great uncertainty but potentially very substantial patient benefit, innovative payment methodologies would be needed to distribute risk and to facilitate timely patient access. Although the report did not directly assess the reimbursement of gene therapies, the principles of these findings could be extrapolated

across. The report highlights the validity of mitigating uncertainty through the generation of comprehensive clinical data, particularly in trials which include longer (5-10 year) patient follow-up to fully assess the therapeutics' long-term clinical benefit.

3.10. Enabling market access

Clinician adoption is a major factor in the success of advanced therapies. This includes the subjective opinion of both prescribing physicians and the patients themselves. The efficacy of some therapies can depend on the skill and training of the attending physician, many of whom are likely to have little to no experience with the product, and clinicians who feel unable to use the product effectively or feel uncomfortable using the product may avoid its use. Bespoke training and/or dedicated clinicians may be required for the administration of some therapies. Autologous therapies are expected to be more akin to service provisions more analogous to IVF treatment than the prescription of a medication, and the experience of both patient and physician will be a major determinant of the treatment's commercial success. Peer-recommendation through patient advocacy groups and internet-mediated discussion is likely to be a powerful driver for market penetration. Advanced therapy administration protocols must therefore be as simple, comfortable, undemanding and user-friendly as possible, designed with clinician needs and patient experience in mind.

MANUFACTURING COMMERCIAL OPERATIONS AND SUPPLY CHAIN

Chapter 4

4.1. Summary of Chapter 4

Advanced therapies are characterised by a high degree of technical complexity and face substantial challenges for their scalable manufacture. The novel nature of cell-based therapies and an associated lack of precedence presents a particularly unique set of challenges; bioprocessing equipment options are limited, and many available platforms are imported and adapted from blood product processing, research-scale cell culture, or antibody production, and are therefore suboptimal for scalable manufacturing. Cell and gene vector bioprocessing can be divided by expansion phase into upstream and downstream halves, each involving a series of unit operation steps. The immaturity of the advanced therapy manufacturing ecosystem in combination with rapid growth means that raw materials are often in short supply. Securing backup suppliers is therefore a vital requirement in de-risking the supply chain.

A growing number of stakeholders are offering advanced manufacturing and supply chain solutions, including GE Healthcare, Invetech, PCT, and Lonza. Twelve further manufacturing organisations were identified. Each of these offers either virtual-model (development and) manufacturing services, bespoke integrated manufacturing solutions, and/or off-the-shelf bioprocessing equipment. Advanced therapy manufacturing in high-profile companies is generally achieved primarily by the latter two at present, with many leading advanced therapy companies opting either to out-source manufacturing to CMOs with deep experience in cell bioprocessing, or contracting custom-built integrated manufacturing solutions. Smaller or earlier-stage biotechs infrequently have the financial resources for these strategies.

Automation in cell bioprocessing is a major driver for cost-effective manufacturing, and should generally be implemented early in clinical development to avert high-risk late-stage process modifications. Single-use and disposable manufacturing systems often constitute major components of scalability. Automation can play a key role in supporting product quality through increasing robustness, consistency, and decreasing contamination risk, while decreasing operational costs. Manufacturing may be centralised to a single site or distributed; contributory factors include product shelf life and other characteristics, market potential, and cost. A number of leading cell therapy developers are opting to delay implementing automation until their second-generation product, restricting the manufacturability of their first-generation product.

Expert Insight

Timothy Moore,

Executive Vice President, Technical Operations, **Kite Pharma**

The cell therapy industry is embarking on the first phase of an exciting journey with a goal to bring life-saving treatments to patients with hematologic cancers who have no other options. There is a growing sentiment that the potential for cell therapy will flourish once the trail has been blazed. As we carve out this new path to reinvent cancer therapy, it was imperative to establish the first generation of cell therapy manufacturing and supply chain processes. This work is not trivial as the next generations must be built on a solid foundation. At Kite, we believe we have created a solid manufacturing and supply chain platform that is built to evolve and embrace new technology. This foundation is designed to address the needs of the here and now, while on balance, successfully embrace inspired collaborations that will allow us to bring next generation manufacturing and supply chain breakthrough technologies to the industry.

The success seen to date in cell therapy has inspired entrepreneurial thinking industry-wide.

This is most evident by the number of companies investing in this transformational therapy space, both in the manufacturing and supply chain environment, to continually evolve solutions aimed at improving cost, quality and reliability. Together, we plan to advance the manufacturing processes in collaboration with key industry suppliers to develop highly automated manufacturing unit operations, deeply integrated IT solutions to support knowledge management and continuous improvement, as well as efficient supply chains to ensure chain of custody and chain of identity are maintained throughout the end to end supply for autologous CAR-T/TCR products.

We believe that over the next five years, automation, process equipment, and supply chain management will make substantial advancements that can greatly impact the cost, quality and most importantly, the speed with which a patient receives therapy. At the end of the day, that is what drives innovation because every day matters in the lives of these patients.

Expert Insight

Robert Preti Ph.D.

Chief Executive Officer and President, PCT

PCT Cell Therapy Services, LLC

A Hitachi Group Company

Cell therapy, like every innovative industry that has come before it, has its own set of unique challenges. And just like these other industries, cell therapy solutions are forming directly along the challenges that are being presented.

The journey of a cell therapy, from conception to commercialization, is long, complicated and resource intensive. In order to reach success, a cell therapy product must be manufactured to high quality standards using a robust, cost-effective process that will be able to scale up and remain sustainable over the commercial life of the product.

To best ensure this success, cell therapy developers must plan ahead for the future of the cell therapy product, no matter what phase they are currently in. A common mindset for cell therapy developers is to focus on what they need in order to complete the current clinical phase and to enter the next phase of development. The most thoughtful among developers create strategic manufacturing plans to avoid costly, time-consuming roadblocks that could ultimately reduce the potential for commercial success.

In an ideal world, it would be most beneficial for cell therapy developers to set objectives for quality, cost of goods, scalability and sustainability before proof of concept clinical trials. In reality, this is not always possible before some clinical data is established. Given that the quality of the cell therapy product is so closely connected to the manufacturing process, any changes to the process, no matter how small, have the potential to create comparability risk. This can lead to additional costs and delays if such changes are introduced late in clinical development.

Personalized cell therapy (or patient-specific cell therapy), because of its individualized nature, carries a unique set of manufacturing challenges as compared to both off-the-shelf-cell therapeutics and traditional pharmaceutical and biologics. The main challenges include finding a method to manufacture cell therapies for clinical and ultimately commercial use in a way that considers cost of goods, quality, scalability and sustainability.

Current cell therapy manufacturing processes rely on a great deal of time, manpower and cleanroom space, all of which can lead to burdening cost of goods with the overhead operating expenses associated with idle capacity stemming from uneven demand over time.

In a traditional cell therapy manufacturing model, a developer invests much time and resources into creating a dedicated manufacturing facility intended for the manufacture of one or two therapies. In the case of cell therapies, the operation costs, inability to scale appropriately to meet demand and other challenges can be daunting, creating insurmountable obstacles to commercial viability.

There needs to be an industry-wide effort to apply innovation and engineering to cell therapy, thoughtfully rebuilding unit operations for cell therapy from the ground up, to transform cell therapy manufacturing processes and test methods in a way that achieves true scalability and sustainability.

To allow for the long-term viability of the cell therapy industry, cell therapy manufacturing processes must be slowly taken out of the cleanroom and sent into production spaces more suited for high-volume production. In addition, automation, closed systems and integration will play a critical role in achieving this new manufacturing environment. When this occurs, then, cell therapy manufacturing will begin to see commercial success.

4.2. Typical stages of advanced therapy manufacturing

Cell bioprocessing is generally segmented into a series of discrete unit function steps which may differ between cell types and according to the specific needs of the product. A typical cGMP process for cell-based products follows these steps:

- Receipt of starting material and accessioning (e.g. apheresis or bone marrow, or possibly cell line/cell bank for allogeneic therapies)
 - Cell processing- Washing to remove bulk of unwanted cell types
 - Selection/enrichment- Target cell selection or enrichment
 - Cell engineering- Activation, genetic modification
 - Cell culture- Static or bioreactor platforms, typically 1-30 days
 - Cell processing- Washing to remove impurities
 - Product formulation- Volume reduction, formulation and potentially cryopreservation
 - Final product storage/shipping to clinical site for patient infusion
- Upstream
- Downstream

cGMP gene therapy manufacturing processes generally involves fewer and often simpler steps:

- Vector amplification and cell expansion
 - Bioreactor cell/vector expansion- Bioreactor culture
 - Cell disruption- Transduction
 - Purification- Chromatography, DNA removal
 - Polishing- Microfiltration/ultrafiltration
 - Fill & finish- Transfer to storage, cryopreservation
- Upstream
- Downstream

4.3. Major challenges in advanced therapy manufacturing

Medicinal product manufacturing environments are globally subject to GMP protocols, regulatory mandates enforced by national level agencies but internationally harmonised that aim to ensure production of high quality products that pose no risk to the consumer or public.

ATMP manufacturing in particular requires a stringent and carefully controlled bioprocess to control for the intrinsically complex and variable nature of cell therapy products.⁷⁰

The value chain for advanced therapies in 2017 places notable emphasis on novel manufacturing solutions. The industry is now limited by the usefulness and scale of available manufacturing solutions; innovation of scalable bioprocessing solutions is crucial for the commercial success of advanced therapies over the coming 5-10 years. Existing bioprocessing solutions are largely adopted from biopharmaceutical manufacturing or blood product supply chains, and are usable but wholly sub-optimal for long-term commercial sustainability due to high failure risk, high costs, and poor flexibility for optimisation. Early advanced therapies are manufactured through manual, labour-intensive processes which limits their supply, demands high production costs, and ultimately curtails ROI. The unsustainability of this model is becoming increasingly apparent as technology developers realise the importance of innovative manufacturing solutions; multiple leading advanced therapy companies are commissioning exclusive and customised supply chain solutions from major manufacturing stakeholders (e.g. Kite Pharma and GE Healthcare), while a fertile bioprocessing industry is rapidly developing new commercially-available solutions.

Designing advanced manufacturing solutions early in product development is crucial to de-risk development. Any modifications to the manufacturing process implicate comparability studies to demonstrate equivalence, and major unforeseen alterations can be highly disruptive to timely completion of strategic development goals. Comparability studies are time consuming, require ongoing cash burn, and where reasonable comparability cannot be demonstrated, clinical trials may need repeating.

Upfront process development and manufacturing optimisation before the major value inflections offered by clinical trial results is an understandably high-risk investment, compounded by a relatively long time to ROI. Further, there are limited viable options for full-scale bioprocess solutions, and manual elements of manufacturing may be justifiably present at market launch. However, it is clear from historical and ongoing case studies that manufacturing remains central to costing a therapy, and therefore bioprocess optimisation to reduce therapy price remains central to commercial success.

4.3.1. Impact of suboptimal manufacturing: Provenge

The need to optimise manufacturing scalability is well demonstrated by Provenge, a dendritic cell cancer vaccine developed by Dendreon and authorised for marketing by the FDA approved in April 2010 and EMA in June 2013 for the treatment of advanced prostate cancer. Within a month of launch it became clear that manufacturing bandwidth was limiting revenues; Dendreon announced that only 2% of eligible patients would be able to receive treatment. Despite at that time also announcing a \$400 million investment into a new manufacturing plant, stock prices fell by 36% over a two-month period. In November 2010, Dendreon secured a new increased pricing point of \$93,000 with Medicare, and stocks remained relatively stable for the next 8 months. However, the need for this price rise as a result of manufacturing complications ultimately undermined clinician's desire to prescribe Provenge. Reimbursement issues were also a major contributor to the products failure; physicians did not want to front payment for the expensive therapy at risk of being denied reimbursement by the patient's insurer. Dendreon filed for bankruptcy in 2014.⁷¹ Ultimately, Provenge failed for a number of interrelated reasons centring around meeting market demand and cost, both issues addressable through manufacturing solutions.

4.3.2. Capacity shortfall

There is increasing understanding that research-scale manufacturing solutions are insufficient for the commercial launch of ATMPs, and resolving this issue requires substantial manufacturing expertise. In pursuit of this, numerous service providers offer either bespoke solutions for integrated manufacturing, or CMO-style virtual manufacturing models. Some of the major manufacturing stakeholders are PCT, Cobra Biologics, Invetech, Lonza, GE Healthcare, Oxford Biomedica, PharmaCell, MaSTherCell, and Apceth. Many other CMOs or service providers exist and the ecosystem around ATMP manufacturing is rapidly expanding, offering increasing opportunities for ATMP manufacturers to 'shop around'- but the availability of manufacturing solutions is counterbalanced by the sheer diversity of ATMP manufacturing needs and the depth of expertise required for successful manufacture.

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology, PCT, A Hitachi Group Company

For cell therapies to truly become commercially viable, the industry must begin to think of developing a very different future state of manufacturing. Cell therapy manufacturers will need to start shifting their model, moving away from the cleanroom and toward putting their processes into production spaces that are much more suitable for high volume production. Automation, integration and closed processing systems can result in a simpler manufacturing space that is used for multiple processes at one time. This leads to a healthier bottom line, ultimately helping cell based therapies become globally accessible.

4.3.3. Raw materials shortages

As a young and emerging industry, the supply of starting and raw materials such as cell culture media is relatively volatile. Creating a robust and low-risk supply chain requires developers to identify backup suppliers where possible, and where backup options do not exist, work with materials suppliers to de-risk their supply chain in turn. The lack of competition for materials supply also impacts product pricing, and the use of high-cost media can significantly contribute to COGs.

Expert Insight

William Montieth

Chief Operating Officer, PCT, A Hitachi Group Company

Scott Oppenheim

Director, Supply Chain, PCT, A Hitachi Group Company

Given that cell therapy is still in a state of infancy, there are a number of unique supply chain considerations that haven't been fully addressed yet. Obtaining high-quality raw materials is one of many reasons for the high COGS seen in cell therapy products. There's a very limited supplier base that cell therapy developers can procure materials from, which limits their power to secure the best prices. In some cases, there is only one source for a specific material.

4.3.4. Shelf life and distribution

Small molecules are usually manufactured at single sites for global distribution, made possible by a long and undemanding shelf life. Biotherapeutics may require refrigeration, but tend to have shelf lives sufficient for cold distribution and local storage for use as necessary. In stark contrast, organs for transplant cannot (to date) be stored, and must be delivered fresh from the donor to the recipient within a matter of hours. The limitations presented by an inability to store donated organs cannot be overstated, and the infrastructure in place around managing this need is extremely costly. Cell based therapeutics lie somewhere in-between these extremes.

Expert Insight

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Transportation has to be considered as a unique challenge for cell therapies. At the earliest stages of process development, it's critical to assess whether the cell therapy product needs to be cryopreserved or refrigerated, as this will impact the ability to deliver it in a timely manner. Logistical considerations for a refrigerated supply chain of short dated or cryopreserved products can significantly impact COGS. For example, the use of courier service and cryo shippers to assure the maintenance of proper and timely storage conditions are a necessity. In addition, cell therapy developers will need a logistics scheduling system to manage the collection, shipment, processing and shipment back to the infusion site to ensure the critical attributes of the incoming and outgoing materials are maintained.

Furthermore, there are a limited number of suppliers who perform the specialized delivery services needed for cell therapies. Not only is maintaining a certain temperature a concern, but timing is also important. For example, there is usually a limited time to deliver the apheresis product to the facility for manufacture and then back to the patient for infusion. The courier chosen must have the ability to deliver these time- and temperature-sensitive products in a consistent, safe manner.

ATMPs have wildly varying shelf lives, depending primarily on whether they are cryopreserved. Holoclar (Chiesi), an autologous limbal stem cell product indicated for ocular chemical burns, provides a clear example of where short shelf life and an autologous supply chain has presented logistical barriers.⁷² Patient biopsies are taken in a clinical setting, shipped fresh to the Holostem facility, and cryopreserved to await patient preparation. When the patient is ready the product can be thawed for undergo secondary culture, a process could take between 5 and 9 days depending on how the cells respond. Upon release, the product must be transplanted to the patient within 36 hours. The patient and clinical team therefore need to be prepared for delivery within a 4-day window. Holoclar's shelf life and associated logistical concerns have majorly impacted its price.

Expert Insight

Martin Lamb

Executive Vice President, Sales & Marketing, TrakCel Ltd

The Impact of Cellular Orchestration Platforms on Cost of Goods

Cellular Orchestration Platforms (COPs), such as TrakCel, are designed to improve supply chain performance for cell and gene therapies (CGTs). This is achieved by:

- Providing full traceability of therapies from donor to recipient – this is especially important for autologous cell therapies, where following modification and expansion at a manufacturing site, starting material derived from a patient must be infused back into the same patient. As the number of therapies being received, processed and shipped by clinical sites, manufacturers and logistics providers grows this will become increasingly challenging.
- Driving compliance with regulations, the trial protocol and Sponsor SOPs at clinical sites, through the implementation of prescriptive 21 CFR Part 11 compliant workflows. Again, as the number of parties involved in cell therapies grows in late stage clinical development and commercialisation, the need for consistency and control increases.
- Capturing Data from multiple parties in the supply chain, giving Sponsors a single-system view of needle-to-needle supply chain performance allowing for analytics and performance optimisation.
- Scheduling of activities in the supply chain to ensure upstream tasks occur only when there is downstream capacity available for subsequent process steps. For example, providing apheresis centres with visibility of manufacturing capacity so starting material is collected only on days when capacity is available for cell modification and expansion.
- Simplifying QA release processes and supporting product quality by providing Quality Staff with all the information on a product's chain of custody required to certify it is safe for infusion into a patient.

Through the above functionality, COPs can significantly reduce Costs of Goods during clinical development as illustrated below. Savings in this table are based on the following estimated costs for a clinical trial (based on standard pharmaceuticals/biologics – for CGTs, we would expect the cost to be at the high end of this scale, if not higher):

- Phase I \$1.4M - \$6.6M
- Phase II \$7.0M - \$19.6M
- Phase III \$11.5M - \$52.9M

Major cost drivers include clinical procedure costs (15-22%), study administration costs (11-29%) and clinical site monitoring (9-14%). For illustrative purposes, and based on the complexities of CGTs, we will use the higher figure in these ranges for CGTs.

