Europe's Emerging Science

Putting Advanced Therapies into Practice to Deliver Better Health

A guide to Advanced Therapies

ebe
european biopharmaceutical enterprises

VitalTransformation

The European Biopharmaceutical Enterprises' mission is to be Europe's expert voice for emerging bioscience & technology and the leading platform for the health innovation ecosystem.

EBE represents biopharmaceutical companies of all sizes. Today 60% of its members are micro, small and medium sized companies.

Headquartered in Brussels, EBE is uniquely positioned as the biotechnology arm of EFPIA, the European Federation of Pharmaceutical Industries and Associations, to support the biopharmaceutical ecosystem.

This document was prepared by the Advanced Therapies and Emerging Science Working Group at EBE. EBE intends to reach out to all the stakeholders in the biopharmaceutical ecosystem and increase their awareness of the challenges faced by emerging science and the huge opportunities it presents.

www.ebe-biopharma.eu

This guide was produced in collaboration with Vital Transformation.

Vital Transformation understands the implications of new medical procedures, technologies and policies. We measure their impact on current clinical practices in close collaboration with health care professionals, researchers, and regulators. Through our web platform and client network, we are able to communicate our findings with international decision makers and stakeholders.

www.vitaltransformation.com

Coauthors
João Guerreiro (jdtg00@gmail.com) and Filipe Grácio

Editors
Daniela Couto and Alison Kilian

Design
Peter Koekoek

Welcome Letter

Europe is a world leader in the fundamental science underpinning Advanced Therapies and in the therapeutic use and regulation of tissue, cell and gene therapies.

By Roberto Gradnik, EBE President and Eduardo Bravo, EBE Vice-President

Although still in the early stages of commercialisation, there is growing evidence of the transformational prospects offered by these products.

To date, most benefit has been demonstrated in autologous treatments, in which cells or tissues are taken from a patient and manipulated in some way, before being administered back to the same individual.

At present the majority of these autologous treatments are delivered at hospital-scale, with the processing in laboratories on site.

The first therapy using autologous cells to be approved by the European Medicines Agency (EMA) under the Advanced Therapies regulation was ChondroCelect, for treating damaged knee cartilage. The product is proof that the process of extracting, processing and administering cells can be done in a quality-controlled, repeatable way.

Using a patient's own cells avoids the risk of immune rejection. However, for non-regenerative indications, it can be difficult to scale-up delivery and so make a commercial success of autologous products. To open up the true medical and commercial potential of Advanced Therapies, allogeneic products are needed that are suitable for any patient.

This calls for alternative sources of cells and tissues and the development of technologies to manufacture them at scale. These advances are necessary not only to deliver on the therapeutic potential, but also to make Advanced Therapies commercially viable and affordable for Europe's healthcare systems.

The first allogeneic stem cell therapy Prochymal, was approved by the regulator Health Canada in May 2012. The product, based on stem cells from healthy adult donors, is used to treat children with graft-versus-host disease (an acute immune reaction to a bone marrow transplant). The approval demonstrated there is a route to market and to commercialise allogeneic stem cell-based therapies and a number of other allogeneic products are in clinical development.

In gene therapy Europe has blazed the trail to commercialisation, with the EMA becoming the first western regulator to grant an approval when it gave the green light to uniQure NV's Glybera, a treatment for a rare inherited disorder which makes it impossible to digest fat. The EMA was also first to grant approval to a stem cell-based therapy, Chiesi's Holoclar, an autologous treatment for Limbal Stem Cell Deficiency, caused by chemical or physical burns to the eye.

Building on these foundations, Europe needs to maintain momentum, creating the conditions for widespread commercialisation and ensuring its healthcare systems are ready to adopt these novel technologies.

This report provides a guide to Advanced Therapies, seeks expert views on how to drive adoption, and considers hurdles in scaling-up manufacturing, meeting the requirements of regulators and securing reimbursement.

Advanced Therapies are a reality, with early products hinting at significant therapeutic potential. To secure the benefits, there must be support for clinical translation, and a regulatory and reimbursement framework that will allow these products to move on from the one-off, hospital-scale model, to become a commercial, European-scale sector.

With this report, we hope to further the collaborative discussion on emerging sciences and advanced therapies – with the ultimate outcome of delivering better care for patients.

Signed,

Roberto Gradnik, EBE President

Eduardo Bravo, EBE Vice-President

Contents

Contents

Executive Summary

Advanced Therapies made from genes and/or cells represent one of the most promising fields of medical research, offering the prospect of disease reversal. This can be achieved through administering cells to activate healing processes or correct a defect, delivering a gene to override a mutation, or by engineering tissues to produce replacements for diseased or worn out body parts.

Europe has taken a lead in academic research into advanced tissue therapies, in translation through to the clinic, setting out robust regulatory pathways for assessing and ensuring the quality and safety of these complex products, and in beginning to shape care pathways to accommodate these novel therapies in its healthcare systems.

There are a number of heartening examples of Europe's strengths in this field – some of which are detailed throughout this report. What is also evident from the pioneers, however, is just how difficult it is to bring Advanced Therapies through development and to the point where patients have access.

So for example, after completing a convoluted and lengthy examination by the EMA – in which Glybera was turned down four times – it then took more than 18 months to negotiate patient access to the product. Of the €50 million invested to get Glybera to the point of approval, €15 million was accounted for by the regulatory process. Despite the impressive work of such pioneers, more remains to be done to ensure Europe reaps the benefits of Advanced Therapies, both in relation to their potential therapeutic impact – with the contribution they stand to make to the sustainability of Europe's healthcare systems – and in the commercial returns that will flow from establishing a strong Advanced Therapies sector.

This study of the field first provides a brief introduction to the science of Advanced Therapies. It then looks to the views of experts, setting out their visions of emerging technologies in biomedicine, and addressing topics such as the use of 3D printing to produce replacement tissues.

The momentum comes from two directions – the push from advances in the basic science, in which Europe excels, and the pull from huge unmet medical need and the potential Advanced Therapies hold to address it.

However, the policy framework must be optimised to support translation of this potential into approved products that can be manufactured at scale and delivered to the bedside.

The report outlines policy measures, including continued funding of high quality science, support to translate research to the clinic, and the need to foster synergies and collaborations, providing companies working to commercialise products with access to academic and clinical experts.

One thing now becoming evident is that Advanced Therapies require a more service-oriented approach from pharmaceutical companies, particularly in the case of autologous products that are specific to individual patients. Such a shift points to one of the greatest hurdles in

commercialising Advanced Therapies, which is the difficulty in scaling-up and achieving economies of scale – in products that are based on living cells, DNA or tissues, with all the difficulties of standardisation and quality control which that implies.

The report also examines the barriers that Advanced Therapies are facing in the regulatory and reimbursement sphere.

Whatever the difficulties, Advanced Therapies are beginning to deliver. The pharmaceutical and biotech sector is engaged and the first products are underscoring the extent of the therapeutic potential.

Now Europe needs to act in concert – between member states and between different disciplines and sectors – to secure this promise.

Introduction: Scientific Background on Advanced Therapies

Cell Therapy: How does it work?

The ability to use human cells and formulate and deliver them as approved pharmaceutical drugs with the power, to regenerate or replace human cells and tissues, to replace or over-ride a defective gene, or to activate healing processes within the body: these are some of the enticing prospects offered by Advanced Therapies.

While only taking their first steps into the market, Advanced Therapies cover a large range of products and are built upon decades of research and hundreds of clinical trials.

Here we explain some of the basic principles and technological foundations of this exciting field. In most cases, Cell Therapy aims to stimulate the repair of diseased or damaged tissue by harnessing the body's own lead repair agent, the stem cell. Cell therapy can also be used to control inflammation and treat inflammatory diseases.

The processes of maintenance, repair and replacement occur naturally throughout life, in the mending of broken bones, the healing of cuts and grazes, the replacement of worn out cells, and the daily generation of new blood cells.

The stem cells responsible for supporting growth and promoting repair – adult stem cells - are specialised to generate specific categories of cells, for example, blood cells, bone cells, skin cells, muscle cells.

Testimonial: **Cell Therapy - "A Swiss Army Knife"**

Eduardo Bravo - CEO of Tigenix

"I think the beauty of the cells compared to biologics is that while biologics have a single target and a single effect, cells have the ability to modulate their response according to the environment. So for example, a biologic targeting TNF-alpha will completely neutralise the cytokine, whether the patient needs it or not. We have demonstrated that the cells are only activated if they find themselves in an environment where they need to, otherwise they will behave in the same way as naturally occurring stem cells and remain quiescent. I think this ability of the cells to react to their environment, modulating their response accordingly, makes them the right approach. Are they going to be the right approach for every disease? I don't think so. Is it possible that 50 years from now we may design some perfect biologic? Yes, maybe. But today, there is nothing currently being developed that can be a substitute for the subtle response that cells have in the face of common chronic disease that have a number of causes."

Adult stem cells (also called somatic or tissue stem cells) can be found in most tissues in the body. They maintain and repair the organ or tissue in which they reside, generating the new cells required for the everyday normal functioning of the human body. They can have very different behaviours: blood stem cells (or haematopoietic stem cells) for example, produce millions of blood cells daily, while other adult stem cells remain dormant for long periods until they are activated, be it by the need for more cells to maintain the tissue, or in response to injury or disease.

Adult stem cells reside in specific and specialised niches and will give rise to cells within that niche. Despite what their name suggests, they can be isolated from adults, children and foetuses.