Cost driver	Estimated Cost	Potential savings and rationale
Clinical site monitoring	\$0.6M at PhI, \$2.7M at PhII, \$7.4M at PhIII	Up to 25% - COP enforces compliance, which in turn should reduce the monitoring effort, supporting risk-based monitoring
Clinical procedures	\$1.5M at PhI, \$4.3M at PhII,	Up to 10% - COP workflows

	\$11.6M at PhII	should make this more efficient. Integration with other systems eliminates duplicate data entry. Scheduling ensures procedures performed at the right time.
Study Administration	\$1.9M at PhI, \$5.7M at PhII, \$15.3M at PhIII	Up to 15% - Automated data capture removes paper records/transcription errors and reconciliation challenges vs if data is captured in multiple systems

Further supply chain challenges, and associated costs, need to be captured in each therapy's Cost of Goods (COGs). While a COP may not directly impact on these processes *per se*, data captured by the system allows Sponsors/Developers to take a holistic view of their supply chain and identify opportunities for optimisation. These include:

- **Logistics** – COPs can provide logistics providers visibility to future needs, allowing for better forecasting and utilisation of courier services and improved management of specialised shipping system inventories, which in turn can reduce costs. Also, data captured can be used to analyse courier performance, route selection and potential points of failure.
- **Manufacturing/QC testing** – In many cases, scheduling is performed manually across the supply chain. Automating this process can enhance utilisation of manufacturing assets, which has a significant impact on the cost of goods. Integration with manufacturing equipment allows for a more efficient review of manufacturing data at the time of release.
- **QA/QP release** – This is a major cost and process bottleneck for even traditional pharmaceutical manufacturers. Capturing data and documentation across the entire supply chain, from multiple sources (as is often the case for CGTs) can be challenging and adds significantly to release timelines – particularly for initial batches. By capturing key data, COPs can help alleviate this – one QP we spoke to quoted up to 40 man hours at a cost of \$10,000 to release a first batch of product when compiling data from multiple stakeholders, which can fall by around 85% if all information is available in a single system.

TrakCel's experience to date has been focused on supporting our clients' products through clinical development. We are well aware of the challenges ahead when products are commercialised. One client we spoke to when compiling this paper cited that, in order to justify their current market capitalisation, larger autologous CGT developers will need to sell 5-10,000 treatments per year. This in turn equates to 40-60 batches of product released every day. How is this going to be possible using manual traceability and supply chain orchestration? What will the labour cost of achieving this, let alone the risk of product failures in terms of lost material and damaged reputations, amount to? COPs were developed to *enable* cell therapies to reach their potential – this will not happen without traceability, consistency across all stakeholders, automation and holistic data-driven decision making across the supply chain provided by these systems.

<http://journals.sagepub.com/doi/pdf/10.1177/1740774515625964>

4.4. Designing scalable manufacturing systems

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology, PCT, A Hitachi Group Company

For a commercially successful cell therapy, developers need to meet several manufacturing criteria, including consistently high product quality, reasonable cost of goods, production that meets demand and sustainable capability throughout the commercial life of a product. To meet these criteria, it's critical for developers to think about manufacturing as early as possible in their development of a cell therapy product. Those who address manufacturing needs too late and then find out they need to make changes to achieve economic viability face a huge risk with regard to comparability of products made by original vs new processes. Investors are unlikely to agree to changes to the manufacturing process that may help to ensure profitability if they require that clinical trials be repeated.

4.4.1. Single-use technologies

Single-use and disposable manufacturing tools offer low-risk bioprocessing solutions. Traditional stainless steel bioreactors used in biopharmaceutical manufacturing typically require deep cleaning between batches, and commonly used in academic or R&D contexts, single-use technologies can accommodate for the variable needs of cell bioprocessing, and are becoming increasingly adopted in commercial-scale supply chains. Lonza's largest viral gene therapy manufacturing facility, announced June 2015, uses single-use bioreactor bags to manufacture 2,000L of viral gene therapy product across eight cleanrooms, demonstrating the growing movement towards disposable manufacturing solutions.

4.4.2. Automation

Expert Insight

Thomas Heathman

Business Leader, Technology Development, Manufacturing Development & GTP Services, PCT, A Hitachi Group Company

It is critical for cell therapy developers to start as early in the product development cycle as possible and understand how scalability can be achieved, be it off-the-shelf or patient-specific, and minimize the cost per dose as the production rate increases. This includes rigorous characterization of bioreactor platforms for off-the-shelf therapies at the small scale, so that comparability of the physical environment can be maintained as the scale increases throughout development.¹¹⁵

In addition, cell therapy developers should work closely with their manufacturing partners to leverage their knowledge and expertise, helping to ensure that the process, including supply chain and logistics, is scalable and will be commercially viable for the future. The timing, cost and comparability risk of modifying process steps during clinical development should be carefully managed and balanced against increasing cost advantages, to ensure the future sustainability of the cell therapy product.¹¹⁵

Automation offers step-change improvements to several manufacturing challenges. By automating otherwise manual steps, manufacturing becomes more scalable, robust, reliable, and consistent, and product quality can be enhanced. Human error is consistently identified as the highest risk element of the manufacturing process, responsible for the majority of protocol deviations and therefore batch failures. Automation mitigates these risks by offering repeatable and reliable bioprocessing.

Automating manufacturing opens opportunities to further refine the product process. Implementing in-line, on-line and at-line process testing allows up or downstream feedback, enabling compensation for batch variability, early identification of failed batches, and generation of a wealth of process data that can be leveraged for ongoing process optimisation.

Implementing automation technologies does require upfront capital investments, but this is a necessity to reducing long-term manufacturing costs, and to producing a commercially viable product, therefore offering an indirect return on investment.

4.4.3. Quality assurance and quality control

In Section 2.5: *Understanding and characterising* cellular products we discussed the critical need to fully characterise advanced therapies in de-risking product development and downstream commercialisation. A widely-implemented solution to this need, further to developing a battery of batch-release/ end-stage assays, is to implement in-process testing to monitor and control each batch as it is manufactured. Integrating in-process testing can obviate separate QA/QC processing, currently a major barrier to optimisation due to time constraints associated with the necessary tests, to facilitate greater manufacturing throughput and increase product shelf life.

Expert Insight

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Currently, most patient-specific cell therapy manufacturing processes are manual. There isn't the economy of scale that is seen with the more traditional small molecule environment, where large batches of product with multiple doses can be made at one time. Cell therapies are produced manually in a traditional cleanroom, which means that capacity will become a limiting factor when attempting to scale up (or, in this case, scale out).

In order for cell therapies to reach commercial viability, companies will need to introduce appropriate automation and closed system processing into their manufacturing processes. Automation doesn't just mean faster – it will also greatly reduce costs once the process is taken out of the cleanroom and moved into a closed system. This drastically lowers infrastructure and support costs as a validated closed system can be housed in a controlled non-classified (CNC) environment versus a Grade B or Grade A cleanroom environment. Once this migration out of the cleanroom occurs, multiple products can then be run in one room. Concerns over cross contamination, sterility risk through the environment or human manipulation is minimized. Investing in automation before commercialization may have a significant long-term effect on reduction of costs and profitability.

4.4.4. Reducing COGs

Cost of goods sold in advanced therapy production may be substantially higher than in biopharmaceuticals, due most significantly to high cost of materials, high labour costs, and the need to maintain validated cleanroom space. Reducing production costs could involve degrading cleanrooms to Grade D, possible only with a completely closed process; reducing labour costs through automation; and simplifying the manufacturing process by excluding unnecessary steps. Manufacturing costs may be particularly elevated in autologous processes, which do not benefit from economies of scale.

Expert Insight

Brian Hampson

Vice President, Global Manufacturing Sciences and Technology PCT, A Hitachi Group Company

Automation and the related opportunity for integration will play a larger role as these new types of factories come into existence that will justify the investment in the development of automation technologies and platforms. Integration of multiple unit operations (steps) into a single unit operation presents benefits including lower labor and material costs as well as quality advantages associated with less transfer of cells between unit operations. However, there is still an unmet need for cell processing platforms that can perform a variety of cell manipulations across a range of scale – but this innovation is starting to happen.

Having deep knowledge of the technology landscape ensures developers are able to choose automation platforms that offer the best available solutions for their specific process requirements. Automation strategies need to address a range of considerations, including:

- Process automation, such as closed-loop control of a culture process
- Task automation, such as a cell selection step, or coupled wash and formulate steps
- Test automation, such as a compendial safety test method
- Factory automation: for information such as electronic batch record; for execution such as manufacturing execution systems

Expert Insight

David Sourdiv

Co-Founder, Executive Vice President, Technical Operations, Collectis

How will bioprocessing improve in the next 5 years?

Cell therapy is now transitioning from the world of grafts, where it has been confined for decades, to the world of pharmaceutical products. In the coming decade, off-the-shelf cell therapy will become a reality that will have a broad impact on the field. Standards and regulations will evolve with that revolution.

Cellular systems will be both better defined and more extensively and precisely engineered. Gene-editing transformative potential will also start materializing with designer cells and systems tuned for therapeutic applications.

Expert Insight

William Montieth

Chief Operating Officer, PCT, A Hitachi Group Company

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Director, Supply Chain, PCT, A Hitachi Group Company

Managing cost of goods sold (COGS) for patient-specific cell therapies (PSCTs) has unique challenges when compared to traditional biologics. The greatest differentiator: PSCTs are manufactured one batch at a time for one patient. As a result, this limits the cost savings from traditional economics of scale. Current high COGS for cell therapy products are driven by a combination of several factors – labour intensive manual manufacturing processes, high infrastructure and support costs, expensive raw materials as well as lack of economy of scale. And because these therapies are patient specific and the health of the patient impacts availability for collection of starting material, scheduling variability can inhibit the efficient utilization of planned resources. This can result in a higher waste stream due to aborted processing runs. An additional impact on COGS is the associated cleaning and segregation requirements when viral vectors are used in cellular processing for the transduction of cells.

As cell therapy processes mature, the need to drive down COGS to achieve commercial viability becomes critical. COGS for cell therapies must be reduced through technology optimization utilizing such methods as automation, isolator technology and closed system processing which reduce the infrastructure and support cost of a traditional Grade B or Grade A clean room environment and results in reduced sterility and processing errors through human intervention.

Near and long-term planning is critical to mitigate supply chain risks in cell therapy manufacturing. By performing this type of analysis, the cell therapy developer has a road map for their manufacturing strategy, process improvements, required capital and raw material costs. Without performing COGS analysis in the process development stage, it is difficult to predict if and how the manufacturing process can be fully optimized for commercial viability. As regulatory filings proceed, changes may become more difficult to make and cell therapy developers could end up locked into certain material suppliers and more costly processes. Regulatory agencies have shown support for comparability study between manual and closed system/automated processing during the clinical and post approval life cycle of a product, thus providing a pathway for this change.

4.5. Centralised and decentralised manufacturing models

Advanced therapy supply chains must be intelligently designed to maximise product availability. Owing to long shelf lives and simple distribution needs, small molecules can be manufactured in a single manufacturing site and readily shipped across the world. For cell therapy developers, opting for single or multiple manufacturing centres will depend upon the preferred business model, regulatory, economic, and supply chain factors.⁷³ Autologous therapies in particular may benefit from multicentre manufacturing solutions, particularly where bioprocessing can be confined to black-box systems installed within the healthcare setting. Multicentre manufacturing models are subject to substantial comparability requirements, where centres must demonstrate the precise replication of products between centres, but can offer logistical advantages. Different elements of the supply chain have various levels of associated risk (Figure 4) and this must be considered when designing a manufacturing model.

	Harvesting Starting Material	Starting Material Logistics	Manufactur e	Product Release	Therapy Logistics	Treatment
Patient Identification	Red	Green	Green	Red	Green	Red
Sample Identification	Red	Red	Red	Red	Red	Red
Temperature Excursions	Green	Red	Amber	Green	Red	Amber
Time Excursions	Amber	Red	Amber	Green	Amber	Amber
Resource Allocation	Red	Red	Red	Amber	Amber	Red

Figure 4: Risk heat map for autologous cell therapy supply chains. Red indicates high-risk, amber medium, and green low. Adapted from ‘Successfully managing the unique demands of cell therapy supply chains’ white paper, Rachel Griffiths and Dr Matthew Lakelin.⁷⁴

4.5.1. Shipping and logistics

Transporting advanced therapies can be a high-risk aspect of the supply chain, particularly for fresh product cell therapies which often suffer from short shelf lives and can be extremely sensitive to environment factors such as temperature, gas concentration, and even vibration. Logistics complications such as delays to customs release or within airports due to air traffic or unforeseen circumstances can incur time exclusions. Minor process changes such as moving to a cryopreserved final shipped product can substantially mitigate these risks, and shipment condition tracking devices should be employed to validate the post-transport quality of each batch. Provenge provides a clear example of the importance of shelf life management, where an initial decision to ship fresh was later overturned following unsustainable costs and high wastage, and a cryopreservation process modification implemented.

Chain of identity management becomes a high-risk demand with autologous therapies, as products must be effectively tracked throughout their manufacturing, analysis, release, and shipment to ensure that a high-quality product is delivered to the correct hospital and administered to the correct patient. Batch identification through patient initials and date of birth is considered insufficient, but labelling must be simple enough for use across sites. Supply chain management tools such as TrakCel and Vineti (previously Vitruvian Networks) aim to manage this risk.

Where appropriate, the use of qualified and trained personnel in receiving the shipment can be critical to ensuring proper handling upon receipt. Collection centres may not be equipped with adequate storage space and mitigating the risk of batch waste in this case requires competence on the part of the clinical establishment.

4.6. When to invest in manufacturing?

Deciding on the stage and degree of investment in manufacturing is a strategically important decision. We searched for press releases between 25/04/17 and 01/01/2016 announcing manufacturing decisions (Table 11), finding the most common manufacturing investment period was in preparation for phase II trials. Several companies also invested prior to pilot clinical trials, plus some expansions to manufacturing resources in anticipation of commercial launch. Press releases listed include both integrated infrastructural development and virtual model out-licensed manufacturing agreements.

Date	Company	Announcement
18 th April 2017	Cobra Biologics	£15m gene therapy manufacturing expansion to meet increasing ATMP CMO needs
11 th April 2017	GE Healthcare; Asymptote	GE acquires Asymptote for undisclosed sum to support enhanced cell ATMP manufacture and cold supply chain
10 th April 2017	GE Healthcare; Cellular Biomedicine Group	Strategic collaboration between GE and CBG to develop CAR-T and stem cell manufacturing industrial process controls
28 th March 2017	Nohla Therapeutics	UC Davis to manufacture NLA101 stem cell product on behalf of Nohla ahead of clinical trials and market
18 th January 2017	Erytech; Invetech	Invetech to develop custom scalable automated manufacturing system for Erytech ahead of phase II trials
18 th January 2017	Servier; MaSTherCell	MaSTherCell to develop CAR-T commercial manufacturing system for Servier ahead of phase II trials
9 th January 2017	Orchard; PharmaCell	PharmaCell to provide manufacturing services for Orchard <i>ex vivo</i> gene therapies ahead of phase II trials
15 th December 2016	Bluebird Bio; Apceth Biopharma	Apceth to continue manufacturing support for European commercial-scale production of gene therapy candidate
13 th December 2016	Kite Pharma; Vitruvian Networks	Collaboration to develop logistics and data analytics software for commercial scale CAR-T production
19 th September 2016	PCT, a Hitachi Group Company; Adaptimmune	PCT to manufacture T-cell products for Adaptimmune over 5 years, ahead of late-stage trials
1 st August 2016	Atvio Biotech (Orgenesis); MaSTherCell	Atvio to provide contract development and manufacturing services to support MaSTherCell expansion
1 st August 2016	Pfizer; Bamboo	Pfizer acquires Bamboo Tx, including phase I/II gene therapy manufacturing assets
21 st June 2016	Kiadis Pharma; PCT, a Hitachi Group Company	PCT to manufacture Kiadis' products for phase III trials
20 th June 2016	Kite Pharma	Kite Pharma opens T-cell manufacturing facility ahead of late-stage clinical trials
17 th April 2016	Freeline Therapeutics; Rentschler Biotechnologie GmbH	Freeline Therapeutics acquires AAV gene therapy manufacturing platform from Rentschler Biotechnologie ahead of clinical development
15 th March 2016	TxCell; PCT, a Hitachi Group Company	PCT to manufacture regulatory T-cells on behalf of TxCell for early-stage clinical trials
10 th February 2016	Lonza; Renova Therapeutics	Lonza to manufacture gene therapy products on behalf of Renova for pivotal phase 3 clinical trials
2 nd February 2016	Invetech; Ceylad	Invetech to develop and supply stem cell manufacturing systems for Ceylad product commercial launch
21 st January 2016	Asterias; Cancer	Cancer Research UK to manufacture stem cell product

	Research UK	for Asterias for phase I/II clinical trial
19 th January 2016	Cellctis; CELLforCURE	CELLforCURE to manufacture CAR-T products for Cellctis ahead of phase I trials
13 th January 2016	GE Healthcare; FedDev Ontario; Centre for Commercialization of Regenerative Medicine	GE Healthcare, Federal Economic Development Agency for Southern Ontario, and the CCRM, to build CAD\$40m advanced therapeutic cell therapy manufacturing centre

Table 11: ATMP industry announcements since 1st January 2016 regarding manufacturing. Blue fill indicates integrated manufacturing; green fill indicates virtual model manufacturing agreements; no fill where N/A.