These different categories of adult stem cells are all derived from pluripotent stem cells that occur in the embryo. At this initial stage of life up to 14 days after fertilisation all cells are pluripotent – meaning they are able to generate any cell in the human body. Pluripotent stem cells do not exist in the fully developed human and can either be derived from embryos of less than 14 days (embryonic stem cells) or generated in the laboratory (induced pluripotent stem cells). Induced pluripotent stem cells are adult cells, such as skin cells, that have been reprogrammed by having specific genes activated to induce pluripotency.

Pluripotent stem cells offer greater therapeutic potential than adult stem cells, in that they can be differentiated into any type of cell in the body. However, the difficulties of reproducibly differentiating pluripotent stem cells into the desired cell type for therapy presents greater challenges than those encountered in differentiating adult stem cells. In addition, there are some safety issues, including the potential that the cells will run out of control and promote the formation of tumours.

Embryonic stem cells have the potential to be differentiated into any cell type, and therefore to be used to replace any cell in the human body. While there are ethical constraints on research and commercialisation of cell therapies based on embryonic stem cells, the law varies from one country to another, and such research is allowed under license in some countries.

Although the vast majority of cells in the human body are specialised for a particular function, they retain the same DNA as pluripotent stem cells. An essential difference is found in which bits of DNA are activated and which are not.

One of the major advances in the field in recent years has been the development of induced pluripotent stem cells. These are generated by reprogramming regular cells back to a pluripotent state. The first clinical trial of a cell therapy based on an induced pluripotent stem cell is in progress in Japan, where the technique for generating them was invented by Shinya Yamanaka in 2006.

Personalised Medicine

Personalised Medicine is not a single technology or therapy, but rather a new model and approach to healthcare, in which a therapy is tailored to a particular patient, based on his/her unique characteristics. This is in direct contrast to the traditional approach of a single drug that is suitable for everyone. The concept stems from increased understanding of the biological and genetic diversity of the patient population and how these affect individual responses to drugs. By collecting genetic information or other key biomarkers from the patient, a biological profile can be built and matched to a drug's mode of action. If there are different drugs available for a single condition, this will allow the matching of most efficient drug for each profile.

One other distinction that is critical to understanding the state of play in cell therapy, is between autologous cells that are taken from a patient and manipulated in some way before being re-administered to the same patient, and allogeneic cells, taken from a donor and then processed in some way before administration to a patient.

Autologous cell therapies can be considered a potent embodiment of the principles of personalised medicine.

While allogeneic cells offer the possibility of scaling up and making therapies available off the shelf, there is the possibility of sparking an unwanted immune reaction to foreign cells, particularly if repeated dosing is required.

However, some areas of the body, for example the eye, are immune-privileged, meaning allogeneic cells do not promote immune reactions. Researchers have taken advantage of this to develop a number of cell therapies for treating eye conditions, and these are some of the most advanced products in development. While research into these treatments accelerates, the first stem cell product to be approved in Europe is an autologous treatment that restores full vision in people who have a burn to one of their eyes.

Cell Therapy: Impact on patients

It may still be in its infancy, but there are a number of approved cell therapies and many products in the pipeline. The latest survey by the UK Cell Therapy Catapult for example, shows there were 41 cell therapy clinical trials in progress in the UK in 2014, up from 34 in 2013.

There are currently more than 15 cell therapies in Phase III clinical trials and moving towards marketing authorisation, targeting immune, cardiac and musculoskeletal diseases. Of these, two thirds are autologous. However, the UK Cell Catapult data hints that allogeneic therapies are catching up, with half the products in clinical trials in the UK in 2014 based on donor cells.

As noted above, the first allogeneic stem cell therapy to be approved, in Canada and New Zealand, was Prochymal, developed by Osiris and since acquired by Mesoblast. The product, for treating graft versus host disease in children, uses mesenchymal stem cells from adult donors.

Mesenchymal stem cells, which are multipotent but not pluripotent, are found in bone marrow, adipose tissue and the placenta, among other sources. These have the ability to differentiate into a number of different cell types. However in the case of Prochymal and other products in development, it is their ability to suppress the immune system that is the focus of their therapeutic effect.

Therapies based on pluripotent stem cells have had a chequered path towards clinical use. In part this is because of the ethical and political controversy that surrounds their source. This has resulted in limits in funding and research, and increased the risk for investors in the field.
But the difficulties can also be attributed in part to the complexity of the basic science and the need to build a thorough understanding of how to control the differentiation of embryonic stem cells to the desired therapeutic cell. Inevitably, the pluripotent qualities of embryonic stem cells have raised safety concerns with regulatory agencies. As of the end of 2014, there were no approved therapies derived from either embryonic stem cells or induced pluripotent stem cells.

However, there are embryonic stem cells in clinical trials. The first data in a peer reviewed journal showing a positive clinical effect was published in The Lancet in January 2012. The paper showed that retinal pigment epithelium cells derived by Advanced Cell Technology (now renamed Ocata Therapeutics) from embryonic stem cells had a positive effect on two patients with advanced vision loss caused by macular degeneration, with both of the patients showing an improvement in their vision.

This came after the announcement in November 2011 from one of the leading embryonic stem cell pioneers, Geron Inc, that it was abandoning its ground-breaking Phase I trial in acute spinal injury. While the decision was taken on economic grounds, rather than as a result of any safety concerns, it wiped out the leading corporate force in embryonic stem cell translation and commercialisation. As a company, Geron had spent 15 years taking embryonic stem cells from initial discovery to FDA approval for a clinical trial, with every step of the way requiring invention and negotiation.

Following Geron's decision, the intellectual property and other assets were acquired by Asterias Biotherapeutics, a subsidiary of the US regenerative medicine specialist Biotime Inc. In August 2014 Asterias announced it had started a new clinical trial in spinal cord injury. Asterias is also using embryonic stem cells to derive immune system calls for use in cancer immunotherapy and has a collaboration with the charity Cancer Research UK, the largest funder of cancer research in Europe, to carry out a Phase I/II trial in lung cancer.

Other embryonic stem cell-derived products in or advancing towards clinical development include Neuralstem Inc's trial in spinal cord injury, Viacyte Inc's trial of pancreatic precursor cells derived from embryonic stem cells in the treatment of diabetes, and Pfizer research unit Neusentis' retinal cell treatment for macular degeneration.

While the manipulation required to create induced pluripotent stem cells raises issues for their clinical application, they do not face the same ethical concerns as embryonic stem cells.

As yet, there are no clinical trials of cell therapies based on induced pluripotent stem cells in North America or Europe. However, in the US, Ocata is seeking approval to test platelets produced from this source, as a potential replacement for platelets derived from blood donations. Japan, as the frontrunner in induced pluripotent stem cell research, has invested heavily in the field. The first human studies, in the treatment of macular degeneration, began

Autologous versus Allogeneic Cell Therapies

Autologous cell therapies use cells derived from a patient's own body, and then administered back to the patient. An established example is stem cell-based skin grafting, in which cells are extracted and expanded in the laboratory into sheets of skin that can be used to cover burns. These cells will not be seen as foreign by the immune system, avoiding immune rejection – although it should be noted that certain manipulations, could lead to immune reactions from autologous therapies.

In the case of allogeneic cell therapies, the source of the cells will be a donor. While this potentially allows for cells to be available "off the shelf" to treat any patient, care must be taken to ensure these foreign cells do not cause an immune reaction, or to provide immune-suppression therapy.

Some stem cells show an immunomodulatory behaviour, while certain tissues, for example the eye, benefit from what is called "immune privilege" allowing for successful transplantation without immune complications in the vascular cornea and with numerous types of cells in the retina. One long-standing example of allogeneic use of stem cells is the bone marrow transplant, in the treatment of blood disorders such as leukaemia and lymphoma. However, donor and recipient must be tissue-matched, and there are cases where it is not possible to find a suitable donor.

CAR-T Cell Therapies

In CAR-T Cell therapies, immune cells (called T-Cells) from the patients are genetically modified to express new receptors on their surface that are specific to particular antigens found on the surface of tumour cells. When these cells are delivered back to the patient, they selectively identify and kill cancerous cells.

While there are no CAR-T Cell therapies currently approved for human use, several promising products are expected to reach the market shortly. Perhaps the most advanced is Novartis' CTL019, which has shown breakthrough results in treating children suffering from Acute Lymphoblastic Leukemia (ALL), a rare cancer affecting cells of the immune system, and is expected to be filed for approval in 2016. Other therapies are following, with Pfizer and GSK both establishing partnerships to develop new products. Meanwhile, U.S. start-ups in the field, such as Kite Pharma and Juno Therapeutics raised almost $400 million in initial public offerings last year. Both companies have received orphan designation for their therapies, with Juno's JCAR015 being granted Breakthrough Therapy Designation by the FDA.

at the RIKEN centre in September 2014. Other human studies are expected to follow, including a proposed trial in Parkinson's disease.

While an approved induced pluripotent stem cell therapy may be some years off in Europe, these cells are proving to be invaluable tools in the development of new drugs, making it possible to generate cell-based models of disease. Because there are no ethical constraints, they have opened up the study of mechanisms of pluripotency to a wide field of researchers.

However, as the gold standard model of pluripotent cells, it is important to continue to support research in human embryonic stem cells.

While the pharmaceutical industry has to date taken only a limited interest in stem cell-based therapies, it has made major investments in cell therapies based on immune system cells in the treatment of cancer. These therapies involve extracting immune system cells from patients, processing them in some way that enables the cells to recognise a tumour, and then re-injecting them.

The first such product to win regulatory approval was Dendreon Corp's Provenge, for the treatment of prostate cancer, which was approved by the FDA in 2012 and the EMA in 2013. Although not a commercial success, Provenge has been a trial-blazer for the field. There are now a number of similar products in clinical development, with cancer immunotherapies based on chimeric antigen receptor T-cell (CAR-T) cells turning in impressive results. These include Juno Therapeutics, whose product for patients with high risk or relapsed forms of leukaemia is now in phase I/II.