4.6.1. Portfolio strategy in automation investment

Investors traditionally prefer to delay investing in drug manufacturing optimisation until a product is sufficiently far through clinical development (and therefore low-risk and valuable enough) to justify dedicating the required resources to enhance manufacturing scalability. However, it should be well understood that upscaling advanced therapy manufacturing can be economically impossible without modifications to the process, in particular where manufacturing is particularly labour intensive. Any modifications to the manufacturing process will require comparability studies, and these can be extensive; more dramatic modifications to the manufacturing protocol may even require re-authorisation or clinical trial repetition. Investors must commit to early-stage process development to achieve sales, cash flow and ROI from their first-generation product.

However, many investors have shown a preference to authorise a first-generation product with a manual and poorly scalable process, before investing in scalable, automated second-generation product. Investors must be aware of the limitations on ROI for the first-generation product when adopting this strategy.

4.7. Major manufacturing stakeholders

4.7.1. GE Healthcare

GE Healthcare are a subsidiary of General Electric and produce a significant range of medical equipment, predominantly imaging devices and other hospital services. The company have interest in cell-based drug screening through three core collaborations: a cell analysis research alliance with BGI (2012), a license to Cellular Dynamics' drug screening platform (2012), and a license to CRISPR-Cas9 technology with the Broad Institute (2014).

GE Healthcare produce cell bioprocessing equipment for commercial use, with the Xuri technology family their flagship platform. GE Healthcare have shown considerable interest in growing their cell therapy capabilities, signing co-development agreements with LeukoDx in 2016 and with Zenith Technologies in 2017. They also acquired cell bioprocessing company Biosafe Group in 2012 and cryogenics supply chain solutions company Asymptote in April 2017.

Further to commercial manufacturing solutions GE Healthcare directly supports over 100 clinical stage companies across its various product lines, including in advanced therapies.⁷⁵ GE Healthcare are developing bespoke manufacturing solutions for two CAR-T companies, Kite Pharma (2015) and CBMG (2017).

In January 2016 GE Healthcare announced a \$31.5 million co-investment with the Canadian government (through the CCRM) to open BridGE@CCRM Cell Therapy Center of Excellence, a research institute aiming to accelerate the development and adoption of cell therapies. GE Healthcare and Mayo Clinic co-established Vitruvian Networks in April 2016, aiming to develop software infrastructure to bring “the internet of things” to advanced therapy manufacturing.⁷⁶ The platform aims to coordinate and de-risk the entire supply chain network while incorporating business intelligence and data analytics capabilities.

GE Healthcare is engaging with the advanced therapy industry through several angles, not only producing commercial bioprocessing equipment but also supporting the research ecosystem, developing an advanced supply chain management platform, and providing bespoke bioprocessing systems to two CAR-T companies.

4.7.2. Invetech

Invetech are a large manufacturing company with interest across a range of engineering exploits. Invetech specialise in automation, providing bespoke solutions to clients across medical, industrial and consumer markets. Through their Cell Therapies Group (established in 2004) Invetech have completed over 35 projects for more than 25 advanced therapy companies, including Argos Therapeutics (2014), Ceylad (2016), NanoCollect (2015), NeoStem (a Caladrius subsidiary) (2015) and Erytech (2017). They do not offer contract manufacturing services but work directly with technology developers or manufacturing organisations to integrate bespoke and often automated bioprocessing solutions.

4.7.3. PCT, A Hitachi Group Company

PCT, one of the most widely used CDMOs, having agreed manufacturing contracts with Orchard Therapeutics (2017), Adaptimmune (2016), TxCell (2016), Kiadis (2016), Kite Pharma (2015), IRX Therapeutics (2015), Immunocellular Therapeutics (2015), Medstar Georgetown University Hospital (2013), Hackensack University Medical Center (2013), Baxter (2012), and Sotio (2012). PCT also announced a collaboration agreement with supply chain management platform TrakCel and one with instrument developer Invetech, both in 2015. PCT has 55,000ft² of development and manufacturing space across two separate US facilities (Allendale, New Jersey on the east coast, and Mountain View, California on the west coast), and announced in October 2016 a \$17.5 million CDMO facility in Yokohama, Japan, to be constructed by parent company Hitachi Chemical and to be fully operational by April 2018.

4.7.4. Lonza

Lonza offer manufacturing solutions across chemical, water processing, consumer, agricultural, pharmaceutical, and other industries. In the advanced therapy sector they manufacture a range of off-the-shelf bioprocessing solutions, but also engage directly with technology developers as a CMO. Lonza currently have two advanced therapy manufacturing facilities, a cell therapy suite in Walkersville, Maryland, and a 2,000L, 100,000ft² viral therapeutics facility in Houston, Texas. In the advanced therapy sector Lonza have agreed manufacturing contracts with Selecta (2017), Renova (2016), bluebird bio (2016), Massachusetts Eye and Ear centre (2016), Benitec (2015), TiGenix (2015), Regeneus (canine cell therapy) (2014), and Celladon (2014). Lonza were awarded a \$9.5 million contract from the NIH to develop and manufacture clinical-grade iPSCs, plus the associated manufacturing infrastructure (2016), and are collaborating with Nikon to build a cell and gene therapy manufacturing facility in Japan (2015).

Lonza are a major manufacturing organisation across the globe and are heavily engaged with the advanced therapy community, offering commercially available bioprocess instruments and widely used virtual model manufacturing services.

4.8. Other manufacturing organisations

Numerous contract development and manufacturing (CDMO) organisations exist globally, some of which with integrated product pipelines for their own therapeutics. Table 12: **Non-exhaustive list of CDMO organisations focusing on EU and US geographies.** Table 12 lists clinical and commercial scale C(D)MOs not included in the above sections.

Company	Geography	Public partners	Notes
Apceth Biopharma	Germany	Bio Deutschland, Dechema	Also developing an integrated MSC immuno-oncology portfolio
PharmaCell BV	Netherlands	Orchard Tx (2016), Immunocellular Tx (2015)	Experience in clinical trial manufacturing with commercial-scale resources
Cobra Biologics	Sweden	Undisclosed	Provides range of goods & services across range of therapy types
Oxford BioMedica	UK	Manufacturing agreement Novartis (2013). Gene therapies out-licensed out to Sanofi (2009), GSK (2006), Immune Design Corp (2012).	Substantial lentiviral manufacturing facility used to develop Novartis' CTL019. Integrated gene therapy pipeline commercialised through out-licensing partnerships.
Roslin Cell Therapies	UK	Advanced Cell Technology (2011), Lonza (2010)	Specialists in iPSC and ESC development and manufacturing.
Cancer Research UK Biotherapeutics	UK	Asterias (2014)	300m ² manufacturing facility; Asterias phase I/II trials contract.
Sartorius	Germany	N/A	Produce bioprocess equipment, no CMO services
Atvio	Israel	None announced	50% owned by Orgenesis
MaSTherCell	Belgium	TxCell (2015), Servier (2017)	Wholly owned by Orgenesis
Cell forCure	France	Cellectis (2014)	1,400m ² semi-automated cGMP facility with space for 8 different products. LFB Group subsidiary
SAFC (Sigma-Aldrich)	US	Applied Genetic Technologies Corporation (2014)	Wide-ranging bioprocessing products. Manufacturing agreement with AGTC

Cell Therapies Pty	Asia-Pacific	PharmaBio, Peter MacCallum Cancer Centre, Medipost	Major Asia-Pacific CMO with presence in Japan, Australia, Malaysia, South Korea
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Table 12: Non-exhaustive list of CDMO organisations focusing on EU and US geographies.

UNDERSTANDING BIOPHARMA INTEREST

Chapter 5

5.1. Summary of Chapter 5

Having shown reservation during the earliest development stage of the advanced therapy sector, major pharmaceutical organisations now play a defining role in characterising the commercial ecosystem. Some of the first applications of modern cell and gene engineering technologies was in developing healthy and disease phenotype tissue models, initially developed for basic research but now heavily integrated into medium to high-throughput drug screening pipelines. Today, GSK are responsible for the authorisation of one of the only two market authorised gene therapies, Novartis are widely anticipated to achieve the first CAR-T MA later this year, and Pfizer have bought up a number of gene therapy assets. Sanofi, AstraZeneca, Roche, Bayer, Shire, Johnson & Johnson (Janssen), and Bristol Myers-Squibb have all developed links to cell or gene therapy assets. Most deals are occurring in early-mid clinical development but becoming increasingly early-stage as the precedence expands and stakeholders generate an increasingly clear understanding of the risk landscape. Some deals are at unprecedentedly early stages of development (Roche signed a \$500 million plus deal with SQZ Biotech, a proof-of-concept stage MIT spinout), testament to the importance of understanding the science behind a technology. Deals have focused on gene therapies (particularly haemophilia and cardiology), CAR-Ts, and manufacturing infrastructure. Although deals are to date relatively low in number, pharmaceutical companies may be considered for exit opportunities and should be consulted as part of investment due diligence, particularly where there is evidence of exceptional scientific value.

5.2. Big Pharma strategy in the advanced therapy sector

The expansive product portfolio and robust financial infrastructure of larger pharmaceutical companies places them well to handle the volatility associated with early stage advanced therapy development as they can support ongoing R&D costs through diversified revenue streams. Pharmaceutical companies are key stakeholders in both directly developing, acquiring, and sponsoring and supporting smaller biotech companies.

Table 13 (below) compiles publicly announced acquisitions, licensing deals, research alliances, and other industry news relating to the activity of large pharmaceutical companies in the ATMP sector. Clinical news and regulatory filings are excluded. Research was undertaken on 27/04/17.

Date	Announcement	Field
10/5/17	Pfizer announce gene therapy collaboration with Sangamo Therapeutics for haemophilia A	Gene therapy for haemophilia A
20/4/17	DePuy Synthes Products (a wholly owned subsidiary of J&J Innovation) acquires 3D printing technology from Tissue Regeneration Systems Inc for bone healing application	Bone healing tissue engineering
01/08/16	Pfizer acquires remaining 78% Bamboo Therapeutics shares for \$150M with milestone payments worth up to \$495M	Gene therapy manufacturing infrastructure
11/7/16	Roche publishes data showing superiority of Organovo 3D printed liver tissues for drug screening	Drug screening
11/5/16	Johnson & Johnson opens life sciences incubator JLABS	Health technology incubator
16/3/16	GSK and Miltenyi Biotec establish cell and gene therapy collaboration, financial terms undisclosed	CAR-T manufacturing
2/2/16	GSK and Adaptimmune expand co-development and licensing collaboration in deal with up to \$500M	CAR-T cancer immunotherapy
11/1/16	Shire buys Baxalta (a Baxter subsidiary) for \$32 billion	Gene therapies & other

8/1/16	Pfizer invests \$46M in four early-stage companies exploring biologics, immuno-oncology, neurodegeneration, gene therapy	Cardiology, oncology, neurology,
21/12/15	Bayer and CRISPR Therapeutics establish joint venture, later named as Casebia Therapeutics, worth \$335 million	Gene editing therapy
7/12/15	Roche and SQZ Biotech announce R&D partnership worth up to \$500 million	Cancer B-cell immunotherapy
19/11/15	Servier exercises exclusive worldwide licensing option to lead Collectis product, UCART19	CAR-T cancer immunotherapy
19/11/15	Pfizer acquires US commercialisation rights to UCART19 from Servier , pay \$80M upfront plus up to \$185M in milestones	CAR-T cancer immunotherapy
10/10/15	Roche and Cellular Dynamics (a Fujifilm subsidiary) enter supply agreement	iPSC drug discovery tools
29/6/15	AMAG Pharmaceuticals acquire Cord Blood Registry for \$700 million	Cell banking
4/6/15	Novartis pulls out of Gamida Cell deal	Cancer immunotherapy
23/4/15	Merck (US) to use Organovo's 3D printed liver tissues platform for preclinical study	Drug screening
23/4/15	MedImmune (subsidiary of AstraZeneca) and Juno Therapeutics enter clinical development collaboration, financial details undisclosed	CAR-T cancer immunotherapy
6/4/15	Bristol-Myers Squibb and uniQure enter exclusive co-development collaboration for gene therapy products; \$100M near-term payments plus up to \$471M in milestone payments	Cardiovascular gene therapy
3/4/15	AstraZeneca and Harvard Stem Cell Institute enter 5-year R&D collaboration for pancreas tissue drug screening	Drug screening
30/3/15	Fujifilm fully acquires Cellular Dynamics International for \$307 million	Cell manufacturing, drug testing & screening, cell banking
30/3/15	Merck (US) and Intrexon enter development and commercialisation licensing collaboration; \$115M upfront with up to \$826M in milestone payments for first 2 programs	CAR-T cancer immunotherapy
20/3/15	GSK enter development, manufacturing and technology transfer collaboration with MolMed	Gene therapies supportive technology
7/1/15	Novartis to collaborate with Intellia Therapeutics and Caribou Biosciences over gene editing tech, finances undisclosed	CRISPR gene editing for drug discovery
5/1/15	Amgen and Kite Pharma enter strategic alliance; Kite receive \$60M upfront and up to \$525M future payments plus royalties	CAR-T cancer immunotherapy
8/12/14	Pfizer to co-develop haemophilia gene therapies with Spark Therapeutics ; Spark receive \$20M upfront payment with up to \$245M in milestones	Haemophilia gene therapy
10/10/14	Novartis expands process development and manufacturing agreement with Oxford BioMedica for three years; Novartis pay \$14M upfront including \$4.3M equity subscription	CAR-T cancer immunotherapy development & manufacturing
21/8/14	ViaCyte Inc. sign rights agreement with Janssen R&D LLC (subsidiary of Johnson & Johnson)	Diabetes cell therapy product & encapsulation platform
19/8/14	Novartis invests 15% stake in Gamida Cell	Cancer immunotherapy
23/6/14	Bayer and Dimension Therapeutics enter development collaboration; Dimension receive \$20M upfront and up to \$232M in milestones	Haemophilia gene therapy
18/6/14	Pfizer and Collectis enter co-development collaboration, Pfizer pay \$80M upfront and up to \$185M in milestone payments	CAR-T cancer immunotherapy
2/6/14	GSK and Adaptimmune enter co-development and licensing collaboration in deal worth over \$350M	CAR-T cancer immunotherapy
29/5/14	Janssen R&D LLC (subsidiary of Johnson & Johnson) to license LADD immunotherapy platform from Aduro , deal worth up to	Cancer immunotherapy

	\$325M with financial details undisclosed	
8/4/14	GSK and MD Anderson enter research alliance	CAR-T cancer immunotherapy
2/4/14	Baxter acquires Chatham Therapeutics for \$70M	Haemophilia gene therapies
17/2/14	Servier enters commercialisation collaboration with Cellectis	CAR-T cancer immunotherapy
3/12/13	AstraZeneca and Lieber Institute launch 2-year R&D drug discovery collaboration using gene-modified stem cells	Drug discovery
1/10/13	GSK to commence trials with TrakCel	Supply chain management
6/9/13	Novartis enters licensing and research collaboration with Regenerex, financial terms undisclosed	Stem cell product development
1/5/13	Novartis announces development and manufacturing collaboration with Oxford BioMedica, Novartis to pay between £2.5M and £4M throughout collaboration	CAR-T cancer immunotherapy development & manufacturing
6/3/13	Roche and BioLamina enter cell culture R&D agreement	Stem cell culture
3/1/13	AstraZeneca and Cellular Dynamics enter iPSC drug discovery R&D collaboration	Drug screening
20/12/12	Novartis buys \$43M 173,000ft ² cellular immunotherapy manufacturing facility from Dendreon Corp	CAR-T manufacturing
6/8/12	Novartis and University of Pennsylvania enter R&D alliance	CAR-T cancer immunotherapy
8/5/12	Pfizer and Centre for Commercialization of Regenerative Medicine (CCRM) establish innovation fund	Drug screening and therapeutic regenerative medicines
29/4/09	Sanofi-Aventis enters collaboration with Oxford Biomedica to develop ocular gene therapies; pays \$26m upfront plus \$24m over following three years plus undisclosed license, milestone and royalty payments on any resulting gene therapies	Ocular gene therapies

Table 13: List of major pharmaceutical companies' movements in advanced therapy sector. Table includes acquisitions, licensing deals, collaborations, research alliances, and other relevant announcements. Source: Company press releases.

5.2.1. Summary of pharma interest in ATMPs

Table 14 (below) summarises the strategic interests of major pharmaceutical organisations in both cell and gene-based advanced therapy products.

Company	Gene therapy	Cell therapy
GSK	Integrated 4-product portfolio; products licensed in from research partners. One market-stage product.	Co-development agreement with Adaptimmune autologous CAR-T company with option for full acquisition.
Pfizer	1 integrated clinical-stage product; co-development agreement with Spark for 2-product haemophilia pipeline; commercialisation rights to Sangamo haemophilia A lead product	Co-development agreement with Cellectis allogeneic CAR-T platform with exclusive US commercialisation rights.
Novartis	No public information.	Leading CAR-T platform expected to reach market in 2017. Investment in MSC treatments for organ transplant.
AstraZeneca	No public information.	Co-funding phase I trial testing antibody in combination with Juno CAR-T product.
Roche	No public information.	Research alliance with SQZ Biotech to develop innovative and widely applicable

		B-cell antigen presentation platform.
Bayer	Joint venture with CRISPR Therapeutics to develop novel gene editing technologies. Co-development agreement with Dimensions Therapeutics for haemophilia <i>in vivo</i> gene therapy.	No public information.
Shire	Integrated Huntingdon's disease gene therapy in clinical development.	No public information.
Johnson & Johnson	No public information.	Investment in ViaCyte encapsulated stem cell treatment for T2 diabetes. License to LADD novel immuno-oncology platform.
Bristol Myers-Squibb	Co-development agreement with UniQure to develop up to 10 cardiology gene therapies.	No public information.
Sanofi	Co-development agreement with Oxford BioMedica worth up to \$50 million for up to 10 gene products.	Acquired Genzyme in 2011 for \$20.1 billion; own three market-stage cell therapies. Later sold some assets.

Table 14: Summary of major pharmaceutical companies' cell and gene therapy pipelines and involvement.

5.2.2. GlaxoSmithKline

GlaxoSmithKline (GSK) have established several co-development agreements to gain traction in the ATMP space, through which they successfully developed and authorised the first *ex vivo* gene therapy. Building on the success of the pathfinding Strimvelis project, GSK now has an expanding gene therapy pipeline and are exploring cellular immuno-oncology through a co-development agreement with Adaptimmune (UK).

GSK has two key strategic alliances supporting their gene therapy pipeline which now boasts three mid/late clinical stage gene therapies in development (two phase III and one phase II), plus a further three preclinical stage gene therapies. All gene therapy products were developed by their research alliance partners at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), with additional support through a co-development agreement with MolMed. GSK's partner roles are co-located in the San Raffaele Biomedical Science Park, Milan, Italy.

GSK entered an alliance with SR-Tiget in 2010, taking exclusive worldwide rights to the Italian-developed ADA-SCID gene therapy which eventually went on to become Strimvelis. MolMed was a key collaborator in its development both before and after it was licensed by GSK, and the companies formalised their ongoing agreement in March 2015. Their latest joint effort involved a €34 million commitment in exchange for expertise in viral vector cellular transduction, which was bumped up to €48 million in September 2016.⁷⁷

The agreement supports GSK's expanding *ex vivo* gene therapy pipeline, strategically commercialising products developed at SR-Tiget. GSK are currently undertaking two rare-disease phase III trials for *ex vivo* stem cell gene therapies; one in Wiskott-Aldrich syndrome, an X-linked, poorly treated disease occurring in 1 in 250,000 men in the US; and metachromatic leukodystrophy (MLD), a liposomal storage disease with around 3,600 new cases globally every year.⁷⁸ A phase II trial in β -thalassemia is also underway, and three preclinical gene therapies in development, the most advanced of which is indicated for mucopolysaccharidosis type 1 (MPS 1).

After selling much of its cancer drug portfolio to Novartis for \$16 billion in 2015, GSK has renewed its oncology programme through a co-development agreement with Adaptimmune.

Adaptimmune's lead product NY-ESO-1 is a T-cell receptor (TCR) platform, and GSK have an option to assume full responsibility for the program as part of their agreement, valid throughout clinical development.⁷⁹ NY-ESO-1 is currently in phase I/II trials for sarcoma, multiple myeloma, non-small cell lung cancer, melanoma and ovarian cancer. Under their agreement, GSK have a license to four additional products.

GSK's collaboration with Miltenyi Biotec evidences their understanding of the importance of manufacturing in the ATMP sector. The collaboration seeks to support GSK's portfolio of cell and gene therapy products through developing automated bioprocessing solutions for autologous therapies.⁸⁰

5.2.3. Pfizer

Pfizer entered the gene therapy space in August 2016, acquiring Bamboo Therapeutics for \$150 million plus milestone payments up to \$495 million, following an initial \$43 million investment in early 2016. The move was largely attributed to the presence of Bamboo's production-ready phase I/II-scale gene therapy manufacturing facility. Recruitment for a phase I/II trial in giant axonal neuropathy (GAN), an ultra-rare neurological disorder, is currently underway, with an additional three preclinical-stage products in Bamboo's pipeline.

Pfizer also has gene therapy interests through a co-development agreement with Spark Therapeutics, established in December 2014, appointing Michael Linden to lead the programme. Pfizer paid \$20 million upfront for the deal, plus future royalties and up to \$245 million in milestone payments. Spark Therapeutics is responsible for clinical development of the haemophilia gene therapy candidates, following which Pfizer will assume responsibility for global commercialisation. Pursuant to terms of the deal Spark has received two \$15 million payments (December 2015 and January 2017) following the completion of product and clinical development milestones. Pfizer have followed up this investment through an exclusive collaboration with Sangamo, announced May 2017.⁸¹ Through the deal Pfizer received exclusive commercialisation rights to SB-525, a clinical stage gene therapy for haemophilia A, while Sangamo received in \$70 million upfront, up to \$475 million in milestone payments, and double digit royalties.

Pfizer entered the cellular immuno-oncology field in 2014 through a large co-development agreement with Cellectis, securing rights to potential future CAR-T cancer treatments. Pfizer took a 10% stake in the company at the time, paid \$80 million upfront, and promised up to \$185 million in regulatory, commercial and milestone payments. Pfizer also have exclusive commercialisation rights to UCART19, Cellectis' lead product, for the United States- acquired through Servier, who exercised a right to worldwide exclusive commercialisation rights to UCART19 in November 2015. In March 2015 the Financial Times reported that Pfizer were in talks with Cellectis about a potential acquisition deal worth up to €1.5bn, but no deal has as yet emerged.⁸²

5.2.4. Novartis

Novartis were the first large pharmaceutical company to enter the CAR-T space, signing a research alliance with the University of Pennsylvania in August 2012 to develop CTL019. Novartis has also invested \$20 million in a first-of-its-kind translational research institute at the University of Pennsylvania, the Center for Advanced Therapies, dedicated to the discovery, development and manufacturing of adoptive T-cell immunotherapies. Interim data from Novartis' phase II JULIET trial is confirmed for release in June 2017, with market authorisation expected later in 2017- likely to be the first CAR-T authorisation.⁸³

Novartis entered a collaboration with Intellia Therapeutics and Caribou Biosciences in January 2015, bringing access novel CRISPR technology platforms. Novartis have not publicly discussed any gene therapy programmes, and the gene editing technology will likely be applied to its CAR-T product as well as enhancing its drug discovery platforms.

Novartis entered a research and exclusive global licensing deal with start-up Regenerex in September 2015, after a clinical study testing MSCs in kidney transplants prevented the need for immunosuppressants in 5 out of 8 patients.^{84,85} The deal also brings access to Regenerex' haematopoietic stem cell-based Facilitating Cell Therapy (FCRx) platform, which will be used to investigate genetic deficiencies as well as manufacture MSC products.

Novartis announced the dissolution and re-integration of its Cell & Gene Therapies Unit in August 2016, cutting 120 positions.⁸⁶ Although the move suggests a move away from novel ATMP therapies Novartis stated it remains fully committed to developing CTL019.

5.2.5. AstraZeneca

AstraZeneca has adopted stem cell technology for drug discovery purposes through collaborations with Cellular Dynamics International (2013), Lieber Institute (2013), and the Harvard Stem Cell Institute (2015). Cell-based drug screening is understood to be widely implemented among the pharma industry, generally developed through integrated programmes which limit public information.

AstraZeneca made its first move into cell-based ATMPs in April 2015, when its R&D arm MedImmune entered a non-exclusive clinical development collaboration with Juno Therapeutics.⁸⁷ Under the agreement, MedImmune will co-fund a phase I trial combining Juno's lead CAR-T product with MEDI4736, a monoclonal antibody developed by AstraZeneca.

5.2.6. Roche

Roche has made several investments in cell-based drug screening but largely held back with major investments in ATMP therapeutics, reportedly restraining itself to monitor the developing industry and identify technological advancements likely to usher in the next technological generation.⁵⁹

In December 2015 Roche made its first plunge, entering a strategic research alliance with SQZ Biotech, a small spin-out from Robert Langer's lab at MIT running on a single \$5 million Series A round. The technology platform leverages an innovative B-cell antigen presentation platform with broad application, currently indicated to pursue immuno-oncology indications but with the scope for wider application. Roche hopes that the technology can overcome many of the challenges associated with current immuno-oncology approaches, and although did not disclose upfront finances, promised over \$500 million if the technology delivers. Roche have not announced any information regarding which cancers or antigens they will target, or when clinical trials can be expected.

5.2.7. Bayer

Bayer originally entered the gene therapy space in June 2014 when it announced a collaboration with Dimension Therapeutics. Under the deal, Dimension received a \$20 million upfront payment plus future clinical development and commercial milestones worth up to \$232 million. Dimension are responsible for all preclinical activities and a phase I/IIa clinical trial in haemophilia A, with funding from Bayer. Positive interim results from the trial were announced in January 2017, showing a clinical response sustained at 52 weeks.⁸⁸

Bayer made big waves at the end of 2015 by announcing the formation of a joint venture with CRISPR Therapeutics, named as Casebia Therapeutics in November 2016. The venture combines the gene editing capability of CRISPR Therapeutics with Bayer's expertise in protein engineering and knowledge of the three disease areas: blood disorders, blindness, and congenital heart disease. Bayer will provide a minimum of \$300 million in R&D to the venture over the next 5 years, which may lead to exclusive licensing deals between the parties. Newly created know-how from the collaboration beyond the three disease indications will be exclusively available to CRISPR Therapeutics for human use, and to Bayer for non-human use, such as in agricultural applications.

The deal was acknowledged as 2016 Dive Awards Most Valuable Pharma Deal of the Year in recognition of its unique setup and strategic thinking, despite other deals involving higher amounts of cash.⁸⁹ Casebia will be based in London with operations taking residence in Bayer's San Francisco CoLaborator incubation facility, and aims to develop CRISPR-Cas9-enabled *in vivo* gene therapies.

5.2.8. Baxter

Baxter started developing gene therapies in 2014 by acquiring Chatham Therapeutics' gene therapy programmes at the cost of \$70 million. The move follows a 2012 research agreement supporting Chatham's recombinant gene therapy platform as a potential treatment for haemophilia B (BAX 335), for which Baxter assumed full ownership through the 2014 acquisition. Baxter spun out Baxalta in 2015 to develop Baxter's biopharmaceuticals, and in January 2016, Shire agreed to acquire Baxalta for \$32 billion.

5.2.9. Shire

After acquiring BAX 335 in January 2016 Shire went on to cancel the product in August of that year, following moderate phase I/II clinical data, choosing to refocus on preclinical-stage gene therapy candidates. Shire signed a collaboration and licensing agreement with Sangamo BioSciences in 2012 to develop Sangamo's zinc finger DNA-binding protein gene therapy technology intended to treat a range of monogenic diseases, contributing \$13 million upfront and promising undisclosed further payments. In 2015 the collaboration disbanded, with each party walking away with the assets most suitable to their strategic goals. Sangamo kept haemophilia A and B gene therapy products for which it granted Shire first right of negotiation, while Shire kept rights to their Huntingdon's product and an additional undisclosed target.

5.2.10. Johnson & Johnson

Johnson & Johnson have showed modest interest in the ATMP sector to date, supporting an encapsulated pancreatic cell technology and a cancer immunotherapy platform as well as launching a life sciences incubator, JLABS. In February 2016, Janssen BetaLogics (a subsidiary of Johnson & Johnson) was acquired by ViaCyte in a mutual effort to co-develop an ESC-derived encapsulated pancreatic cell cure for diabetes. The Johnson & Johnson Development Corporation is a long-standing investor in ViaCyte, and through the Janssen acquisition, contributed a further \$20 million. ViaCyte's lead candidate, VC-01, is currently in phase I/II clinical trials for type 1 diabetes.

In May 2014, Janssen licensed Aduro's lead immunotherapy platform, live attenuated double-deleted (LADD) *Listeria monocytogenes*, in a deal worth up to \$365 million through a combination of upfront, licensing, and milestone payments. The approach involves engineering the bacteria to present tumour antigen(s) before injecting them back into the

patient, leveraging the natural immunological response to the bacteria to also activate the patient's immune system against the tumour.

5.2.11. Bristol-Myers Squibb

Bristol-Myers Squibb (BMS) have made a single punt at the ATMP sector through a 9.9% stake in UniQure, alongside an exclusive research alliance with the company to develop multiple gene therapies in cardiology taken.⁹⁰ Through the 2015 deal BMS made an investment of around \$100 million in its partner, including an equity stake of at least \$32 million, milestone payments up to \$254 million for their lead product and up to \$217 million for each other gene therapy developed under the collaboration, and royalty payments. The collaboration covers 10 potential therapies, for which UniQure are responsible for their manufacturing.

5.2.12. Sanofi

Sanofi-Aventis originally entered the advanced therapy space as early as 2009 through a collaboration with Oxford BioMedica to develop gene therapies for ocular disease. Sanofi paid \$26 million upfront and committed up to \$24 million over the following three years, plus undisclosed license, milestone and royalty fees, in exchange for the option on exclusive worldwide licenses for up to four ocular products resulting from the collaboration. Sanofi exercised two options in June 2012 for StarGen and UshStat, triggering a \$3 million payment to Oxford BioMedica. Positive interim clinical data on a UshStat was announced in May 2012 and StarGen in August 2012, both for phase I/IIa trials.

Sanofi-Aventis further expanded into the advanced therapy sector in 2011, when it fully acquired Genzyme for \$20.1 billion. Genzyme has a long history in the cell therapy and regenerative medicine sector, bringing Carticel, Epicel and MACI to market, some of the first cell therapies, through its Cell Therapy and Regenerative Medicine (CTRM) business.⁹¹ Genzyme also collaborated on the development of Prochymal and Chondrogen with Osiris Therapeutics, marketing the products outside of the US and Canada.⁹² Osiris regained full rights to the products in 2012 following expiry of the prior agreement in accordance with its original terms. In April 2014 Sanofi announced the sale of the CTRM business to Aastrom for a total of \$13 million.⁹³

5.3. 'Big Pharma' strategy in the cell and gene therapy space

Large pharmaceutical companies are traditionally averse to high-risk investments and have to date been slow to adopt cell and gene therapies, although this is rapidly changing, and multiple organisations are explicitly shifting the focus of their pipelines away from small molecules and towards advanced biologics.⁹⁴ Sanofi is to demolish a \$118 million small molecule manufacturing plant it completed in 2011 but never used, stating that "in the meantime, the company's product portfolio had evolved towards a majority of biologics products rather than chemical products... Thus, the production requirements for chemical clinical batches had greatly decreased".⁹⁵ In February, Sanofi announced the construction of a €270 million (\$286.3 million) biologics manufacturing plant with Lonza, at the CDMO's Swiss site.⁹⁶ Further, Roche announced in November 2015 a major strategic shift towards more specialised small molecules and biologics, stopping short of specifically announcing an advanced therapeutics focus but demonstrating discomfort with traditional small molecules, cutting 1,200 jobs.⁹⁷

The authorisation of Glybera in 2012 was the first big win for the gene therapy industry, and although the drug was a commercial flop with only one purchase, it made history as the first

authorised *in vivo* gene therapy. GSK's Strimvelis followed in 2016, demonstrating the feasibility of the *ex vivo* approach. GSK continues to lead the gene therapy space with an additional three fully integrated products in mid-late stage trials and three further products in preclinical development. Pfizer integrated gene therapy assets in 2016 through the acquisition of Bamboo Therapeutics, after collaborating with Spark Therapeutics earlier that year, going on to take over the lead haemophilia A gene therapy from Sangamo in May 2017. Further, Bayer are undertaking a joint venture with CRISPR Therapeutics (Table 14).

Collaborators	Product(s)	Stage	Indication(s)
GSK/Adaptimmune	NY-ESO-1 CAR-T	Phase I/II	Synovial sarcoma, MM (CD3 ⁺), melanoma, NSCLC and ovarian cancer
Roche/SQZ	Immunotherapy antigen presentation platform	Proof of concept	Platform technology with broad application
Pfizer/Cellectis	Up to 15 CAR-T targets	Phase I	BPDCN, AML, B-cell ALL
Amgen/Kite	Unnamed CAR-T product	Preclinical	Oncology, disease type unannounced
GSK/ SR-Tiget	Various gene therapies	Discovery-market	ADA-SCID, Wiskott-Aldrich syndrome, MLD, β -thalassemia, MPS 1
Pfizer/Spark	SPK-FIX gene therapy	Phase I/II	Haemophilia B
AstraZeneca/Juno	JCAR015 with MEDI4736 CAR-T combinational	Phase Ib	CD19 ⁺ B-cell NHL
Merck/Intrexon	Unnamed CAR-T product	Phase I	CD19 ⁺ Lymphoma, B-cell lymphoma
Novartis/UPenn	CTL019 CAR-T	Phase II	CD19 ⁺ DLBCL
Amgen/Kite	BiTE platform CAR-T	Phase I	Undisclosed (<i>expected oncology</i>)
Janssen (J&J)/Aduro	LADD immuno-oncology platform	Phase I	Prostate cancer, lung cancer
BMS/UniQure	Up to 10 gene therapies including S100A1	Preclinical	Up to 10 targets, including cardiovascular disease

Table 15: Collaborations entered into by pharmaceutical companies in the advanced therapy sector. Big pharma companies are developing ATMPs exclusively through external partnerships. MM= Multiple myeloma; NSCLC= Non-small cell lung cancer; ADA-SCID= Adenosine deaminase deficiency severe combined immunodeficiency disorder; MLD= Metachromatic leukodystrophy; MPS= Mucopolysaccharidosis; BPDCN= Blastic plasmacytoid dendritic cell neoplasm; AML= Acute myeloid leukaemia; ALL= Acute lymphoblastic leukaemia; NHL= Non-Hodgkin lymphoma; DLBCL= Diffuse Large B-Cell Lymphoma. Source: Company press releases.

Cell therapies have substantially higher supply chain complexities than the much simpler pills-in-a-bottle model enjoyed by small molecules, or even of gene therapies. The specialised handling and complex supply chain management required present high barriers to adoption, and the cell therapy industry has been largely pushed forward by spin-outs and young biotech companies rather than large drug makers. However, again, this is changing; Novartis are developing a leading CAR-T product, Pfizer have a stake in the CAR-T race through a collaboration with Cellectis, and GSK are collaborating on Adaptimmune's lead CAR-T platform.

Aside from GSK most pharmaceutical companies seem to be engaging with cell and gene therapies by in-licensing promising platforms and products developed by smaller biotechs rather than developing them in-house. By means of example, Roche made its first move into the cell therapy sector in December 2015 through a \$500 million licensing deal with SQZ Biotech, a small and relatively unknown MIT spinout. The deal provides an excellent demonstration of the value large pharmaceutical organisations place on external innovation, which in turn presenting clear scope for returns on investment for those able to identify and invest in promising technologies.