Testimonial: T-cell immunotherapy: the power to turn the immune system against cancer

Keith Thompson, CEO, Cell Therapy Catapult UK

The Cell Therapy Catapult was established to address current barriers to commercialisation, by smoothing the path and demonstrating that Advanced Therapies can be developed, licensed and adopted.

As Keith Thompson notes, until recently, large companies have mostly been watching and waiting on developments in Advanced Therapies.

The past year or so has seen a breakthrough in the area of T-cell immunotherapies for treating cancer. These autologous treatments, in which a patient's T-cells are extracted and manipulated to enable them lock onto antigens found on cancer cells, sparking an immune reaction, "shown remarkably impressive results in clinical trials," Thompson says.

Academic trials have reported significant responses in patients with advanced blood cancers and Adaptimmune Ltd, became the first UK Company to publish positive results of T-cell therapy in solid tumours.

This clinical success has unlocked investment from both pharmaceutical companies and venture capitalists. "Where the clinical signal is big enough – once you get over that hurdle – investors move in and this helps start to address the other barriers to innovation," Thompson notes.

Much of this investment is focussed on scaling-up and developing quality control systems.

With more than two decades of research behind Advanced Therapies, it is now becoming evident that one significant technical attribute of this class of product will be the potential for much shorter timelines. Traditional drugs can be as long as fifteen years in discovery and development. In comparison, following its initial move into T-cell immunotherapy in 2012, Novartis expects to file its first product for approval with the FDA in 2016.

"Some of these technologies will go from initial proof of concept to first filing in 5 – 6 years, which in my mind is absolutely impressive," says Thompson.

In the case of Advanced Therapies for rare diseases - where products will address huge unmet medical need, but the market potential may be limited - it is critical to maintain the pressure and encourage further innovation. To do this Thompson suggests the following:

- Support breakthrough therapies through the regulatory system
- Properly reward / reimburse the investment made by innovators
- Ensure health systems are ready to adopt these therapies
- End hospital exemption once equivalent product is licensed
- Give academics incentives to pursue clinical translation

Cell Therapy Glossary

Term	Abbreviation	Definition
(human) Embryonic stem cell	(hESC) / ESC	Undifferentiated cell derived from a pre-blastocyst or blastocyst (up to 14-days post fertilisation) that is pluripotent.
Adult Stem Cell		Stem cell derived from an adult body or foetus
Age-related macular degeneration	AMD	AMD affects the macula, the part of the eye that allows you to see fine detail. It does not hurt, but it causes cells in the macula to die and is one of the main causes of vision loss in developed countries.
Allogeneic		Where donor and recipient are different.
Autologous		Where donor and recipient are the same.
Chondroblast		Cells responsible for the formation and maintenance of cartilage. As these cells synthesize the cartilage extra cellular matrix, they will eventually become chondrocytes, commonly referred to as cartilage cells.
Graft versus host disease	GVHD	GVHD is a complication that can occur after a stem cell or bone marrow transplant, in which the newly transplanted donor cells attack the transplant recipient's body.
Haematopoietic stem cells	HSC	Stem cell that gives rise to all red and white blood cells and platelets.
Immunosuppression		Suppression of the immune response in order to prevent the rejection of grafts or transplants, or to control autoimmune diseases.
induced Pluripotent Stem Cell	iPS / iPSC	Embryonic stem cell-like cell that is produced by reprogramming a cell to a state of pluripotency.
Lymphocyte		White blood cell part of the immune system. Responsible for the specific immune response to infectious agents, lymphocytes include the T-Cells, B-Cells, and NK-Cells.
Osteoblast		Cells responsible for the formation and mineralization of the bone. As the tissue calcifies the cells become osteocytes, commonly referred to as bone cells.
Pluripotent		Having the ability to develop into all cell lineages, except those related to extraembryonic tissues.
Potency		Extent to which a stem cell can differentiate into different cell types.
Stem Cell	SC	Cell capable of both asymmetric cell division and self-renewal, and of providing cells capable of differentiation.

*Definitions based on PAS 84:2012 Cell therapy and regenerative medicine. Glossary from BSI / BIS.

Introduction: Scientific Background on Advanced Therapies

Gene Therapy: How does it work?

Over the past 25 years remarkable advances have been made in gene therapy, with over 2,000 clinical trials registered to date. However, progress has not always been smooth. In 1999 Jesse Gelsinger died in a trial at the University of Pennsylvania after developing a severe immune reaction to a viral vector. In the same year, four of ten children suffering from X-linked severe immunodeficiency developed leukaemia following gene therapy. As a result, trials were halted, stricter regulations were introduced, and novel, safer vectors, designed to have better targeting, were developed.

Gene therapy aims to treat, cure or even prevent diseases by altering gene expression in a patient's cells. A gene therapy can be used to replace defective genes, promote regeneration through the introduction of new genes, or to prompt the immune system into fighting an infection or cancer.

Delivering the genes requires a vector. Most vectors are viruses that are engineered so that they retain their ability to insert their DNA into human cells, but are unable to replicate once inside the human host. Non-viral vectors, for example lipid carriers or nanoparticles, are in development, but there are no approved gene therapies using non-viral vectors.

Somatic gene therapy targets any cell in the human body apart from the germline cells of the eggs and sperm. Germline gene therapy, which would mean therapeutic genes are passed down to progeny, is prohibited. [1]

Gene therapies fall into two main classes: in-vivo therapies in which the vector is injected into the patient, and ex-vivo, in which the cells are transfected outside the body and then transplanted back into the patient.

While most of the gene therapies currently in the pipeline target cancer, there are products in development for treating inherited genetic disorders, cardiovascular disease and infectious diseases. The first and only gene therapy product approved by EMA to date is uniQure's Glybera,

So how does it work? Our DNA is made of thousands of genes that encode the huge number of proteins and peptides required for the correct functioning of the cells in the body. If a gene encoding a particular protein suffers a mutation it can lead to a serious disease. By providing those cells with a correct copy of the mutated gene, gene therapy can potentially provide a cure. The right vector must be selected and engineered to deliver the DNA to the correct target cells and ensure the gene is expressed at appropriate levels.

[1] Gene therapy can target virtually any cell in the human body that contains DNA. An important distinction is made between germline gene therapy targeting eggs and sperm, and somatic gene therapy targeting all other types of cell. Germline gene therapy would result in permanent changes that would be transferred down from generation to generation. While this would theoretically allow for successful gene therapies to cure genetic diseases through a family line, it introduces the risk that any problem that arises would be inherited. Germline gene therapy is prohibited or faces limitations in many countries. In Europe, gene therapies must use vectors or delivery methods that guarantee germ cells are not targeted.

Gene Therapy: Delivery vectors

Gene therapies require DNA coding for the desired protein to be delivered to the target cell using either a viral or non-viral vector.

Vectors have been developed to suit different requirements, for example, the amount of genetic material they will be required to carry, how they modulate the immune response, how long the gene is required to remain active in the target cell, ability to deliver the DNA to non-dividing cells and specificity towards different types of target cells.

A key property is the method of DNA delivery into the cell. For example, retroviruses, lentiviruses and adeno-associated viruses integrate the target gene into the host cell chromosomes, while adenoviruses deliver the DNA to the nucleus without the integration step.

There is a growing body of clinical evidence showing these vectors are safe. Adeno-associated vectors and lentiviral vectors, for example, have been tested in thousands of patients.

Non-viral vectors include lipids and cationic polymers that can complex with the DNA and protect and facilitate its delivery. In addition, naked DNA can be delivered in the absence of any carrier. Non-viral vectors are cheaper and easier to manufacture, and are often considered safer than their viral counterparts. In the past they have shown low efficiency when compared with viral vectors, but new delivery methods and developments such as nanoscale carriers, mean non-viral vectors are emerging as a real alternative.

Gene Therapy: Ex-vivo versus In-vivo

In ex-vivo therapy the gene transfer occurs outside of the body. Autologous or healthy donor allogeneic cells are harvested and treated with the vector carrying the therapeutic gene before being administered back to the patient. This makes it easier to ensure only the target cells are transfected or transduced, and reduces the risk of the vector causing an immune reaction. On the other hand it presents logistical difficulties, as an approved facility with the necessary equipment must be available in the location where the patient is being treated.

Examples of ex-vivo gene therapies include gene therapy treatment for adenosine deaminase-severe combined immunodeficiency (ADA-SCID), in which patients have an enzyme deficiency that prevents them from producing

Testimonial: Gene Therapy and Unmet (Unfair) Expectations

Luigi Naldini – Professor of Cell and Tissue Biology, "Vita-Salute San Raffaele" University; Director, San Raffaele Telethon Institute for Gene Therapy (TIGET), Milan

"I think the promise of gene and cell therapy was oversold in the beginning, and there was a failure to deliver. In addition, gene and cell therapy are significant interventions. Gene therapy implies genetic modification, so there is also an intrinsic resistance, while cell therapy falls in the area of transplantation. These are not normal drugs and there is heightened concern – which makes a lot of sense at the beginning – leading to a cautious approach. In addition, there was an unjustified expectation of having the perfect therapy at hand. Some people wanted 100 per cent efficacy with no side effects – I don't think that is a reasonable expectation. For example, stem cell transplants that are proving successful in the clinic could have never have been developed if they had faced the same rules that led to the suspension of early gene therapy trials.

One of the trials which contributed to the delays faced by the field was the first gene therapy trial in SCID-X1. While initially showing success, some of the children developed leukaemia. Now 10 years after that trial, two of those treated children died from either the leukaemia or the disease. This is much less than the death rate in patients receiving standard of care. In other words, gene therapy showed itself to be better in terms of efficacy and side effects compared to the existing treatments, yet the trial was halted on the basis of an unacceptable rate of side effects.

To a certain extent there was an expectation of high benefit and minimal side effects – which was a lot to ask for. But there was also probably a fear factor: if you want to touch the genome and play god with it, then you must have an obvious benefit. I think this is changing now, with more involvement of the industry, more clinicians advancing therapies than before. Attitudes to gene therapy are shifting to be more on a footing with attitudes towards traditional drug development."

the white blood cells needed to fight infection. In clinical trials, bone marrow cells harvested from patients have been transfected with the ADA gene and administered back, restoring long-term ADA activity.

In in-vivo gene therapy, the vector is administered directly to the patient. Targeting a limited set of cells within the body is more challenging, since it is highly dependent on the specificity of the delivery vector. The success and effectiveness of the procedure is also limited by the fact that cells may not be accessible and the vector itself may be removed by the immune system. Despite limitations, the procedure is less invasive than collecting and then re-injecting treated cells. In any case, for many conditions, it is not possible to remove cells and process them ex-vivo. In-vivo treatment is more flexible and scalable, since it can be available off-the-shelf.

Gene Therapy: Impact on patients

The first gene therapy to receive regulatory approval was in China in 2003, when Gendicine, developed by SiBiono Gene Tech Co., was approved for treating head and neck cancer. Following this, Oncorine, developed by Shanghai Sunway Biotech, received the backing of the Chinese regulator in 2005. Neither of these products is available in any western markets.

It was another seven years before Glybera became the first gene therapy to be approved in a regulated market in the western world. With Glybera providing proof that gene therapies can receive approval in Europe, other products are expected to be filed for marketing authorisation within the next couple of years. Products currently in Phase III clinical trials include the MolMed gene therapy against Graft-versus-host disease; Transgene's immunotherapy for metastatic lung cancer; and Mologen's immunomodulator for treating colorectal cancer.

Introduction: Scientific Background on Advanced Therapies

Tissue Engineered Therapies: How does it work?

Tissue engineered therapies offer the promise of not only replacing and repairing tissues such as skin, cartilage and bones, but also whole organs.

The EMA's Advanced Therapies Medicinal Product regulation includes a precise definition of what a tissue engineered product must look like to be developed and registered as a pharmaceutical that can be sold across Europe. However, the field of tissue engineering is viewed more broadly than this, and products offer the possibility of being approved as either medical devices or advance tissue medicinal products.

Traditionally, tissue engineering has been associated with the manufacturing or regeneration of tissues and organs, with or without a supporting scaffold.

In the majority of cell therapies, cells are administered directly into the patient, where they work towards the repair or regeneration of a tissue. Tissue engineering involves producing the functional tissue in vitro and then transplanting it into the patient. Cells need not only be expanded in the laboratory, but also directed to organise themselves into a functional tissue.

The advantage of engineering tissues rather than implanting cells, is that the implants can be effective immediately. For example, using cultured cartilage to mend torn meniscal cartilage in the knee has the advantage over administering autologous cells that a repair could be load-bearing as soon as is the cartilage is implanted.

Similarly, cultured skin grafts, such as Epicel, approved for use by the FDA as a Humanitarian Use Device, can immediately cover wounds. It should be noted that there is a divergence in the regulatory approaches between the US and Europe, with the EMA viewing skin replacement products as tissue engineered constructs, while the FDA does not.

Tissue engineering involves techniques to encourage cells to form tissues, but it also includes the use of scaffolds to provide both physical support for the development of a 3D tissue construct and to prompt biological and chemical cues that are crucial to a final functional tissue. Scaffolds can have a natural origin, such as a collagen allograft from a donor, or artificial, where the scaffold is built from a biomaterial.

Both types of scaffolds have been used to fashion replacement tracheas, for example. In the first such procedure of its kind, a donor trachea was decellularised to leave a collagen scaffold that was then seeded with mesenchymal stem cell-derived chondrocytes from the recipient.

There is no need for immune suppression and the seeded cells differentiate in situ forming epithelium. However, the donated scaffolds biodegrade over time, leading the transplanted trachea to become floppy.

Paolo Macchiarini, who was part of the team that carried out the first donor trachea transplant, was also the first to test artificial scaffolds, and in June 2011 carried out the first transplant of an artificial trachea seeded with the recipient's stem cells.

As the example highlights, artificial scaffolds are 3D structures that both serve as a support and provide a template for tissue regrowth and regeneration. They can be made from a number of different biomaterials, including polymers and bioceramics and are fabricated using a number of different techniques.

They share some key properties:

- Biocompatibility - all scaffolds must promote cell adhesion and normal functioning, with no, or minimal, immune reaction upon implantation;
- Biodegradability - scaffolds must degrade over time into non-toxic by-products allowing for the host cells to replace them;
- Mechanical Properties - the scaffold's mechanical properties must match those of the original tissue;
- Scaffold Layout - the scaffold should have an inner structure that allows cells and nutrients to penetrate and for waste products to be removed.

Tissue Engineered Therapies: Biomaterials in tissue engineering

Typical biomaterials used in tissue engineering are ceramics and natural and synthetic polymers. Ceramic scaffolds have been mostly used in bone regeneration products. Their structure, rigidity and chemical composition is similar to the mineral phase of bone and the material promotes the differentiation and proliferation of osteoblasts.

Natural polymers offer the advantages of being biologically active and biocompatible. However, they are difficult to manufacture in a reproducible way and have poor mechanical properties. Synthetic polymers offer greater flexibility because they can be tailored in a reproducible manner, to have the appropriate mechanical properties or degrade at a particular rate.

3D bioprinting

3D bioprinting makes it possible to lay down biological materials, including living cells, in a precise spatial position, creating complex structures with an organised cellular structure and microvascular networks. The process is automated and precise, opening the way to commercial applications.

However, there are challenges to applying 3D bioprinting, notably achieving the resolution needed to reproduce different tissue structures at the microscale, a requirement that will be essential to making more complex and larger organs.

While bioprinting is some way from clinical application, it is one of the most promising technologies in terms of the generation of whole, solid organs, such as kidneys.

Tissue Engineered Therapies: Impact on patients

The roots of tissue engineering are in the use of donor transplants and skin allografts, and these remain the areas where there are the most products.

In addition to Epicel, there are several other skin substitutes, including Apligraf and Dermagraft, while cartilage replacement products include ChondroCelect, bone replacements include Osteocel, Trinity Elite and Allostem, and for treating burns to the eye there is Holoclar, which promotes regeneration of the surface of the cornea.

The European Medicines Agency's Classification of Advanced Therapy Medicinal Products

While Advanced Therapies is used as a generic term covering several technologies, they are regulated in the European Union under the Advanced Therapy Medicinal Products (ATMPs) framework* as Gene Therapy Medicinal Products, Somatic Cell Therapy Medicinal Products and Tissue Engineered Products.

The ATMP classification distinguishes advanced therapies from treatments such as blood transfusions, skin grafts and organ, islet cell, or bone marrow cell transplants, where cells and tissues are fulfilling their natural function, and allows products that involve engineering or re-purposing of cells and tissues to be developed and registered as pharmaceutical products and sold across Europe.

Human donor islet cells, intended to treat severe cases of type I diabetes, are not classified as an advanced therapy because there is no change in the biological characteristics of the cells, which are intended to have the same function in the recipient.

However, non-modified cells used for a different function, for example, bone marrow cells, intended to treat after-effects of heart attacks, are classified as an ATMP.

The Expert Point of View

Emerging Technologies in Biomedicine: What to expect in the next 10-15 years

Experts identified tissue engineering, cell therapy and gene therapy as important emerging technologies that can be expected to translate into important therapies in the near future.

The experts expect to see an increasing number of cell therapies getting approval, and say the shift towards allogeneic therapies will fuel growth of the sector. Attitudes towards therapies based on induced pluripotent stem cells are more mixed. While their value as a drug discovery tool is recognised by all, there are doubts about clinical applications in the near future, with some going as far as suggesting there may be a risk to the sector as a whole if anything were to go wrong in a clinical trial of a therapy derived from induced pluripotent stem cells. However, others believe induced pluripotent stem cells are ready for human clinical use and we should expect the first trials in Europe shortly.

On the back of the regulatory success of Glybera, gene therapy companies have attracted a lot of interest and investment from the private sector. While the focus is mostly on rare, inherited disorders with few individual sufferers, our experts noted that there is a substantial therapeutic benefit for each patient.

Over the past two years CAR T-cell gene therapies have accumulated impressive evidence of clinical benefit and attracted significant funding from private investors. US start-up Kite Pharma, which is working with CAR-T cells, raised, over $300 million in venture capital and $128 million in an initial public offering in the past 12 months. Another start-up, Juno Therapeutics received the FDA's breakthrough designation in November 2014 for its CAR T-cell for the treatment of lymphoblastic leukaemia and went public in December 2014, raising $265 million. In Europe, the UK T-cell company Adaptimmune raised more than $100 million in a private funding round in September 2014. Also, companies including Novartis, GlaxoSmithKline and Amgen have entered the field. Novartis has been in talks with regulators and has said it expects to file its first T-cell therapy for treatment of acute lymphoblastic leukaemia for approval in 2016.