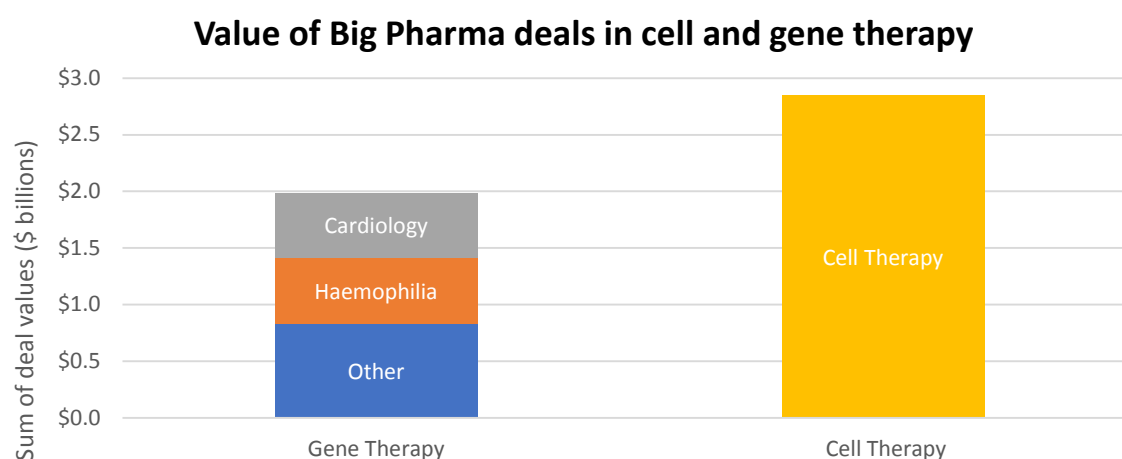


Figure 5: Sum value of deals undertaken by Big Pharma in cell and gene therapy space. Within gene therapy there was 1 cardiology deal, 3 haemophilia deals, 2 other deals including 1 in neurology; in cellular therapeutics, 7 immuno-oncology deals only. Source: Company press releases.

Pharmaceutical companies responsible for developing or commercialising ATMPs have shown awareness of the need to address manufacturing and supply chain challenges. GSK entered a collaboration with Miltenyi Biotec, Pfizer acquired Bamboo Therapeutics, Novartis acquired Dendron's cellular immunotherapy therapy manufacturing facility in 2012 as well as entering a development and manufacturing agreement with Oxford BioMedica. These strategic movements highlight both the validity of manufacturing as a major hurdle to commercialisation and the opportunity for investors to achieve returns by investing within the wider advanced therapy ecosystem.

5.3.1. Cellular drug screening assays

A major and more immediate application of advancing cell and gene manipulation and culturing technologies is in drug screening. Cell-based models are ethically and financially less restrictive than animal models, and can predict pharmacokinetics, toxicity, and other *in vivo* functions on a medium to high-throughput scale. The use of human cells instead of animal can provide empirical insight into drug behaviour not previously possible until first-in-man application.⁹⁸ Further, genetic modification can be applied to cellular assays to model disease, enabling novel methods of investigating pharmaceutical mechanisms of action.⁹⁹ Cell models can be cultured in 2 or 3 dimensions. Each approach has cost and functionality implications, and the absolute advantage of each approach is controversial in the literature. 3D organoids aim to model the function of an entire organ, and innovators aim to link individual organ systems in pursuit of 'body-on-a-chip' systems aiming to model entire physiological

systems.^{100,101} In December 2012, Roche announced a collaboration between 10 large drug-makers and 23 academic centres to develop a collection of 1,500 iPSC-derived cell lines for use in early drug testing against a range of neurological disorders as well as diabetes.¹⁰² The project, dubbed StemBANCC, is managed by Oxford University and has a €55.6 million budget. Pharmaceutical companies are developing cell-screening platforms both in-house and through external collaborations.

5.3.2. Areas of therapeutic focus

Pharmaceutical companies have focused interest in only the most promising areas of investigation as per their traditionally risk-averse strategy. CAR-T products are a major focus with deals in the space totalling \$2.8 billion, with stakeholders including GSK, Pfizer, AstraZeneca, Merck, Amgen, and Novartis. To date, CAR-Ts are the only publicly announced cell-based therapeutics in development by big pharma, although several organisations hold access to platform technologies applicable to additional indications. The gene therapy sector has previously pursued orphan indications due to the relative accessibility of low-risk market authorisation and market exclusivity incentive, but other monogenic disease treatments are emerging, most notably haemophilia and β -thalassemia. Cardiology is another area of interest with one collaboration between UniQure and BMS for S100A1, a gene therapy indicated for congestive heart failure.

5.4. Case study: Novartis and CTL019

The University of Pennsylvania (UPenn) published their first CAR-T data in August 2011 in the *New England Journal of Medicine*. The paper described first-in-man data of their novel CAR T-cell product, achieving ongoing remission (at 10-month follow-up) in a 65 year old male with refractory chronic lymphocytic leukaemia (CLL).^{103,104} Further clinical data was generated through a series of later

publications, culminating in a 2014 paper describing complete remission in 27 of 30 patients with relapsed or refractory acute lymphoblastic leukaemia (r/r ALL).^{105,29} 67% of patients achieved sustained remission, with an overall survival rate of 78%. This stream of publications generated data unlike anything ever achieved in cancer treatment, let alone in terminal patients.

Title	Condition	Phase	Start Date	End Date	Enrolment
ELIANA: Determine Efficacy and Safety of CTL-019 in Pediatric Patients With Relapsed and Refractory B-cell ALL	ALL; MM; NHL	Phase II	30-Apr-2015	31-Jan-2023	72
ENSIGN: Study of Efficacy and Safety of CTL-019 in Pediatric ALL Patients	B-cell ALL	Phase II	14-Aug-2014	14-Jul-2022	67
JULIET: Study of Efficacy and Safety of CTL-019 in Adult DLBCL Patients	DLBCL	Phase II	29-Jul-2015	01-Jan-2024	130
Expanded Treatment Protocol in Acute Lymphoblastic Leukemia	ALL	Phase II	Unknown	Unknown	Unknown
CD19 CART Long-Term Follow-Up (LTFU) Study	BCL	Phase II/III	02-Nov-2015	05-Sep-2036	500
CART-19 for Multiple Myeloma	MM	Phase I	31-May-2014	31-Dec-2017	13

Table 16: Novartis CTL019 clinical trials. BCL- B-cell lymphoma; DLBCL- Diffuse Large B-cell lymphoma; MM= Multiple Myeloma; ALL= Acute lymphoblastic leukaemia; NHL= Non-Hodgkin lymphoma. Source: www.clinicaltrials.gov

The data coming out of the Carl June lab at UPenn data generated a huge amount of interest, and in August 2012, UPenn and Novartis announced an exclusive research and licensing agreement to further develop the CAR technology. Novartis promised \$20 million in funding for ongoing research at UPenn in relation to the technology.¹⁰⁶ The novel therapy, dubbed CTL019, entered formal phase II clinical trials under Novartis in 2014, and achieved complete remission in 93% of 59 paediatric patients with r/r ALL. However, 88% of patients developed cytokine release syndrome, and complete remission rates fell to 31% at 12-month follow-up. Several other clinical trials are underway in other indications (Table 16), the largest of which (JULIET) is due for interim data release in June 2017.

Novartis filed a BLA for CTL019 in March 2017 for relapsed and refractory paediatric and young adult patients with B-cell ALL, based on the results of a phase II trial (NCT02435849) named the ELIANA study. The FDA granted priority review for the application, and a response from the FDA is expected later in 2017.

ADVICE FOR INVESTORS

Chapter 6

6.1. Chapter summary

Technology platforms offer a lower risk business strategy than therapeutic products and can be more broadly applicable, but are limited in absolute revenue potential by their dependency on partnerships. Investing in advanced therapies implicates a diverse risk profile with complexities and nuance behind their individual resolve. Investors must be equipped with sufficient technical understanding of not only the products themselves but any associated needs to realise value. Understanding clinical data is crucial to assessing the value of a therapy, including both safety and efficacy profiles. While ATMPs are generally safer than small molecules in phase I trials, there are serious risks and these should be fully understood and addressed. Novel strategies for safety risk management in CAR-Ts are the installation of activating and/or suicide-inducing control switches to control the product's *in vivo* function. Clinical trials should be designed with strategic insight to both maximise their chance of success and facilitate market access.

P&R concerns should inform clinical trial design and market access strategies, where comprehensive endpoints and follow-up periods should be expanded and extended to formally and validly capture the full value of a product. A strong P&R strategy encourages market access, but implementation and adoption must be supported by ensuring the product is simple to use and therefore easily implemented into clinical practice with minimal disruption to standard operating procedure. Market access also requires engagement with the patient and physician communities. Competitive risk is substantially mitigated where a product is first to market, especially in orphan indications.

Manufacturing in advanced therapies is currently subject to high levels of risk; scalable (including automated) manufacturing solutions must be implemented early in development to mitigate the need for demanding comparability studies, which in turn requires deep understanding of the product and its mechanism of action. Virtual model manufacturing is widely used. Supply chain solutions should be de-risked through informed design, comprehensive tracking and traceability, and cryopreservation or other shelf life extension solutions implemented where necessary. Regulatory bodies globally have taken unprecedented steps to assist the development of advanced therapies and demonstrate flexibility and support in their outlook; this can be best leveraged through early and ongoing engagement by technology developers.

Major biopharmaceutical companies are expressing increasing interest in advanced therapies, generally through collaboration and co-development type agreements, although the recent history of several major and minor acquisitions of both late but also early and very early stage biotechs holds good promise for expedited exit options or partnering agreements with large pharmaceutical organisations. The increasing shift of 'big pharma' from small molecules to biologics and advanced therapies should not be overlooked when making investment decisions.

In publicly markets, small cap companies have great potential for returns as demonstrated by several success stories, while advanced therapies are perceived as less susceptible to political disincentives in pharmaceuticals trading. Raw materials companies and platform companies have seen particular success. Several barriers exist to attracting limited partnership (LP) investment in VC funds but these can be overcome through informed and strategic decision-making. Despite a global drop in value in the pharma, medical and biotech sector at the start of 2017, the advanced therapy subsector has seen a series of large deals, acquisitions and IPOs. The sector remains attractive for investors, with a new generation of companies

building on previous failures and successes to build investable and robust platforms and portfolios. However, investors should be careful and selective as successes to date have been concentrated to a minority of cases.

6.2. Potential of technology platform vs product

Technology platforms are fundamentally different from therapeutic products themselves as they provide a scientifically original means by which a portfolio of candidates can be developed, or otherwise break down the host of commercialisation barriers into more manageable partitions. Common business models associated with platform companies are lower-risk than those aiming to bring products to the market, as candidates developed from a technology platform can be out-licensed for external development for a more achievable financial realisation of value than attempting to bring each product to market. ‘Horizontal’ and ‘vertical’ business strategies generally do not combine well for two reasons: investors perceive a multiplication of business risk, and partners perceive potential competition from the company’s internal product development efforts.¹⁰⁷ Additionally, these two routes require different teams, financing models and strategies. A successful platform is widely applicable to multiple projects without requiring large upfront capital investments to suit each purpose. Platform companies can maintain their competitive advantage by focusing resources on maintaining the technological lead rather than on advancing high-risk product candidates. Platform companies are limited in their revenue potential by the availability of interested partners with no or limited potential for direct market sales.

6.3. Major risk factors when investing in advanced therapies and recommendations to their mitigation

6.3.1. Product functionality and evidence

The most fundamental analysis that must be undertaken when considering an investment is that of whether the product functions as intended, the degree to which this function can be performed, and the validity and extent of evidence behind these claims. For a therapeutic technology the investor must understand proof-of-concept rationale, assess data quality, and understand the implications of this evidence in the context of downstream clinical and commercial needs. For example, animal model proof-of-concept data may provide some strong early evidence, but similar results may not be achieved in humans. Small-scale and early-stage data in isolation must be statistically significant, and even then, is unlikely to be representative of late-stage clinical trial performance. Early data is unlikely to include long-term follow up to evidence the temporal extent of clinical benefit. Technical expertise and scientific training is essential to exploring the nuance of robust data generation.

6.3.2. Safety

ATMPs are generally safer compared to small molecules at the same developmental stage in part because many are based on human cell types found naturally in the body, and cell-based technologies very rarely fail in phase I trials. Despite this, serious risks do remain that require attention. Strategies to mitigate safety risks are technology type-dependent, but include intelligent product design, extensive preclinical testing and development, and taking precautionary steps to compensate for potential future safety concerns by removing or inactivating the product.

CAR-T trials have caused the deaths of several patients to date. Clinical trial design Juno, one of the previously purported CAR-T industry leaders, halted its lead clinical program in March

2017 after 5 of the 38 treated patients died from cerebral edema.¹⁰⁸ There have been other deaths related to CAR-Ts, including one death also from cerebral edema in a Kite Pharma trial announced May 2017, and a number of deaths related to cytokine release syndrome (CRS) (also referred to as cytokine storm) within academic trials.^{109,110} CRS is a result of exceedingly high levels of inflammatory cytokines in the blood following immune system over-activation by the infused CAR-Ts. This side effect has been largely mitigated by leading CAR-T products through careful dose selection, preconditioning regime optimisation, and in some cases, building in kill-switches or other control mechanisms.

A key example of this is the implementation of CAR-T 'switch on' control by Cellectis and Bellicum, whereby infused CAR-Ts remain inactive until co-activation by an external signalling molecule. Bellicum also uses a 'suicide switch' which offers an additional level of control. This approach to safety provides key advantages over 'naked' CAR-Ts which may be more prone to uncontrolled CRS or other side effects.

A second avenue of improved CAR-T safety is in target antigen selection. Many CAR-T programmes target CD19, a B-cell specific antigen that functions as a tumour-associated antigen in liquid blood cancers. Targeting CD19 with CAR-T therapies usually results in the complete ablation of all B-cells in the patient, and although this is not significantly clinically detrimental, antigen presence in peripheral tissues could cause on-target toxicity. Efforts to restrict CAR-T activity to cancer cells is currently a major area of research focus, and developers are developing dual-specificity products that only activate in the simultaneous presence of two specific antigens.

Several high-profile deaths littered throughout the history of the gene therapy field have inhibited commercial interest for years. One of the most infamous was the case of Jesse Gelsinger, who died in 1999 following treatment with pioneering AV vector gene therapy for ornithine transcarbamylase deficiency, an X-linked genetic liver disease.¹¹¹ In 2001, two separate groups in Paris and London treated 9 and 10 children suffering from SCID-X1 respectively. 4 of the Parisian and 1 of the London patients went on to develop leukaemia, later identified to (in 2 cases) be a result of the gene vector over-activating oncogenes.¹¹² The technology behind gene therapies has progressed significantly since these deaths, with improvements to vector design and elucidation of integration pattern profiles resulting in the increased safety of AV and AAV vectors, and the transition of many to lentiviral vectors, which are associated with a safer integration pattern. Only long-term data will confirm the full safety of integrating gene therapies and risks still remain- three patients died in a brain cancer clinical trial undertaken by Ziopharm, confirmed June 2016.¹¹³ However, the commercial gene therapy industry has largely mitigated safety risks associated with gene therapies through ongoing diligence and progressing technology. Ensuring safety in gene therapies refers most specifically to understanding vector integration patterning, ensuring the vector does not integrate into transcriptional promotional regions, and improving the vector accordingly or switching to an alternative type if necessary. Advanced sequencing technologies mean this is increasingly accessible and developers should be able to quantify this risk at preclinical stage.

6.3.3. Clinical trial design

Optimal clinical trial design provides a real opportunity to de-risk development and market access and is predominantly solvable through informed strategy design alone. Early trials can maximise their chance of success by excluding patients least likely to recover, while late-stage trials should expand inclusion criteria to maximise market potential. Recruitment

limitations are a leading cause of clinical trial failure and this risk should be considered particularly when designing early stage trials with more restricted inclusion criteria, mitigated by expanding inclusion criteria and/or opening additional trial sites. To de-risk regulatory approval and P&R, developers should enter discussions with regulatory and HTA bodies to identify the most relevant active comparator for use in clinical trials and to align endpoints with health economics drivers. To enable market access following authorisation and reduce the burden of implementing modifications to clinical practice, clinical trial sites should be located in areas of high market demand that can later become market-stage administrative centres. Regulatory authorities should be directly consulted to confirm the approvability of endpoints and trial design modified respectively.

6.3.4. Pricing and reimbursement

P&R presents a moderate level of uncertainty in achieving ROI on ATMP investments, and optimal solutions can be relatively opaque at a time when few products have achieved commercial success. Highly efficacious products demand a high pricing point relevant to their value, and products aiming to deliver curative results could demand unprecedentedly high prices that payers may struggle to afford, even when cost-effectiveness is validated. Crucial to mitigating this risk is comprehensively understanding the health economics behind the disease, and its treatment by standard of care, competitors, and the drug candidate itself. This understanding should be leveraged through formally capturing value in clinical trials, designing long-term and in-depth endpoints for both direct clinical outcomes and indirect healthcare costs. Fundamentally, it is the prerogative of the technology developer to demonstrate to HTA bodies the true economic, social and humanitarian value of curative treatments, and developers should engage with HTA stakeholders at an early stage to ensure clinical development strategy aligns with pivotal parameters in P&R appraisals. There is little precedence in capturing these peripheral factors as their implications are negligible where drugs offer incremental gains to life expectancy, but where therapies are truly curative, the non-clinical implications of clinical benefit represent a trove of value in supporting drug pricing. This process can involve significant administrative demands and may not be financially justifiable, but this decision should be well informed, and surrogate or predictive data generated where direct data is inaccessible. Pricing should be primary driven by value rather than by cost.

HTA bodies prefer to make decisions based on comparators, normally the standard of care, or other treatment with a more directly comparable mode of action. Technology developers should make an effort to support HTA bodies in their analysis, including through discussions regarding comparators. Clear-cut gains to cost-effectiveness supports reimbursement and clinical adoption, while confused, unclear or marginal gains to cost-effectiveness over comparators can suppress adoption. There is precedence for patient testimonials to support P&R negotiations, particularly where more formal cost-effectiveness calculations are unclear, and technology developers should engage with patient advocacy groups to leverage this angle.