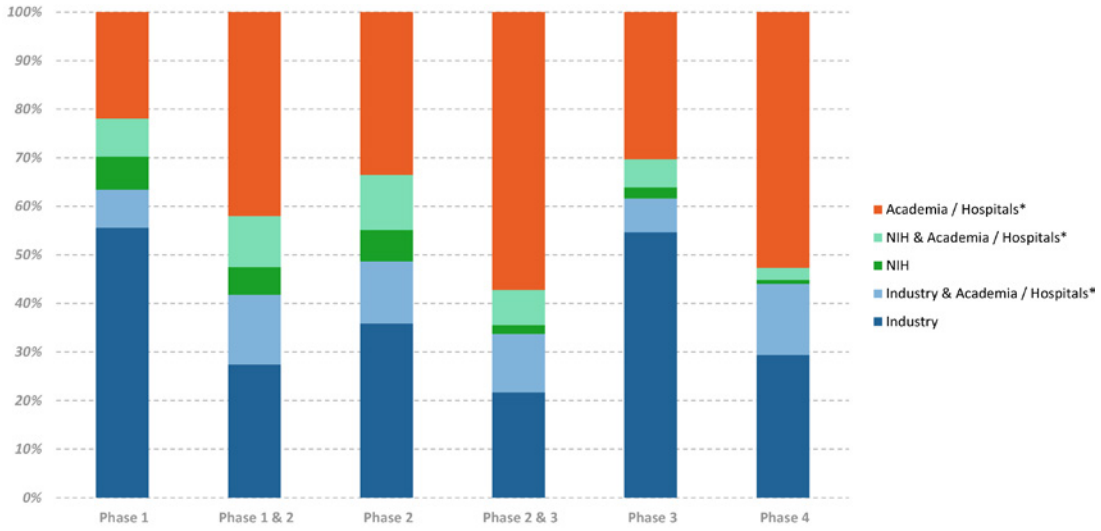
> "Everything that is in the clinic now, that would enable me to make these statements, has scientific roots that go back maybe 15 or 20 years ago" — Sander van Deventer, Managing Partner at Forbion Capital Partners, on the key technologies behind innovative therapies

The experts place particular emphasis on the disruptive nature of Advanced Therapies, saying the ability to administer a single treatment for chronic conditions that will remain effective for extended periods of time, is likely to become a reality in the near future.

Cell, gene and tissue therapies draw on a wide range of scientific research, carried out over the past twenty years and more. Although there have been some landmark discoveries, it is not possible to point to a single advance or technological achievement that made them possible. Rather, there has been continuous, incremental innovation.
As discussed, the approved Advanced Therapies, such

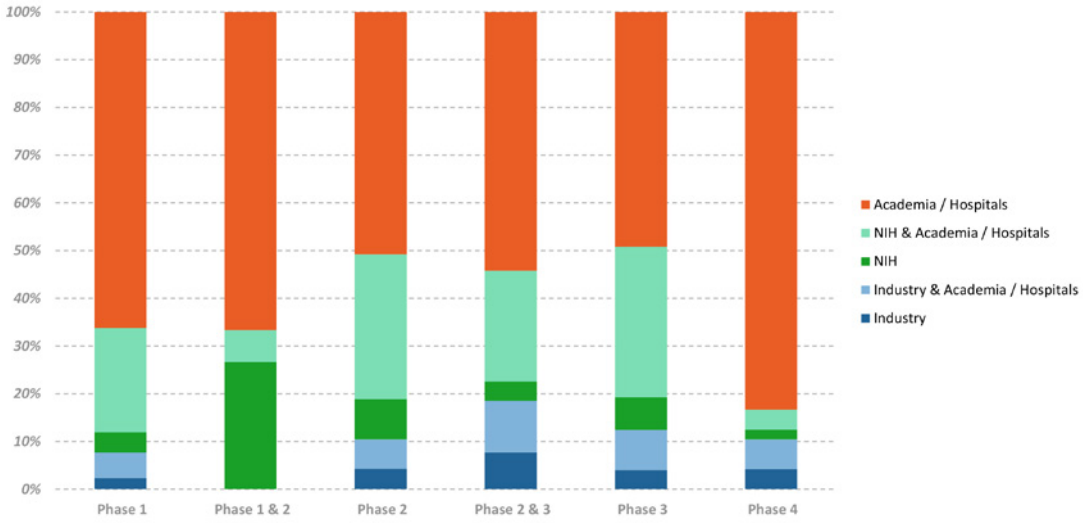
What and who is driving innovation?

Funder by Phases - All



Notes:
Industry includes 'Industry + NIH' (Accounts for 4% of cluster)
Industry + Academia / Hospitals includes 'industry + nih + academia / hospitals' (Accounts for 2% of cluster)
Studies supported by other Federal Agencies not included (<3% of all trials)

Funder by Phases - Cell Therapy



Notes:
Industry includes 'Industry + NIH' (Accounts for 3% of cluster)
Industry + Academia / Hospitals includes 'industry + nih + academia / hospitals' (Accounts for 13% of cluster)
Studies supported by other Federal Agencies not included (<1% of all trials)

While there has been significant financial support from research charities and public funds, there has been limited private investment in the field. There is a clear under representation of Industry on cell therapy trials vs other trials with the increase of "Other" sponsors, which include mostly Universities / Hospitals / Organizations.

as Glybera, ChondroCelect and Holoclar, are important stepping stones. Our experts expect the sector to learn from the mistakes and examples of these first innovators. More Advanced Therapies are expected to follow, though significant effort will be needed ensure patient access, build markets and achieve commercial success.

What and who is driving innovation?

While currently innovation is being driven by unmet clinical needs and scientific advances, commercial opportunity can be expected to play a larger role in pushing the field forward as more products receive regulatory approval.

For now, biotech start-ups and academic groups are the main innovators pushing products through.

> "My guess is that if someone would make a big jump into a cell therapy company, a few would follow." —Eduardo Bravo, CEO Tigenix, on big players entering the ATMP market

A limited number of clinical trials in the field is, to a large extent, associated with the high risk and some high profile failures. One case in point is the UK company Ark Therapeutics, a listed company that took Cerepro, a gene therapy for treating brain cancer, all the way through from first concept to Phase III clinical trials, but failed to win approval for the product from the EMA.

However, there is clear evidence that this is changing, with increased investment in gene therapy since Glybera was approved, and as discussed, the evidence of clinical benefit from T-cell immunotherapy now attracting significant investment. Pharma and biotech have started to show an interest, with several acquisitions and partnerships taking place in the last few years in cell and gene therapy.

How to encourage innovation: Fund High Quality Science

The basis for all Advanced Therapies is high quality science. Basic research must continue to be supported in an environment that allows for innovative technologies to rise to the surface and be translated through for clinical development. And while there have been significant advances in the clinic, our experts advise there are still gaps in understanding of the mechanisms of action. Some of the burdens of conducting clinical trials and standardising procedures could be reduced if there was greater understanding of the factors that underlie the variability of biological products.

> "I think that trickles down into the willingness of financial institutions to be comfortable with high-risk investment. Early stage VC financing is extremely high risk. Out of 10 companies, 9 are likely to fail. The anticipated high failure rate is baked in with the comfort level to deal with that. I don't believe that exists in Europe at the moment." — Krisztina Zsebo, CEO & President of Celladon, on why more VC capital is available in the US than the EU

Funders need to be aware of the lengthy development cycle timescales. Products are likely to need to go back to the bench for optimisation and, rather than being considered a failure, this should be encouraged. Funding for this should come from public and non-profit organisations. EU-level initiatives should look to identify and fund science behind diseases that are not receiving attention from the private sector or public funding in individual member states.

How to encourage innovation: Support Clinical Translation

There is a large funding gap in the translation of Advanced Therapies from pre-clinical development into the clinic. The number of venture capital firms willing to invest in Advanced Therapies in Europe is considerably fewer than ten years ago. The lack of a commercially successful Advanced Therapy makes investors wary of what they see as an unproven field. Academic spin-offs and small start-ups have struggled to push advanced therapies through to the later stages of development when it may be possible to attract private investors. The sector is currently a buyers' market with late stage valuations at remarkably low levels, even for products that have solid clinical data.

> "At the beginning, there is always enough economic support for the science. But then when it comes to translating it to the clinic, things become difficult. This is due to many factors, including regulations, the privacy and protecting rights of the patients, the interests of the hospitals and so forth, but it translates into an enormous amount of money. The price of developing clinical trials is too high, and in reality, often unsustainable in these economical times. I believe this is where things need to be changed. (...) When it comes to innovation and the research & development phase, a radical change of the economical support attribution and distribution is required, and clinical trials must be thought of as a vital, long term investment." — Paolo Macchiarini, Professor of Regenerative Surgery, Karolinska Institute, Stockholm

The level of investment required to conduct the larger studies necessary for market authorisation are beyond the

means of small or even medium-sized companies. The novel characteristics of Advanced Therapies limit the number of Clinical Research Organisations with the experience to carry out Phase III trials. In addition, it is expensive to establish the GMP (good manufacturing practice) compliant manufacturing facilities needed. Our experts say that as a consequence, promising products have been parked after initial clinical trials, not because of disappointing results, but due to a lack of means to go through the next stage.
While the experts agree that once the sector begins to deliver commercial returns, funding will become available, the current funding gap is delaying - perhaps indefinitely - the availability of several promising therapies.

> "We need to have both a sustaining funding programme for an appropriate length of time, but also a clear and consistent regulatory environment." — Alastair Kent, Director of Genetic Alliance UK

Some public entities have tried to step into the traditional place of venture capitalists in supporting start-ups through clinical development. The California Institute for Regenerative Medicine is supporting promising, but risky, new therapies that would otherwise be unable to attract investment for clinical trials. Other alternatives would be the promotion of VC-like funds, such as the UK Enterprise Investment Scheme. Public/private funds could be set up to invest in promising companies, according to priority areas set by governments in collaboration with private entities, to ensure both quality and viable commercial therapies are selected/prioritised. But there is still limited financial support for all the technologies that are parked after initial clinical trials.

> "These are early days for us. We have experience on scientific advice but not a lot on market authorisation. It is common knowledge that some of those that went through MA then had difficulties reaching the patients for different reasons. This should not be viewed as discouragement. If we look at the history of pharmacology, all the advancements went through a very bumpy start, from antibiotics in the 30s, to monoclonal antibodies and recombinant insulins. We are getting to the stage that things are starting to turn around. We have a very healthy pipeline in the scientific advice, especially for cell therapy." — Spiros Vamvakas, Head of Scientific Advice, EMA, on the role of regulators helping with translation

Using clinical trials databases to track the progress of cell-gene- and tissue-engineered therapy

A study of the two major US and European clinical trials registries, clinicaltrials.gov and clinical trialregister.eu, was carried out to assess the evolution of Advanced Therapies over the past decade or so.

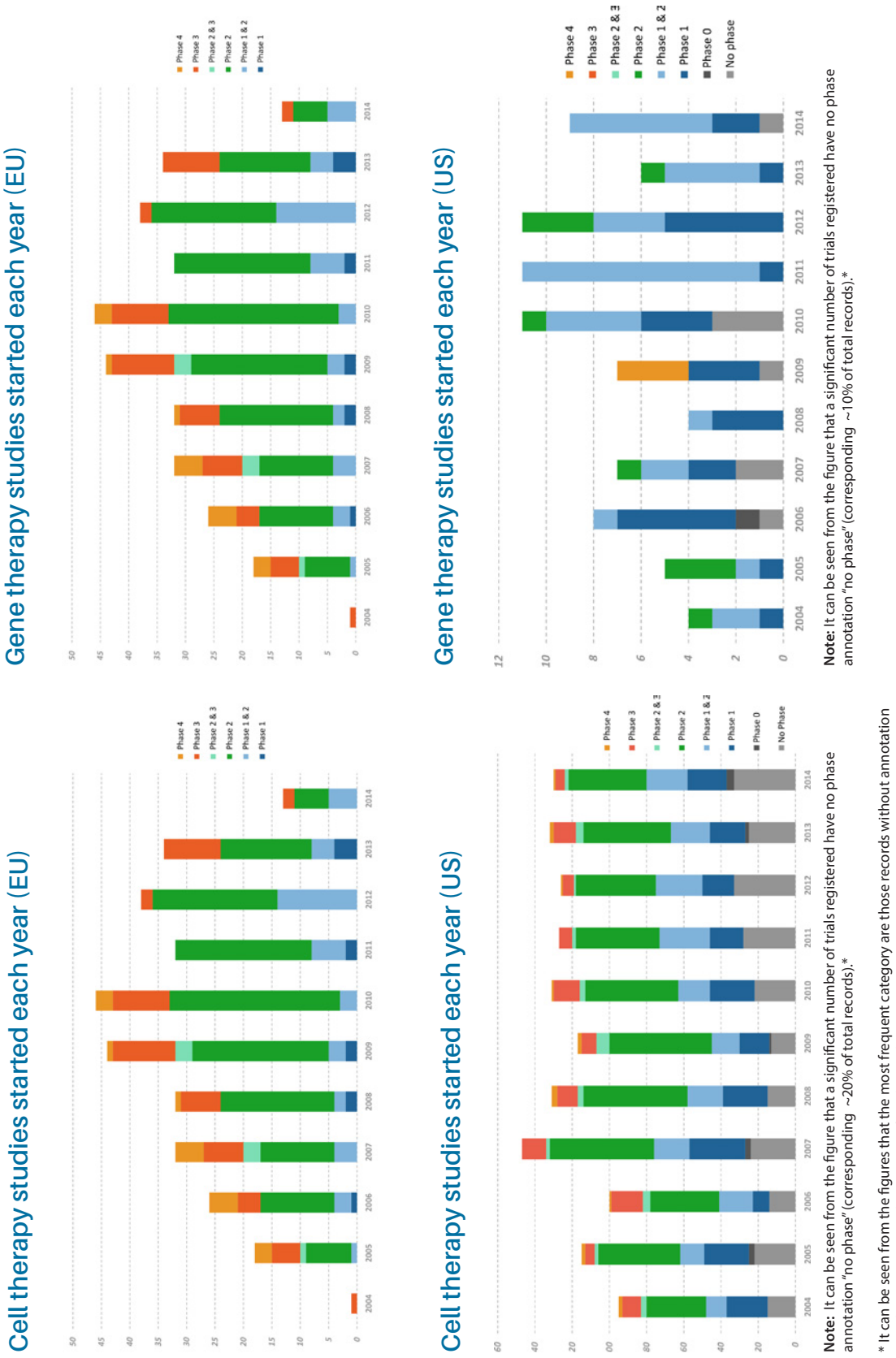
The analysis looked to see how many clinical trials refer to cell therapy, gene therapy or tissue engineered products, how are they distributed over standard phases of clinical trials and how this has changed over time. In addition, the researchers assessed the trends for Advanced Therapies versus all other types of products.

The analysis shows that cell therapy related studies represent about 1% of total studies or less, while gene therapy or tissue engineered products account for a very small percentage of between 0.1 - 0.3%. There does not appear to have been a significant or systematic increase or decrease over the past 10 years.

Up to 2010, the number of new Advanced Therapy studies increased each year. That trend has stopped, and the number of new studies registered each year seems to be stabilising.

Over the past decade, cell therapy or gene therapy products do not show a significantly different trend from the total studies. They are not, for example, rising significantly faster, nor are they declining. Since the mid-to-late-2000s, cell therapies show a similar trend to that of all other studies.

However, Advanced Therapies are in different phases of clinical development from the general trend, with a higher proportion of phase 2 studies.



Studies in the records of clinicaltrialsregister.eu which contained a "cell therapy" IMP, and their starting date, stratified by phase information. On the horizontal axis, the year; on the vertical axis the number of studies started each each year; colors represent the study phase as according to legend.

Testimonial: Clinical trials and Patient Engagement

Alastair Kent - Director of Genetic Alliance UK, Chair of Rare Disease UK

"It is essential there is proper understanding and engagement from the patient community and that the benefits and risks are explored with the ultimate end users, patients and their families. As an example, a few years ago there was a small clinical trial in which stem cells derived from a foetus were used to treat people with Parkinson's disease. There were only a few patients but the trial was stopped because the uncontrolled muscle movement became more pronounced. One of the patients said, 'That is true but my speech improved so much that I can talk to my grandchildren for the first time in about 10 years. That was a really important development for me, and I'd rather have ability and put up with the uncontrolled muscle movements. I don't want someone else to decide on my behalf that this is an unacceptable risk.'"

How to encourage innovation: Establish Synergies and Collaborations

In a risk-adverse climate, there are significant benefits to be gained from collaborations in which academics and clinicians provide knowledge of the basic science and access to patients, while industry shares its expertise in translation, manufacturing and regulation.

> "There are good partnerships in place but not enough. I wouldn't point to any collaboration in particular as an example of success. What you need is to give people opportunities to do things together that work. The more opportunities there are, the more we will be able to have more successful interactions." — Robert Langer, MIT Institute Professor and founder of over 20 Biotech companies, on partnerships and synergies

Small companies can struggle to raise enough funds to comply with regulatory requirements, or to build the infrastructure required to generate meaningful data. Universities and specialised research centres can play an important role, by providing common core facilities, including not only pilot manufacturing facilities but also trained GMP (good manufacturing practice) and GLP (good laboratory practice) personnel. This makes it possible to ensure that products are developed to GLP standards from the pre-clinical stage, something which is extremely difficult to do in a standard academic environment.

The ability to generate pre-clinical data that can form part of early regulatory filings will make new therapies significantly more attractive to investors. Two examples of centres that provide these resources are Canada's Centre for the Commercialisation of Regenerative Medicine and the Cell Therapy Catapult in the UK, which provide core facilities and personnel, technical support for translation and a direct line to industry. The EMA stresses the importance of early engagement to access advice on product development and this can help to validate early stage research.

European universities must facilitate and encourage interactions with industry, take, for example, the creation of university spin-offs like Holostem Terapie Avanzate in Italy, the developer and manufacture of Holoclar and other ATMPs. New approaches are needed for handling intellectual property and material transfer agreements, to remove bureaucracy and speed up partnering.

Current hurdles in translating Advanced Therapies: Scaling up

Advanced Therapies have yet to prove their scalability and economic viability. While our experts believe economies of scale can be achieved that will lower costs, this will require significant effort and investment, both to develop efficient production methods and to build manufacturing facilities.

As the example of Dendreon's Provenge shows, autologous treatments are particularly challenging. These treatments traditionally require: an initial patient intervention to collect biological material; the subsequent manufacturing of the product and quality control testing of the sample; a further intervention to administer the therapeutic product. Manufacturing facilities and personnel must be situated close to treatment centres, which can place limits on expansion and lead to high costs per therapy. Despite work being done to make these processes more efficient and to reduce costs, for example by combining the collection, processing and delivery of the product within a single device and moving from batch-of-one processes to automated systems, much remains to be done.

> "... You need to go to large scale production and that is still an issue in cell therapy. There is a need to show that it is scalable and that has yet to be demonstrated. Once it is scalable you can go to large populations and you can bring down the cost..." — Stéphane Verdood, Managing Partner at Vesalius Biocapital

In the case of allogeneic products, a more traditional model can be employed. However, scaling up is not trivial and new enabling technologies are needed if the industry is to become capable of mass production. Experts believe a lack of large scale manufacturing is one of the main reasons why Advanced Therapies still struggle to attract investment. The funding needed is certainly beyond the means of start-ups and challenging for single big pharma or biotech companies. The sector would benefit from private-private or private-public collaborations targeting the development of new and efficient methods for large scale manufacturing of cell-based products. As new methods are developed, a better understanding of the requirements for large-scale manufacturing would enhance the translation of new therapies and lead to more viable cost structures.