6.3.5. Market access

Market access depends heavily on pricing and cost-effectiveness, but the disparate treatment mode of many advanced therapies to small molecules, biologics, and other treatments may hinder market penetration. Advanced therapies should be designed to be as simple and user-friendly as possible to encourage a healthy perception of the product amongst clinician communities. Therapies which are excessively complex to use risk deviation from the intended protocol, which can jeopardise efficacy, ultimately threatening the reputation and

success of the developer. Where necessary, advanced therapies should be provided with instructional documentation, training, and/or limited to specific clinical sites. Horizon scanning centres can support the awareness of advanced therapies in development, and should be directly engaged with at an early stage to ensure maximum exposure, alongside presence at major conferences and other industry networking events. Patient advocacy groups and charities can provide excellent drivers for market access through increased awareness. Several leading advanced therapy companies (e.g. Celgene) have appointed market access and/or reimbursement officers to address these high-risk needs from an early/mid-clinical stage, and this strategy is recommended for products with moderately or highly complex P&R and market access needs.

6.3.6. Mitigating competition

The ATMP industry is relatively young with few products on the market, therefore limiting competition predominantly to indirect treatments. However, this is almost certain to change, particularly in the cellular immuno-oncology sector where a notable number of late-clinical stage products aim to enter the liquid blood cancer (mainly CD19⁺) treatment market over the coming years. Mitigating both indirect and direct competition requires early engagement with horizon-scanning stakeholders, public activity such as publications and press reports to generate attention and awareness from commercial, investor, academic, and clinical stakeholders. Products may be differentiated from competitors through their indication for specific patient sub-populations, potentially offering the additional incentive of orphan status where the sub-population is sufficiently restrictive. Further means of differentiation are in offering a different price/reward paradigm, or through insights into stakeholder needs or behaviour that competitors do not have.

Positioning as the first to market offers tangible advantages. In orphan indications, the first to market receives a 10-year (EU) or 8-year (US) market exclusivity period, extendable by 2 years with a PIP (EU). This may be revoked in exceptional cases where the product fails to perform as expected. In non-orphan indications, as the first to market, all subsequent therapeutics will need to demonstrate superiority to the drug in order to receive market authorisation, substantially raising the bar.

6.3.7. Manufacturing and supply chain

Current manufacturing and supply chain solutions are largely suboptimal and require further technical innovation for their effective and robust management. More so than any other therapeutic technology, advanced therapy supply chains and manufacturing processes are faced by high levels of risk to their robustness, cost efficiency, and scalability. The limitations of up-scaling labour-intensive manufacturing protocols must be considered from concept stage and throughout business plan design, and solutions to their mitigation implemented prior to phase II trials at the latest. Automated bioprocessing offers step-change improvements to cost, robustness, reliability, flexibility, throughput, and scalability that manual processing is highly unlikely to achieve. Single-use/disposable bioprocess solutions are likely to play a significant role in this. Some leading CAR-T companies are taking a portfolio approach to the limitations of manufacturing scalability, developing and authorising an inefficiently-manufactured first-generation product and investing in bespoke automation solutions for their next-generation products. A major driver behind this decision is the poor availability of automated and high-throughput bioprocessing equipment, and future innovation in ATMP manufacturing may alter the optimal solution to manufacturing scalability. Investors should consider previously adopted strategies but market forces are rapidly changing and optimal solutions may not have precedence. An expanding pool of

C(D)MOs now have deep experience with various cell and gene types, and offer de-risked virtual-model manufacturing to an extensive client list; meanwhile, manufacturing limitations are squarely in the sights of a raft of experienced solutions providers, with off-the-shelf bioprocessing solutions identified as a major source of unmet need and potentially lucrative market opportunity. Shipping and logistics are often overlooked and require careful consideration; shelf-life has been a limiting factor to commercial success in several previous therapies and developers should therefore consider the importance of optimising shipment protocols including considering the utility of cryopreservation or novel logistics solutions. Supply chain management platforms can significantly de-risk tracking and traceability requirements, especially critical for autologous therapies, where the implications of batch loss or mix-up can be fatal to patients. The unreliable availability of raw materials presents further risk; steps taken should include identifying alternative sources where available, and/or working with materials suppliers to de-risk their own supply chain.

Full optimisation of bioprocessing and manufacturing requires a deep understanding of the product's underlying biology, and a comprehensive set of CQA parameters which can be tested either throughout the manufacturing process as CPPs or tested rapidly at batch-release. Extensive preclinical-stage product development leveraged to inform a quality by design approach to both manufacturing and CQA/TPP design is highly recommended.

6.3.8. Regulation

Regulatory authorities across the globe have demonstrated great flexibility, are widely engaged and accessible to the community, and play an active role in enabling and accelerating the advanced therapy sector. Schemes such as PRIME (in the EU) and breakthrough designation (in the US) provide an invaluable opportunity for technology developers to engage directly with, and receive advice from, the EMA and FDA. This support is widely perceived as a major value contribution from the regulatory bodies, supporting and de-risking both clinical development and market access through optimising clinical trial design for market authorisation and P&R negotiations. Regulatory risk has moved down the priority list, and it is now becoming clear that requirements for P&R success may in fact be more demanding than those of regulatory authorisation. Further, the availability of conditional approval mechanisms substantially de-risks ROI and offers expedited cash flow.

6.3.9. Pharmaceutical company strategy and exit potential

The interface between industry stakeholders in the advanced therapy ecosystem is heavily collaborative in character and major pharmaceutical organisations are becoming increasingly engaged through an unusually high number of research alliances, licensing deals, co-development agreements, and manufacturing contracts. Most leading pharmaceutical companies have stakes in advanced therapy platforms including gene therapies for blood disorders, cardiology, neurology, and undisclosed indications, and immuno-oncology cell therapies. The demonstrable intent of biopharma stakeholders to engage with increasingly early-stage biotechs presents strategic incentive to invest in technologically promising companies at an early stage, in turn highlighting the need for technical expertise and understanding within the due diligence process. Biopharma companies should also be consulted as part of due diligence to assess their relevance for a potential exit.

6.4. Perspectives from China

Expert Insight

Qinhua Cindy Ru

CSO, CARSGEN Therapeutics



I have been working in top global pharmaceutical companies for decades, but only started my Chinese pharmaceutical adventure last fall. To be honest, all the concerns that Western investors may have towards Chinese pharmaceutical companies- I share them all. There is no doubt that most Chinese pharmaceutical companies have limited training in global GxP standards, lack global clinical development and regulatory submission experience, and may carry over previous development history and working habits into today's practice.

However, if you look at the other side of the coin, we must admit that today's Chinese pharmaceutical industry is ready for next step. I have observed huge motivation, gigantic energy, rich resources and a deep talent pool, and the Chinese pharmaceutical industry is well prepared to embrace upcoming breakthroughs to evolve into a global player.

Another important factor to consider is today's Chinese FDA (CFDA) and Centre for Drug Evaluation (CDE). They are firmly determined and equipped with strong execution power to reform into a global regulatory player. For both the pharmaceutical industry and healthcare investors, the CFDA is implementing some encouraging and promising policies.

Investing into Chinese biotech start-up means a lot of hurdles along with great opportunities, the same as all other investment opportunities. For Western investors, the most practical way is hiring executives with roots in both sides, who know cultural norms and difference well, and who can communicate efficiently and productively with both sides. More important is that international talents understand and respect the value system of both sides, but strictly stick with globally accepted international standards, and this is significantly critical for business decision making. No mistakes are affordable from this perspective.

In short, my suggestions to Western investors are to be patient, be cautious, but be optimistic.

6.5. Showcase of emerging biotechs

ARTHROGEN

Robert Jan Lamers
CEO



Developmental Stage: Proof of Concept

Ownership: Private

Location: Amsterdam, The Netherlands

Immuno inflammation

Clinical stage Gene Therapy

Arthriti

Arthrogen is a clinical stage biotech company which is developing local gene therapy for inflammatory diseases. The first target indication is in the field of rheumatic diseases. In Q2 2017 the phase Ib clinical trial with lead compound ART-I02 starts, treating patients with rheumatoid arthritis (RA). Unique is our single treatment with long lasting effect, our inflammation induced promotor and our focus on high prevalence indications, like RA.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

In RA and other high prevalence rheumatic indications, there is a clear unmet need. Despite the great developments of the last decades patients still suffer from persisting inflammation in one or more joints. In addition, current standard of care requires regularly hospital visits and come with high costs and off target effects. Arthrogen has a unique single treatment therapy aiming for long lasting local effect, reducing inflammation, of target effects and costs.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

The approval of our first clinical trial with this gene therapy based product in a high prevalence indication being rheumatoid arthritis, is the real major milestone for Arthrogen, achieved in February 2017. The next milestone is the execution of the trial, plus the start of a potential second parallel trial as well as the further development of 4 additional clinical candidates towards 2020.

What is your key message to investors or prospective partners?

Arthrogen is looking for new investors and partners to join us in the clinical development of this exciting new gene therapy for immuno inflammation, with a first focus on arthritis. We welcome the start of discussions during our first clinical trial, to get acquainted and see if there is a mutual interest to collaborate.

What sort of investor are you looking to partner with to take the company through its next stage of development?

For the next stage of development we are looking to partner with investors that are willing to invest experience and expertise beside cash, have a proven track record in investing in the development of gene therapy, have the capacity for significant funding and have a good network in pharma. Moreover, a potential partner will join us in the excitement of developing game changing gene therapies in high prevalence indications.

Further information on Arthrogen can be found at www.arthrogen.nl

BIRD-C

Werner Lubitz

CEO & CSO, Oncology, Add-on Asjuvant Tumor Immunotherapy



Developmental Stage: Proof of Concept

Ownership: Private

Location: Vienna, Austria

Bacterial Ghost Platform Technology

Add-on Asjuvant Tumor Immunotherapy

Oncology

Proprietary technology for Bacterial Ghost (BG) production. BGs have been produced by a GMP contract manufacturer. Preclinical proof of concept investigation have revealed an outstanding activity of BGs as adjuvant for tumour immunotherapy. BGs can be used as add-on adjuvant to conventional tumour therapy regimes such as surgery, irradiation and/or chemotherapy. The immune system is stimulated by BGs to recognise tumour neo-antigens which are released by conventional tumour therapy.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

BGs have a broad range of tumor therapy applications and are not restricted to single tumor entities. The market potential is global. It is anticipated to go to market first in Europe. The main revenue streams are expected by upfront payments, milestone payments and downstream royalties derived from the sales of the BIRD-C BGs to pharma partners.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Major milestones have been the development of BG production to an industrial scale. GMP production of BGs confirmed robustness of the technology and successful performance of techtransfer. Preclinical investigations resulted in proof of concept for BGs as adjuvants in tumor immunotherapy for different tumor models. The major upcoming milestone is to enter a first in human study to proof the tolerability of BGs in humans

What is your key message to investors or prospective partners?

BIRD-C reached the stage to enter clinical trials proofing the adjuvant capacity of BGs in tumor immunotherapy.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Big pharma or private venture capital.

Further information on BIRD-C can be found at www.bird-c.com

CARsgen
Cindy Ru
EVP & CSO



Developmental Stage: Proof of Concept

Ownership: Private

Location: Shanghai, China and San Diego, USA

CAR-T Cell Therapy

Solid Tumor

Orphan Designation Indications

Deeply rooted in China and growing up to be a global leader, CARsgen commits to fulfil unmet medical needs across the oceans, yet with a clear focus on the orphan indications in the western world and which commonly occur in China and the Asia Pacific area.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

CARsgen and its advanced technology in cell therapy areas hold great market potential and could be a nice candidate to remark today's supportive investment environment to global biotech start-ups. The most advanced technology, the shortest company history, and the quickest growth paces of CARsgen give me the confidence on the market potential for our company and technology.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Completed Phase I clinical trial of GPC3 CAR-T therapy in HCC, and bispecific EGFRvIII-EGFR CAR-T therapy in GBM. Submit IND and initiate Phase Ib trial of GPC3 CAR-T therapy in US and Phase II trial of GPC3 CAR-T therapy globally.

What is your key message to investors or prospective partners?

Invest into CARsgen and grasp the growth opportunity in both western and eastern markets.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Investors who have supported similar biotech start-up and launched US IPO successfully; Investors who have more relevant resources in addition to the funding support.

Further information on CARsgen can be found at www.carsgen.com

Developmental Stage: Proof of Concept

Ownership: Private

Location: London, UK

Cell Therapy

Immunotherapy

Oncology

Cell Medica is developing next-generation cellular immunotherapy products for the treatment of cancer. We have three technology platforms which target large indications such as small cell lung cancer, ovarian cancer and pancreatic cancer. Our lead product is in Phase II and being developed for a range of cancers associated with the oncogenic Epstein Barr virus, including EBV+ lymphomas, nasopharyngeal carcinoma and gastric cancer. We have an extensive partnership to develop next generation CAR-NKT cells with Baylor College of Medicine in Houston, Texas. This includes a very exciting project for an off-the-shelf product using the unique advantages of an NKT cell to eliminate the GVHD toxicity risk of an allogeneic product. We are also working with UCL in London to genetically engineer T cell receptors for improved recognition of cancer antigens and for increased potency through higher expression of the T cell receptor.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

Our cellular immunotherapy products target large indications and each of our three technology platforms has the potential to generate multiple products. Our lead product is in Phase II and our pipeline includes three next-generation CAR/TCR products which are planned to enter Phase I studies within 18 months. Our approach to an off-the-shelf product is unique and we believe will prove to be the best-in-class for allogeneic products.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Lead product CMD-003 is being tested in an international Phase II trial in the US, EU and Korea with potential for accelerated approval. Extensive collaboration with Baylor College of Medicine to develop next generation CAR-NKT products for the treatment of solid tumors with Phase I trials planned in the first half of 2018. Unique technology for developing an off-the-shelf CAR-NKT cell product to achieve cost of goods advantage. Partnership with UCL to development the Dominant TCR technology to improve the use of genetically engineered T cell receptors for treating cancer in a safe and efficacious manner.

What is your key message to investors or prospective partners?

Cell Medica has leading-edge cellular immunotherapy products which are in clinical development for the treatment of solid tumors. We have been operating as a specialist cellular immunotherapy company for 10 years and have built a strong execution capability in association with highly recognized research partners. With the backing of deep-pocketed long-term shareholders, Cell Medica's goal is to transform the lives of cancer patients and to build a market leader in the cell-based immuno-oncology field

What sort of investor are you looking to partner with to take the company through its next stage of development?

We are focused on investors and partners who can work with Cell Medica to accelerate our clinical development programmes across three technology platforms. This includes investors who have the financing strength to back late stage Phase II/III trials for regulatory approvals and strategic players who seek to partner next-generation immuno-oncology products aimed at large indications.

Further information on Cell Medica can be found at www.cellmedica.com/

Global BioTherapeutics

Gustavo Cabrera
CEO



Developmental Stage: Optimisation

Ownership: Private

Location: San Diego, CA

Global Biotherapeutics

Gene Therapy

Hepatic Vector Delivery

Type 1 Diabetes

GBT has developed a novel method to safely and effectively deliver therapeutic genes to the liver. This novel method, which we have named Compartmentalized Liver Transduction (CLT), solves most of the shortcoming associated with the conventional IV route of vector infusion.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

From our companies particular perspective, given that we've described a hepatic vector delivery platform with multiple potenial therapeutic applications and a robust IP portfolio, the market potential is very promising. The Gene Therapy space in particular, is very exciting given that it has promised -for decades now- to resolve many conditions. At GBT, we are very excited to contribute with an exciting hepatic based technology with truly disruptive potential.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Our major milestones include the filing of multiple patents protecting our proprietary method and surgical devices and initial POC results which demonstrate that Compartmentalized Liver Transduction works in large animal models of T1D and over expressing FVIII. Our next milestones are to replicate or initial findings in large animal models and interacting with the EMA and the FDA to initiate IND enabling studies.

What is your key message to investors or prospective partners?

Our message would be that our company -GBT- has developed a novel vector delivery platform that solves most of the shortcomings observed in the IV conventional route of vector infusion. In addition, our company is open to collaborations and partnering in order to accelerate GBTs AND our partners Gene Therapy programs.

What sort of investor are you looking to partner with to take the company through its next stage of development?

We would like to engage in collaborations with investors that bring not only monetary value to our program, we are looking for investors and partners that bring knowledge, experience and that truly understand the value of a groundbreaking disruptive approach to hepatic based gene therapy.

Further information on Global Biotherapeutics can be found at www.global-biotherapeutics.com

Immunicum AB

Carlos De Sousa

CEO



Developmental Stage: Proof of Concept

Ownership: Public

Location: Gothenburg, Sweden

Immunio-Oncology

Cell Therapy

Solid Tumors

Immunicum is pioneering an advanced immuno-oncology-based approach that enables a tumor-specific and patient-specific immune response to solid tumors using a proprietary and off-the shelf cellular therapy. The company has gathered positive clinical data in using its lead program INTUVAX® in patients suffering from a range of solid tumors. The therapeutic goal is to activate the patient's own immune response to destroy the cancer cells both at the tumor site and throughout the body. As a result, the approach is unique and differentiated to other products in the immuno-oncology space.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

Immuno-oncology is an incredibly exciting space as activating a patient's own immune system to destroy tumor cells is a very promising approach with broad applicability. Immunicum's lead program INTUVAX® is designed to be complimentary to a number of existing therapies and the safety data gathered in the clinical trials conducted to date is encouraging. Nevertheless, at this stage we cannot comment on the market potential as it is still too early to make assumptions about which indication and patient population our products may treat once they are approved. Nevertheless, total sales of immuno-oncology products in 2022 are estimated at \$20 B in US and \$35 B globally with a CAGR projected at 43% just in the US.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Recent milestones achieved include the data presentation at SITC on INTUVAX® Phase 1/2 study in hepatic cell carcinoma (November 2016) and the FDA clearance of Investigational New Drug application to test INTUVAX® in metastatic renal cell carcinoma in the US (December 2016) as an expansion of the ongoing MERECA trial underway in the EU. Near-term, the company will continue to enroll patients for both MERECA and have top line results for the hepatic cell carcinoma trial.