> "The challenges are at the interface of engineering and biology. As you are doing the manufacturing scale up, you have to have developed the biological tools to know that as you change the process you are not changing the underlying biology of the intended product." — Robert Willenbucher, Head, Janssen Cell Therapy, Janssen Research & Development, LLC

One example of such a public-private collaboration can be found in the UK BloodPharma Consortium, sponsored by the medical charity Wellcome Trust and led by the Scottish National Blood Transfusion Service and including NHS Blood and Transplant, the Irish Blood Transfusion Service, Roslin Cells, several universities, the Engineering and Physical Sciences Research Council and the Cell Therapy Catapult. The consortium is working on the development of a scalable process for producing red blood cells for transfusion starting from stem cells (of both embryonic and induced sources). The enabling technologies developed in the process could greatly benefit the cell therapy field as a whole.

Current hurdles in Advanced Therapies translation: Regulation

Several stakeholders believe the regulatory process is unpredictable, confusing and extremely cumbersome. The experts agree on the difficulties of regulating this still young field and the necessity to evaluate Advanced Therapies on a case-by-case basis. Although the regulators are seen as taking a cautious approach, several experts said the EMA is open to consultation and willing to work with industry in designing trials.

> "What I have seen happening is that universities, through public funding their investigators have attracted, are doing a lot of regenerative medicine related research. Some are building pilot plant manufacturing facilities and in some cases, hiring sophisticated GMP manufacturing personnel to run these facilities. This is enabling the translation of the science at the university level which I think is incredibly valuable. It also provides a source of future product opportunities for larger companies who are willing to invest in late stage development." — Robert Willenbucher, Head, Janssen Cell Therapy, Janssen Research & Development, LLC

However, there is still a gap, in that typically, initial clinical development is taking place in an academic hospital setting, where there is limited experience of regulatory requirements and exactly what data will be required for marketing approval. Our experts suggested that regulators need to provide clearer guidelines in order to avoid the need to carry out repeat trials.

It is also suggested that shorter, adaptive pathways, should be put in place, especially for therapies intended for serious or life threatening diseases where there is no alternative treatment. Patients should be more involved in defining risk-benefit and in specifying meaningful clinical outcomes and endpoints. The aim should be to allow therapies to reach more patients sooner, whilst collecting data for final market

approval. The EMA's adaptive pathways pilot is an important attempt to put a more flexible pathway in place, allowing products to receive early approval and collect further data once they are on the market.

Autologous therapies currently face very strict regulatory demands in their manufacture. The level of validation required is often hard to meet due to the very limited amount of samples that are available for testing. The lot-to-lot consistency required by the regulators is also hard to achieve given the variability of the starting material and current methods of production. Autologous therapies will not be cost-effective if they are required to meet the same quality control standards as mass-produced allogeneic therapies. A greater effort should be placed on process validation, to avoid expensive and time-consuming batch testing.

With the field in its infancy and only a few therapies approved, there is currently a great deal of uncertainty on how the regulatory framework for Advanced Therapies will evolve in the major markets for advanced therapies. A consistent approach is critical, since in order to reach maturity, companies will need to develop standardised products that can be sold in multiple markets. Harmonisation of the requirements of the major regulatory agencies would be a great help.

Current hurdles in Advanced Therapies translation: Hospital Exemption

The Hospital Exemption was intended to allow access to experimental treatments, but it has proved difficult to build market share for the autologous cell therapies in the face of competition from similar preparations, administered under the Hospital Exemption Scheme.

> "The current legislation requires that medicinal products on the EU market have proven quality, safety and efficacy. This requires a lot of work and resources from those seeking a marketing authorisation and thus, it seems unfair if similar products for the same indications are allowed to be used under the hospital exemption. Such a situation is highly demotivating for those aiming for a centralized marketing authorization and will not support development of an ATMP industry in EU." — Paula Salmikangas, Chair of the Committee for Advanced Therapies, EMA

The Exemption Scheme was incorporated into the ATMP regulation in recognition of the pre-existing cottage industry, under which cell and tissue products are prepared on a non-routine basis for treating individual patients, however, it has not been consistently applied across Europe creating barriers to innovation.

While it has made it possible to get clinical proof of concept in areas where there are no alternative therapies, forming the basis for formal trials, some hospitals are using it routinely.

This is undermining companies that are going down the formal approval route, denying patients across Europe access to products that are manufactured to consistent standards. Holoclar, owned by Chiesi Farmaceutici, is an example of this hurdle. This and other cell therapies were initially developed by academic researchers and administered under Italy's consolidated therapies rules. This mechanism allows cell-, gene- and tissue-based therapies to be administered to patients, without full regulatory approval, but after well-documented pre-clinical research and proof of safety and efficacy has been published in scientific journals and following meticulous follow-up of patients based on a well-establish quality control system.

> "Indeed, (hospital exemption) is making a lot of companies question if it makes sense to come to Europe. You may create your own product and then someone may copy it in a hospital and then suddenly start producing from that hospital... And it isn't clear whether they will stop giving this hospital exemption licenses or not." — Eduardo Bravo, CEO Tigenix

The procedure underpinning Holoclar, in which stem cells are removed from a patient's uninjured eye, expanded, cultured and then injected into the injured eye, has been performed multiple times in hospital settings, but it is only now that Chiesi has EMA approval that a single, quality controlled therapy can be made available to patients across Europe, regardless of their location.

> "I think we would like to see a consistent approach across the EU to how this is managed. Different countries interpret things differently. We would like to see the EU taking a proactive stance in making sure that this is a well managed and rigorous approach." — Keith Thompson, Chief Executive, UK Cell Therapy Catapult, on the subject of hospital exemption

While obviously well-intentioned, hospital exemptions can make it extremely difficult to build the market and commercialise Advanced Therapies. In addition, the possibility that a product may be subject to different requirements on quality, traceability, and pharmacovigilance in different member states implies the level of public health protection is different according to the place of

Testimonial: Hurdles in Translating Advanced Therapies

Sander Van Deventer – Venture Capitalist at Forbion

"I think there has been focus on translation, creating value and so on. As far as I am concerned, I don't think it is necessarily a problem that government has not been involved in commercialisation - that is really handled much better by the market. Governments, desperate to spark innovation that will generate economic growth and jobs are trying to create copies of Silicon Valley all over the world. But Silicon Valley was not created by a government. It's really important to keep this is mind.

What governments should do is keep funding - and actually step up the funding of fundamental science.

Secondly, there is definitely a place for government in the very early seed stages. Then they should enable and support commercialisation, allowing start-up companies together with venture capitalists, to pick things up and develop them. There is a third very important point, which is that the government should not stand in the way of innovation. If you want to do a trial with an innovative medicine, currently there are many obstacles. It becomes very expensive and takes a long time. Yet we know that gene therapy is safer than many other medicines that we are using. Still there are these six months moratoria, all these committees that have to look through it. That is a major hurdle. Then, when it comes to registering these products, the regulatory authorities have a big problem because they really have no experience and try to be on the safe side.

The last point I think is this, if you get innovative medicines, you must be prepared to pay for them. In cancer therapy for example, checkpoint inhibitor drugs and oncolytic viruses, are a major step forward. While patients with metastatic melanoma all died in the past, 25% now survive. This is a major step forward, without actually a high level of toxicity. But when these medicines come into the market, there is this talk about this being too expensive, that governments will not pay for them. This is really the final blow, if you are not going to pay what it costs to make these medicines and reimburse the people that put all the money at risk in the development then you really jeopardise the development of innovative therapies."

residence of the patient. Despite making history in 2009 by becoming the first cell therapy to be approved by the EMA under the Advanced Therapy Medicinal Products regulation, ChondroCelect, for repairing damaged knee cartilage, faced the difficulty that similar therapy is available under the hospital exemption rule.[2]

The product's inventor, TiGenix NV, struggled to convince national health authorities to pay for the product, and five years after the approval only Belgium, Spain and the Netherlands, had agreed to reimburse ChondroCelect. In the UK and in Germany, the product is reimbursed on a case by case basis.

Our experts suggest that once a product is approved, the hospital exemption should be revoked, and only the quality controlled product used.

Current hurdles in translating Advanced Therapies: Reimbursement

Reimbursement is currently one of the biggest barriers constraining the development of Advanced Therapies in Europe. Experts say the need to satisfy the differing requirements of national health technology assessment bodies creates an additional level of complexity and currently, health technology assessment methodologies tend to undervalue Advanced Therapies.

> "Healthcare will become unpayable (...) I think it will be impossible in 5 to 10 years. You won't be able to put a new drug or treatment on the market if there is not a health economic reasoning behind. It will be important to make sure every new treatment is having a positive impact on the health budget of both governments and individuals."
>
> — Stéphane Verdood, Managing Partner at Vesalius Biocapital, on the future of reimbursement

Disparate health technology assessment methods and approaches, not only from one country to another, but also within regions in some countries, make the process of securing reimbursement for a new advanced therapy difficult and expensive. The divergence among national health technology assessment bodies adds a further level of uncertainty and risk to the development of Advanced Therapies. Even after demonstrating efficacy and safety to regulators and securing marketing authorisation, these products may find it hard to pass cost benefit scrutiny and secure reimbursement.

Our experts agree there should be an effort to harmonise the requirements of national heath technology assessment bodies. Currently, companies are required to provide duplicate information, in all the official EU languages, and to present clinical evidence over and above the data needed to obtain marketing authorisation. This is a waste of resources. Whilst acknowledging that reimbursement is under national jurisdiction, the experts suggest a common approach to key sections of health technology assessments, such as clinical effectiveness and utility, would hugely accelerate and simplify pricing negotiations.