What is your key message to investors or prospective partners?

Immunicum is committed to advancing a novel immuno-oncology approach to treat solid tumors through its lead program, INTUVAX® an off-the shelf immune primer already in phase 2 development. Results from the phase I/II in kidney cancer show very exciting clinical and survival data.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Immunicum is open to discussions with a variety of investors with mandates to invest in public companies as Immunicum is listed on the First North Premier (IMMU.ST).

Further information on Immunicum AB xxxx can be found at www.immunicum.se

Nanogenic Solutions

Jonathan Lane
CEO



Developmental Stage: Commercialisation

Ownership: Private

Location: West Sussex, UK

Nucleic Acid Delivery

Advanced Therapies

Synthetic Delivery Nano Particle

Nanogenic Solutions provide targeted non-viral (synthetic) delivery of RNA and DNA via a diverse range of delivery routes.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

The advanced therapies (gene therapies) sector is heavily invested into viral vectors. Viral vectors have severe limitations in terms of range of addressable indications, costs of production, repeat dosing to name a few. As a consequence numerous companies are all addressing the same few indications. To survive most of those companies will eventually have to switch to non-viral vectors to achieve reimbursable products with relevant cost/benefit profiles. Nanogenic Solutions has a vector of proven utility for a range of cancers, respiratory diseases and neural cells. Our vector is already very good, but we aim to completely dominate the non-viral vector space.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

We have out-licensed for a cancer indication and we have a global reagents licensee who is using our reagents in a transfection kit for laboratory research. We aim to increase the number of licensees for therapeutics.

What is your key message to investors or prospective partners?

Be forward thinking! Whilst viral vectors might have been first into the clinic, pretty soon their limitations are going to handicap your advanced therapy investments. Making ex vivo autologous treatments has severe limitations of scale. Viral vectors can not be used for repeat dosing or for new indications in the same patient. Companies wedded to viral vectors will be left behind in the near future.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Since we are not developing a therapeutic, we don't require huge amounts of money and are relatively low risk. However, we do have huge out-licensing opportunities. A future investor should be prepared to invest smaller amounts than they would for a therapeutic. We are a very simple company, so due diligence will be relatively inexpensive.

Further information on Nanogenic Solutions can be found at www.nanogenicsolutions.com

Rexgenero
Joe Dupere
CEO



REXGENERO

Developmental Stage: Optimisation

Ownership: Private

Location: London, UK

Critical Limb Ischemia

Autologous Cell Therapy

Regenerative Medicine

Rexgenero is a leading regenerative medicine company with a focus on advanced cell-based therapeutics for the treatment of serious diseases that are poorly treated with existing therapies. Rexgenero is late-stage (Phase III), focused on common diseases and is developing products which have been shown to produce superior clinical outcomes and therefore could represent significant advances in the treatment of patients.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

REX-001 is expected to be one of the first products available for the treatment critical limb ischemia (CLI). CLI is major indication affecting approximately 2 million patients annually in the United States and Europe and is characterised by very poor quality of life and a high risk of infection, amputation and death. For a significant proportion of patients (up to 50%) the only treatment options are ineffective symptomatic treatment of pain, wounds and infection. REX-001 has the potential to be a break-through in the treatment of patients with CLI due to the high proportion of patients who are alleviated of the condition after treatment.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Rexgenero has recently commenced two Phase III studies with the company's lead product REX-001 for patients with critical limb ischemia and diabetes. The next major milestone is expanding the current REX-001 clinical trials into the US, interim data expected in mid- 2018 and full data in late 2018.

What is your key message to investors or prospective partners?

Rexgenero is late-stage cell therapy company with a lead program, REX-001, which has shown superior efficacy and is highly safe in CLI, a major disease with high unmet medical need. REX-001 has just commenced two Phase III clinical trials in patients with CLI and diabetes and these studies have a high probability of success due to previous results in over 100 patients, the innovative trial design and the low safety risk. Success in these studies could lead to marketing authorisation as early as late-2019.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Institutional investors with a focus on biotechnology, particularly advanced therapies. International pharmaceutical companies.

Further information on Rexgenero can be found at www.rexgenero.com

Synpromics
David Venables
CEO



Developmental Stage: Optimisation

Ownership: Private

Location: Edinburgh, UK

Gene Therapy

Cell Therapy

Bio-processing

We have developed a proprietary technology platform that allows us to create customized synthetic promoters optimized for expression level, tissue specificity, inducibility, size, kill-switch control and environmental & pathologic responsive. The application of this technology to cell and gene therapy allows unprecedented levels of gene control that addresses issues of product safety and efficacy.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

Any product which relies on the expression of a gene in vivo would benefit from the inclusion of a customised promoter which confers the optimal properties of promoter size, strength of expression, specificity of expression to cell or tissue type, and in some circumstances would benefit from the ability to include additional gene control through inducible expression or suicide switch. Our technology enables the design of customised promoters which exhibit these properties.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

We completed an initial fund raise of £2.1M in August 2015, and have completed a further fund raise of £5.2M in April 2017. We have signed collaboration agreements with leading gene therapy companies such as uniQure, AGTC and Adverum, and leading bioprocessing companies such as GE Healthcare and Sartorius. We also have deals signed with two undisclosed large pharma companies. We have generated a strong body of data to show the utility of our technology in in vitro and in vivo settings. The next key milestones are further in vivo data exemplifying our technology and also completing a number of additional commercial deals currently under negotiation.

What is your key message to investors or prospective partners?

We have developed a unique technology for the control of gene function in gene and cell therapy applications. We are interested in talking with prospective partners who see the value of adopting our technology in their product development strategies, to enable the develop of unique, patentable, therapeutics. We are also interested in talking with investors who see the opportunity to work with us to both further develop our platform technology as well as explore the development of our own therapeutic candidates.

Further information on Synpromics can be found at www.synpromics.com

TC BioPharm

Michael Leek
CEO



Developmental Stage: Optimisation

Ownership: Private

Location: Edinburgh, UK

Immunotherapy

Oncology

T cells

Described by Frost & Sullivan as 'one of the top five late stage oncology companies', TCB has commenced recruitment for a Phase 2b Clinical Trial of its lead product - ImmuniCell. Based on culture-expanded gamma-delta T cells, ImmuniCell has potential to treat a wide variety of cancerous tumours and viral infections. Manufactured at TCB's MHRA accredited GMP cleanroom facility with a fully integrated in-house clinical and quality infrastructure, TCB is now raising Series B funds of £15m to become acquisition/IPO ready.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

Based on independently prepared reimbursement and sales projections, TCB estimates a 2019 launch for ImmuniCell. Conservative projections estimate peak operating profit 3 years post launch in lead indications at £921m per annum. With an unparalleled safety and tolerability profile versus current standards of care, it is predicted that ImmuniCell will launch as a 2nd or 3rd line treatment (indication dependent) with an initial target population of 62,212 patients in Europe alone across three lead indications.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

Commencing operations in February 2014, TCB has moved quickly, achieving the following:

- designed, built and commissioned cleanroom manufacturing facility (May 2014);
- achieved GMP (Good Manufacturing Practice) compliance (December 2014);
- Regulatory clearance to commence Phase II/III clinical study (September 2015);
- First patient recruited to phase IIa clinical study (March 2016)
- Phase IIb/III clinical study commenced (March 2017)

In addition to progressing ImmuniCell Phase IIb clinical studies, TCB will progress its ImmuniCAR platform into clinical studies during 2018 in partnership with NIPRO Corporation (Osaka, Japan) in a lead target indication.

What is your key message to investors or prospective partners?

TCB is an exciting, late-stage asset with a realistic valuation and significant potential for high-value uplift over the next 12 to 18 months. In order to progress ImmuniCell efficacy studies and move ImmuniCAR into the clinic, TCB is looking to partner with VC and Corporate Venturers for its Series B round (Q3, 2017) prior to Initial Public Offering on NASDAQ.

What sort of investor are you looking to partner with to take the company through its next stage of development?

Late stage Venture Capital, Corporate venture capital, private equity and pharmaceutical collaborations

Further information on TC BioPharm can be found at www.tcbiopharm.com

Telocyte

Peter Rayson
CEO



Developmental Stage: R&D

Ownership: Private

Location: Grand Rapids, USA

Alzheimer's

Telomerase

Aging

Our mission is not to help anyone “live with Alzheimer’s”, but to ensure that all of us can live without Alzheimer’s. Our mission is to cure Alzheimer’s, plain and simple. We intend to save the lives, the minds, and the souls of those who have Alzheimer’s now and to prevent anyone from getting Alzheimer’s in the future.

Can you comment on the market potential for your technology? Why do you believe this space so exciting?

The estimated market in North America alone is estimated at greater than \$25B per year. Currently, Alzheimer's disease is uniformly fatal, lacks any effective therapy, is clinically expensive, and is personally tragic.

What are the major milestones you've achieved to date and what is the next major milestone for the business?

We have firm data on efficacy, have contracted to do the FDA-required animal toxicity study, and are ready to move forward with FDA human trials in 2018. We have key initial funding, a contract for the toxicity study to be done by one of the world's preeminent cancer institutes, and multiple partners, including AWS, SAP, Cooley LLC, CNIO, and others.

What is your key message to investors or prospective partners?

We have the only route to an effective therapy to both prevent and cure Alzheimer's. In addition, we are far along in the pathway to FDA clinical trials, have no effective competition, and there is a large global market.

What sort of investor are you looking to partner with to take the company through its next stage of development?

We seek a VC or pharma investor for a \$6M series A investment.

Further information on Telocyte can be found at www.telocyte.com

6.6. Advanced therapies in the context of small cap company investments

Expert Insight

Derren Nathan

Research & Corporate Broking, Hybridan

In a year where markets both sides of the Atlantic have reached record highs, the performance of Pharma and Biotech stocks in the UK has been somewhat lacklustre. By way of example the Bats UK 100 Index was up 3.83% year to date as at 24 April 2017, whereas the Bats UK Healthcare Sector was up just 2.78% over the same period.

In terms of fundraising activity on AIM and the wider UK market this has also been relatively muted. There have in fact been no pure drug discover IPOs on the UK markets this year. What we have seen is the IPO of BioPharma Credit (BPCR.L) which raised gross proceeds of \$761m well in excess of the initial \$300m target. BioPharma Credit invests in debt instruments backed by long term sales of life sciences products 'which are generally less affected by economic and business cycles'. We have also seen the arrival of Arix Bioscience (ARIX.L) on the Main Market raising £100m, which has a portfolio of interests in five biotech companies and a US research accelerator. Advanced therapies make up some of their portfolio with Autolus focused on the development and commercialisation of engineered T-cell immunotherapy products based on its proprietary T-cell programming technology, and Depixus aiming to commercialise a highly innovative technology platform for the fast, accurate, and inexpensive extraction of genetic and epigenetic information from single molecules of DNA and RNA.

The profile of this year's London IPOs very much suggest that investors are looking to reduce their exposure to risk, with Arix providing a diversified approach and BioPharma Credit being a yield play on cashflow based assets. There is a limited pool of capital for small cap listed biotechs, and with this in mind it is important that such companies can access funds looking for a tax efficient home. Recent changes to VCT and EIS eligibility criteria have certainly affected the number of offerings that can be eligible for such reliefs, but Biotechs are less likely to fall foul of the revenue restrictions given their business models. The R&D intensity of the industry is in the spirit of the rules, and it is precisely for innovation, advances in science and the development of treatments for serious illnesses that tax breaks should be used in order to attract further risk capital.

Similarly, secondary market activity in Q1 was also quiet according to the latest London Stock Exchange statistics (Main Market and AIM) with further issues of £45.2m down 32% from £66.9m in the equivalent period last year.

So what has been holding back investor sentiment? Certainly the focus on driving down drug pricing by politicians in the US hasn't helped. This started last year with Hilary Clinton's attack on Valeant Pharmaceuticals (NYSE:VRX) and Donald Trump has been rather trigger happy in terms of tweets on the subject. We understand that a bill is under consideration that will allow Medicare to lower drug prices. However, we believe that advanced therapies, at the forefront of medical innovation that address serious unmet needs are less susceptible to such pressures. The price tag for advanced therapies is likely to be high, but often the prospective patient population is low, and the treatment can be a one-off programme with a

curative outcome, rather than a lifetime of managing chronic diseases. Therefore, the pharma-economic case for advanced therapies, despite the high up front cost, can be compelling.

Small caps carry significant funding risks as well as risks associated with small concentrated development portfolios. However not all small caps stay small forever and there are potentially very large returns. Big Pharma likes the smaller specialists to do much of the heavy lifting in the early stages of the development lifecycle and is prepared to pay top dollar as candidates jump through the various regulatory hurdles. In January for example French independent Pharmaceutical Company Servier paid €30m up front to Pieris Pharma (NASDAQ:PIRS) with a total deal value of up to €1.7bn for the ex-U.S. rights to preclinical-stage PD-1 bispecific PRS-332 and a stake in four more defined, but as yet undisclosed, immuno-oncology programs.

Sygnis Pharma (LIO1.GR) listed on the Deutsche Börse has been rapidly growing organically and by acquisition and now offers a full suite of tools and reagents for genomic and proteomic research. Sygnis' TruePrime products provide superior advantages over current technologies and solve most of the problems that researchers are facing in single cell analysis today. Sygnis has hopes for TruePrime to become the new gold standard for Whole Genome Amplification, targeting Next Generation Sequencing users, and consequently the NGS (next-generation sequencing) market.

There is definitely a market for advanced therapies in the Small Cap World, but what investors need to see is a clear path to commercialisation and value creation. This is why those with broad portfolios, collaborative research models and those who provide ancillary services to the industry can prove attractive. The very early stage pure play discovery stories are still probably best left to private equity.

We have picked out a number of small cap companies involved in the advanced therapies space. Scancell Holdings (SCLP.L) has developed two cancer immunotherapy platforms ImmunoBody® and Moditope®. ImmunoBody® utilises both cross- and direct-presentation to increase T-cell avidity by 100-fold. Moditope® stimulates powerful anti-tumour T-cell responses against neo-epitopes produced by enzymes induced by cellular stress. Scancell's first ImmunoBody®, SCIB1 is being developed for the treatment of melanoma. Data from the Phase 1/2 clinical trial demonstrate that SCIB1, when used as monotherapy, has a marked effect on tumour load, produces a melanoma-specific immune response and highly encouraging survival trend without serious side effects. In patients with resected disease there is increasing evidence to suggest that SCIB1 may delay or prevent disease recurrence. The Company is planning to initiate a SCIB1 Phase 2 checkpoint inhibitor combination study in H2 2017.

Advanced therapies provide commercial opportunities not just for companies seeking to develop therapies, but also for companies who produce enabling tools which increase the productivity and lower the cost of the drug discovery process. Two UK listed companies that come to mind are Physiomics (PYC.L) and Oxford Biodynamics (OBD.L). Physiomics has added an immune-oncology module to its powerful bio-simulation platform Virtual Tumour, which can help optimise both pre-clinical and clinical study designs. Through its EpiSwitch™ biomarker platform Oxford BioDynamics can help companies reduce the risk, cost and time to market for development programs, and gain significant insights into disease mechanism to support the personalisation of medicine.

For those who wish to make sure they have the raw materials required for prospective regenerative treatments, the practice of storing stem cells sourced from the umbilical cord, has been rising in popularity with over 3 million samples stored worldwide to date. WideCells

Group (WDC.L) is making sure that treatment is accessible to those who have taken this choice, through its first in class insurance products Cellplan, second opinion service and medical concierge offering. It has also recently established the Institute of Stem Cell Technology at the University of Manchester Innovation Centre to focus on stem cell research and regenerative medicine which has already secured its first contract. The online WideAcademy is focused on becoming a thought leader in stem cell technology. WideCells recently raised £649k at 12p against a July 2016 IPO price of 11p.

There are also opportunities for companies in conventional drug discovery to investigate combination treatment regimens with advanced therapies. Sareum Holdings (SAR.L) last year announced a licence agreement for its Chk1 inhibitor programme (27.5% owned) for a headline figure of over \$320m. The licensor, NASDAQ listed Sierra Oncology (NASDAQ:SRRA), in addition to the ongoing trials is also considering trials of the candidate, now named SRA737, in combination with targeted and immuno-oncology therapies.

There are some small cap companies that take a portfolio approach to advanced therapies. MaxCyte (MXCT.L) which IPO'd in 2016, has now expanded to more than 40 high-value cell therapy partnered programmes covering cutting-edge fields of immuno-oncology, gene editing and regenerative medicine, delivering high-value recurring licensing revenue, with more than 15 programmes licensed for clinical-stage use. The Company provides its patented, high-performance cell engineering platform to biopharmaceutical partners engaged in drug discovery and development, biomanufacturing, and cell therapy. MaxCyte has recently raised a further £20m at 275p nearly 4x its IPO price of 70p.

Hybridan is not just limited to exciting smaller companies listed in the UK. TSX listed Oncolytics Biotech (ONC.TO) is developing its first in class systemically administered immune-oncology viral agent (REOLYSIN®) for solid tumours and haematological malignancies. In phase 2 studies this has been shown to double 2-year survival in pancreatic cancer and most recently similar results have been seen in an open label phase 2 study for patients with mutated p53 metastatic breast cancer, when treated with REOLYSIN® in combination with paclitaxel.

6.7. Challenges in encouraging LPs to invest in advanced therapies through VC funds

Expert Insight

Dmitry Kuzmin

Managing Partner, 4BIO Capital Partners



4BIO Capital Partners

Specialists in life sciences

From our experience, there are several major challenges in facilitating LP investment into advanced therapies that stem directly from the field in question. They can become major hurdles to overcome at the fundraising stage, and adequate provisions to overcome them are instrumental for a successful dialogue with LPs.

The first obvious one that everyone who worked with advanced therapeutics will instantly recognize is the fact that the field is perceived (and somewhat rightly so) as esoteric and requiring large amounts of specialized knowledge that most people do not pick up during everyday life. For an outsider, the amount of new data to process can look daunting when compared to either more traditional pharmaceuticals or high-tech areas that have nothing to do with life sciences (an average modern person is much more familiar and comfortable with terms rooted in electronics and IT than medicine and biology). When fundraising for advanced therapeutics sector, one has to make special provisions for their case to be very accessible to an outside listener.

Another one that directly ties to the above is the comparative lack of venture “success

stories” when it comes to the specific technologies in question. This can be traced to very short technology cycles in biotech in the last several decades. Looking back, previous breakthrough technologies become rather obvious, such as therapeutic antibodies ten years ago – but by now they have already matured to become the standard of care, and will look like a relevant comparable to a potential LP. This, coupled with rather long development cycles for individual products, leads to an effect where the “success stories” arrive so late in the tech cycle that when they do, the window of opportunity for venture profits is already closed. Therefore, when drawing up examples, it can be useful to draw from previous technology cycles, noting similarities in development between current advanced therapeutics and previous generations of therapies.

Another major turn-off for non-specialized LPs is the risk structure inherent in biotech industry. A multi-stage development cycle where at each step there is a very real and largely uncontrollable risk of failure requires a very specific mindset to work with. If venture investment in general can make an impression of being a “gamble” to an outside observer, biotech venture investment in particular can seem even more unpredictable. A failed drug, unlike, for instance, a failed software service or a consumer product, usually fails not due to human factor (which can, at least theoretically, be predicted, controlled for and ultimately overcome with enough effort), but rather due to objective technological shortcomings. It is important to not only make LP understand this distinction, but also to let them see that you are well equipped to deal with them.

Lastly, another factor that was already briefly mentioned above is the perceived long product development cycle in biotech industry as a whole. There is a grain of truth in this perception, as the product development cycles in biotech industry are longer than in most others, and many potential LPs are averse to locking up their assets in long-term investments. Nevertheless, it should be noted that this perception in people with general idea of how biotech field functions stems from a classical drug development model. Many novel therapeutics target niches with high unmet medical needs and are granted faster regulatory tracks by the regulatory authorities, considerably shortening their time to market. Therefore, while longer product development cycles are not a total misconception, LPs should be made aware of potential shorter routes to the market.

6.8. Recent trends in biotech and advanced therapies

Expert Insight

Mintoi Chessa-Florea

Global Head of Healthcare Coverage,
Mergermarket



MERGERMARKET

Analytics by Jonathan Klonowski, M&A Deal Researcher, Mergermarket

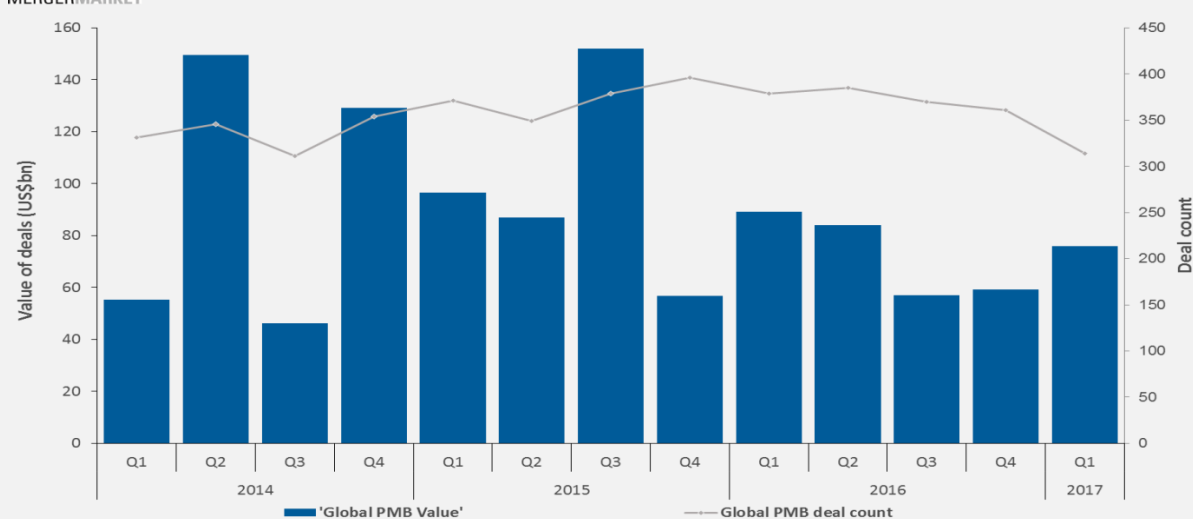
Globally, the Pharma, Medical & Biotech (PMB) sector saw a 14.8% drop in value in the first quarter of 2017 to US\$ 76bn (314 deals) in comparison to the first quarter of 2016 (379 deals, US\$ 89.2bn), according to Mergermarket data. After a stellar start to 2016, the PMB sector faltered in the second half of the year as value decreased 32.8% compared to the first half of the year. However, the first three months of 2017, activity has rebounded slightly towards the levels seen in the first half of 2016.

Within the Biotech subsector, companies have been raising substantial financing rounds from venture capital and private equity funds to develop clinical pipelines using cell and gene therapy. These address genetic conditions and cancer among others, and can range from gene therapy delivery technologies, tissue engineering and regenerative medicine.

Since the start of 2016, the cell therapy and gene therapy spaces have received deals worth a total of US\$ 575m. The largest of these deals saw Zhongyuan Union Cell and Gene Engineering Corp acquire Shanghai Claison Bio-tech Co for US\$ 168m in March 2016. So far this year there have been two gene therapy deals announced, including Hitachi Chemical Co's acquisition of an 80.1% stake in US-based PCT in March.

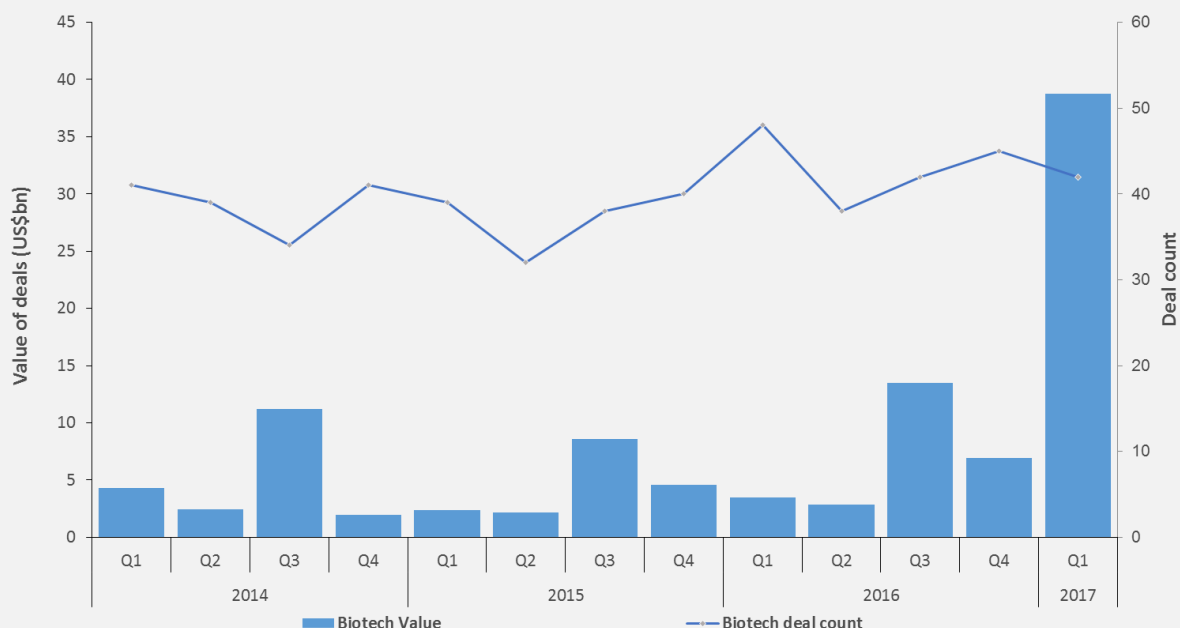


Pharma, Medical & Biotech M&A Quarterly Breakdown



In terms of accessing the public markets, French Lysogene which is using gene therapy to target two rare CNS diseases, raised EUR 22.6m in a Paris IPO in February this year, while UK-based NightstaRx developing gene therapy treatments for eye diseases could list in the UK or US later this year, having so far has raised a total of USD 65m. The eye segment is hot, and in the genetic eye conditions space, Philadelphia-based Spark Therapeutics [NASDAQ: ONCE], which is using gene therapy to treat inherited retinal dystrophies, was valued at USD 1.8bn. RetroSense Therapeutics also developing gene therapy treatments for eye disease and blindness was acquired by Allergan [NYSE: AGN] in 2016 for USD 60m.

Biotech M&A Quarterly Breakdown



Asia, and specifically South Korea, is also part of the gene therapy wave as gene-editing company ToolGeni looks to raise at least US\$ 50m in the coming year from a strategic investor, according to Mergermarket intelligence.

Despite a framework that is still evolving in terms of guidelines on clinical research procedures, protocols that determine effective treatment and managing side effects, cell and gene therapy biotechs, with their associated delivery technologies, are expected to continue to experience substantial growth through either M&A or sizeable cash injections. These therapies harness the power of personalised medicine and are ultimately looking at curing the disease – a paradigm shift from those pharmaceutical days when diseases were monitored and kept in remission.

6.9. European capital markets for advanced therapies

Expert Insight

Albert Ganyushin

Adviser to Life Science Companies and Investor

Former Head of International Listings at Euronext and the New York Stock Exchange

Advanced therapies have been riding the wave of growing investor interest over the last 5 years prompting warnings from some of a bubble forming ahead of the crash reminiscent of events in 2000. The science has moved a long way since then but sceptics remain pointing to high costs and doubts over the potential customers' ability to meet them.

From the capital markets perspective though, the area remains very buoyant attracting significant attention from the VC and public markets. The new generation of advanced companies is increasingly turning to capital markets and forming a growing proportion of life science IPOs. The progress of the advanced therapy pioneers listed in the US (Kite, Spark, Bluebird, etc.), the availability of smaller exciting gene and cell therapy companies in the public markets (Sangamo, Abeona, Bellicum etc.) and the flow of new IPO candidates (CRISPR, Tocagen, etc.) clearly makes advanced therapies one of the most exciting parts of life sciences in the eyes of the investors, especially against the background of broader slowdown in healthcare market. The investment community is instinctively attracted to gene and cell therapies because, among other things, they:

- Address a specific unmet need and have clear targets (blood, HD/HA, CNS, liver, etc.);
- Have a clear biological mode of action, designed from the start, and lower risk of phase 1 failure;
- Are a better way of treating patients, curing by way of modification and repair vs. destruction;
- Have produced spectacular data.

Considering that the regulators seem to be in a permissive mode despite some well-publicised fallouts, many investors are genuinely excited about advanced therapies and the potential to repeat the antibody success (Galapagos, Actelion, Genmab, etc.).

Companies need to be aware that the investor choice globally when it comes to pure play advanced therapies is significant albeit limited by investable size. There are at least 7 US-listed key gene and cell therapy companies with a market cap over \$1bn and another 15-20 key companies with a market cap between \$100m and \$1bn. Most of these are listed on NASDAQ. In comparison in Europe there are 7-8 smaller gene and cell therapy companies, listed mostly on EURONEXT, with a market cap between \$100m and \$1bn. It is notable that in the indicative selection of European companies above, all of them with the exception of Medigene have shown negative LTM performance. This can be compared with the benchmark Euronext Biotech Index close to being completely flat and the benchmark blue chip equity index Eurostoxx 50 up around 20% in the last twelve months.

Company	Listing	Focus	Market cap (\$m)	LTM performance
EDITAS	NASDAQ	Gene editing	756	-41%
INTELLIA	NASDAQ	Gene editing	494	-49%
SANGAMO	NASDAQ	Gene editing for blood, metabolic and CNS diseases	372	-28%
ABEONA	NASDAQ	Gene therapy for CNS and skin diseases	230	128%
UNIQURE	NASDAQ	Gene therapy for blood diseases	136	-63%
ADVERUM	NASDAQ	Gene therapy for rare diseases	118	-32%
AGTC	NASDAQ	Gene therapy with focus on ophthalmology	108	-59%
NASDAQ BIOTECH				11%
S&P 500				17%

Table 3 -Smaller US listed companies - Cell Therapy

Company	Listing	Focus	Market cap (\$m)	LTM performance
ADAPTIMMUNE	NASDAQ	Engineered T-Cell receptor (eTCR) therapy	487	-48%
BELLICUM	NASDAQ	CAR-T and TCR cell therapies	428	31%
LION BIOTECH	NASDAQ	Adoptive cell therapy (ACT)	368	11%
NANTKWEST	NASDAQ	NK-cell therapy	239	-66%
FORTRESS BIO	NASDAQ	CAR-T cell therapy	175	17%
CBMG	NASDAQ	Stem cell and CAR-T cell therapy	142	-34%
PLURISTEM	NASDAQ	Cell therapy for cardiovascular and blood diseases	140	-13%
NASDAQ BIOTECH				11%
S&P 500				17%

The picture is similar for smaller US-listed gene and cell therapy companies. Based on the indicative selection below only Abeona, Bellicum, Lion and restructured Fortress have positive share price performance over the last twelve months with Nasdaq Biotech up 11% and S&P 500 up 17% in the period. Considering such mixed results, the investor appetite for new deals and IPOs can be limited to the most promising smaller companies (with a few on and off transactions and multiple IPO attempts). This said, the overall attractiveness of the sector remains very strong and conducive to capital markets activity. In the last twelve months, we have seen two advanced therapy companies list on Euronext (Lysogene and Gensight) compared with three companies in the US (CRISPR, Tocagen and Fulgent). The price performance results in this selection are again mixed with only Tocagen and CRISPR in the positive territory.

Clearly the risks and unmet expectations are abound, and a few questions that remain unanswered in the eyes of the investors include:

- Manufacturing issues (distributed manufacturing, clinical grade purification, high costs, need to be close to patients);
- Cell therapy issues (safety/understanding the biology, curing vs killing, directing the treatment to the small area);
- Finding the optimal model (service vs product, scalability of service model); and most critically
- Pricing and reimbursement (cost of treatment vs total cost of care, cost per patient, possibility of deferred payment models, especially in gene therapy)

Anytime these issues and fears surface in a context of a particular company, the confidence

and share price performance can be severely undermined. However, both the companies and investors will be acutely aware of the fact that most of the bigger companies in the sector have performed well from the base of being smaller companies not such a long time ago and proven the sector's ability to produce a super return despite the overhang of risks and residual concerns.

Table 6 - Larger US listed gene and cell therapy companies

Company	Listing	Focus	Market cap (\$bn)	LTM performance
KITE	NASDAQ	Oncology cell therapy	4.4	55%
BLUEBIRD BIO	NASDAQ	Oncology gene therapy	3.7	116%
JUNO	NASDAQ	Oncology cell therapy	2.7	-42%
INTREXON	NYSE	Synthetic biology for CAR-T cell and gene therapy	2.4	-29%
SPARK	NASDAQ	Gene therapy	1.9	63%
MESOBLAST	ASX/NASDAQ	Cell therapy for cardiovascular, spine and oncology	1.1	34%
ZIOPHARM	NASDAQ	Oncology cell therapy	1.0	-11%
NASDAQ BIOTECH				11%
S&P 500				17%

6.10. Top questions investors should ask when considering private equity investment in advanced therapies companies

6.10.1. Product and process development

- Do you **sufficiently understand** your product's basic biology, mechanism of action, and *in vivo* effects to de-risk later development?
- How **complex** is your product and are there any ways to simplify it?
- How **robust** is your data and how confident are you in its results?
- Do you expect your product to be sufficiently **safe** and **efficacious**? Do you need to implement additional features or reach other product development goals to ensure **quality**?

6.10.2. Manufacturing and supply chain

- Are there any ways to **simplify** manufacturing whilst maintaining CQA values?
- Is your manufacturing process **scalable** in a cost-effective way? If not, should you **integrate or outsource** manufacturing?
- Might you use a **portfolio strategy** to resolve scalability? Are you prepared to follow through?
- How will you ensure all batches are properly **tracked** throughout the supply chain and reach the correct patient (where applicable)? How will you **store** this data reliably?
- How will you generate data and implement findings to **optimise** the supply chain?

6.10.3. Clinical trial design

- Are your clinical trials sufficiently **powered**?
- Are your inclusion criteria broad enough to ensure **recruitment**?

- Are your inclusion criteria narrow enough to maximise the **chance of success**?
- Are your endpoints both **approvable** and **reimbursable**? Do you need consultation from regulators or payers?
- Are your follow-up times sufficiently **long term**? How can you ensure any projected or forecasted clinical outcomes are **valid**?
- Where are you going to undertake your trial and what are the **market access implication** of this decision?
- Have you fully considered the **optimal patient subpopulation** to treat?
- Does your clinical trial strategy fully capture the **value** of your product?

6.10.4. Pricing and reimbursement

- Do you understand the **cost of the disease** including its current economic burden and indirect healthcare costs sufficiently to justify your pricing strategy?
- Does your clinical trial generate sufficient data to **justify** your pricing strategy?
- Have you analysed the risk of achieving reimbursement, and have you **approached payers or industry associations** to inform this assessment?

6.10.5. Commercial

- What is the (current and future) **competition** in this disease space and how might it be mitigated?
- How well **protected** is your technology? How comprehensive is the IP, and when does it expire? What other protection strategies may be relevant?
- What are the **regulatory risks**? How can you leverage **expedited development pathways** (e.g. PRIME, breakthrough status) to de-risk product development?
- How do you plan to **exit**? What role might biopharma organisations have in this?

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