The current high costs of developing and manufacturing Advanced Therapies inevitably mean they are expensive. Some experts consider the likely prices are not achievable under the current reimbursement model and that innovative pricing models should be developed. For example, it is entirely possible that a single course of treatment with a gene therapy corrects a problem that would otherwise have required a patient to receive regular treatment, for example, enzyme replacement therapy, over many years.

> "Stop requiring people to duplicate evidence that is available already in 28 different formats and languages. (...) simplify the front end of the equation, the 'does it work, how good is it?' and hopefully if we get a consensus on the clinical effectiveness then things like pricing negotiation and reimbursement would potentially become more straightforward as you are building on a shared set of assumptions about the utility of these therapies."
>
> — Alastair Kent, Director of Genetic Alliance UK.

The first gene therapy, Glybera, is the most expensive drug ever, with a price of €1 million for a single treatment, agreed by German payers. However, this should be seen in the context that the therapy works year after year, without further treatment. To date, it has been shown to maintain an effect over six years.

While others argue that Advanced Therapies should only be reimbursed if they are price competitive, they also warn of the difficulties of carrying out a proper economic analysis. As is the case with Glybera, several of these new therapies are one-off interventions that offer tremendous improvements, not only in life expectancy, but also in quality of life when compared to the standard of care. While regenerative medicines will often have a higher up-front cost than conventional therapies, the total costs incurred by health systems or providers will be less.

[2] Note that hospital exemption is specific for Europe and for ATMPs.

EBE Wrap up

In some senses, Advanced therapies are at the frontiers of R&D, using new technologies in pursuit of better patient outcomes. Their promise had, until recently, been harnessed only in research laboratories across Europe - but they are now beginning to make their way into clinical practice. The experts who have contributed to this report highlight the key challenges and the enticing opportunities for advanced therapies in Europe.

Key recommendations to clear the obstacles and deliver on the promise:

1. Clear a pathway from development to delivery: Advanced Therapies offer significant health benefits and the opportunity for Europe to build global markets. However, it is a challenge for companies to work with healthcare providers to generate evidence of the value and also to ensure that healthcare systems are geared up for, and receptive to, the use of these products.

2. De-clutter the regulatory landscape: clearer guidelines are needed and shorter, adaptive development pathways should be put in place, with patients being more involved in specifying meaningful endpoints.

3. Reduce the complexity around reimbursement: There should be standards for health technology assessments of Advanced Therapies based on new cost-benefit models tailored to the specific properties of these products – notably that while there may be a high upfront cost, one-off treatment can be expected to provide benefits over long time scales compared to traditional pharmaceuticals or enzyme replacement therapy.

4. Remove hospital exemptions once a product is approved: the Hospital Exemption Scheme was set up under the Advance Therapies Medicinal Products regulation of the EMA to recognise the existing cottage industry, in which cell and tissue therapies are prepared for individual patients. The scheme should continue to allow clinical trials to take place, but any exemption should end once a commercial product is approved.

5. Keep supporting the basic science: research is needed to increase understanding of the precise mode of action of Advanced Therapies and to allow clinicians to feed back knowledge acquired in clinical trials to inform further fundamental research and drive further improvements in products.

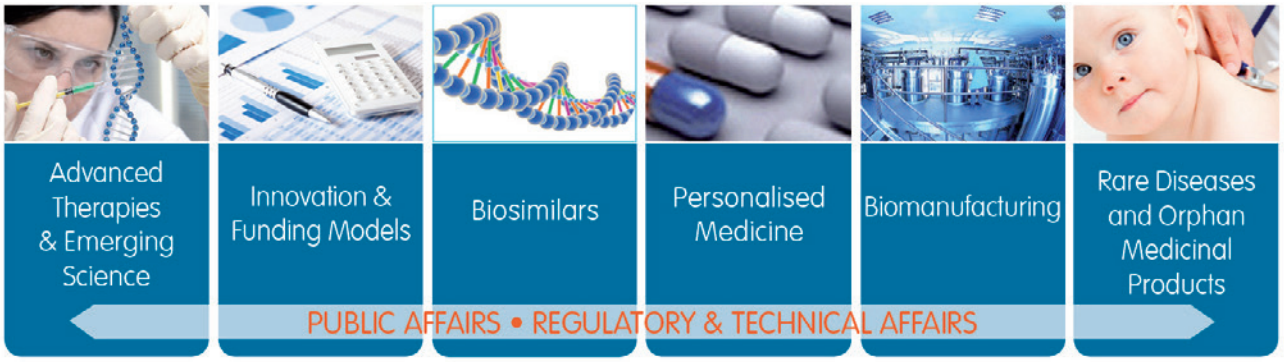
6. Engage with patients to assess and understand the benefits and risks of advanced therapies. The EMA has put patient input into the value assessments of new therapies at the centre of its evolving regulatory landscape, and this should be developed and encouraged, to improve informed consent processes for innovative therapies that address unmet medical needs.

The European Biopharmaceutical Enterprises, EBE, is the leading biopharmaceutical organisation in Europe, with 52 pharmaceutical company members, the majority of which are small and medium sized companies. As a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA) EBE is the Europe's expert voice for emerging bioscience & technology and the leading platform for the health innovation ecosystem.

What do we do?

EBE focuses on enhancing emerging healthcare technologies, promoting science innovation and advocating for policies that foster innovative health solutions in Europe via expertise in:

- Innovation eco-system and funding models
- Emerging biotech & science - regulatory advancement and advocating on the following priorities:



Expert Profiles

USA
Professor Robert Langer - MIT

- MIT Institute Professor
- Founder of over 20 Biotech companies
- Father of Tissue Engineering

Professor Langer is one of the most cited researchers and has more than 1,000 patents to his name. He has been involved in the formation and development of a number of medical biotechs, and has served on the advisory board of over 30 companies. He has also been a member of the FDA Science Council and other academies and institutions. Professor Langer has been honoured with numerous awards for his research and is looked to as one of the most influential people in biotech.

Sweden
Professor Paolo Macchiarini - KI

- Professor of Regenerative Surgery, Karolinska Institute, Stockholm
- Director of the European Airway Institute of Advanced Centre of Translational Regenerative Medicine

In 2008 Professor Macchiarini played a key role in the first tissue-engineered organ transplant in which a trachea (windpipe) from a deceased donor was seeded with stem cells from the recipient, Claudio Castillo. Those cells were then allowed to colonise the trachea in a bioreactor before the trachea was transplanted, in a life-saving - and life-transforming – operation, without the need for immune-suppressive drugs.

USA
Robert Willenbucher, M.D. - Janssen R&D

- Head, Janssen Cell Therapy, Janssen Research & Development, LLC

Rob Willenbucher, M.D. is the Head of the Janssen Cell Therapy, an internal, entrepreneurial group within Janssen Research & Development, which nurtures highly innovative ideas through venture teams in areas of potentially disruptive, cutting-edge research. Each venture team is focused on advancing novel platforms, products or technologies. Rob also serves as the Head of Janssen Cell Therapy, which includes a programme in retinal (macular) degeneration.

Italy
Professor Luigi Naldini - USR

- Professor of Cell and Tissue Biology, "Vita-Salute San Raffaele" University
- Director, San Raffaele Telethon Institute for Gene Therapy (TIGET), Milan

Professor Naldini is one of the founding fathers of gene therapy and was first to describe the use of lentiviral vectors for gene transfer in non-dividing cells. He has continued to explore gene therapy and its translation, leading several clinical trials. He is president of the ECGCT and is on the advisory council of the ACGCT. Professor Naldini is also a scientific advisor on EMA and WHO Committees for the evaluation of novel gene transfer medicines.

Belgium
Eduardo Bravo -Tigenix

- CEO of Tigenix
- Former VP at Sanofi-Aventis
- VP of EBE and member of the EC of ARM

Eduardo Bravo has more than 25 years' experience in the biopharmaceutical industry. He is the CEO of Tigenix, a leading European cell therapy company, which developed ChondroCelect, the first Advanced Tissue Medicinal Product to be approved by the EMA. Before joining the company in 2005 he held several senior management positions at Sanofi-Aventis, including Vice President for Latin America, a division with 2,000 employees and sales of more than €1 billion.

USA
Krisztina Zsebo - Celladon

- CEO & President of Celladon
- Former Venture Partner at Enterprise Partners Venture Capital

Krisztina Zsebo, PhD has served as Celladon's President, CEO and a member of the board of directors since 2004. Dr Zsebo is a biopharmaceutical veteran with 30 years of experience in the industry. She has held numerous executive positions, and has pioneered the development of MYDICAR - a treatment for heart failure that in 2014 became the first gene therapy to receive Breakthrough Designation from the FDA - from basic research to late stage clinical development. Before joining Celladon, Dr Zsebo was a Venture Partner at Enterprise Partners Venture Capital.

EU
Paula Salmikangas - CAT, EMA

- Chair of the Committee for Advanced therapies (EMA)
- Former Chair of Cell Products Working Party (EMA)

Paula Salmikangas, PhD has worked as a senior researcher at Finnish Medicines Agency, Finland since 2003. Her main areas of expertise are biological medicinal products, especially cell-based medicinal products and combination products. Dr Salmikangas has been a member and chair of Cell Products Working Party at the EMA from 2005 - 2012. She was Vice-Chair and member of the Committee for Advanced Therapies (CAT) from 2009 to 2014, and since February 2014 Chair of the CAT.

EU
Spiros Vamvakas - EMA

- Head of Scientific Advice (EMA)
- Topic leader for Adaptive Licensing project (EMA)

Spiros Vamvakas, MD, joined the European Medicines Agency in May 1999. His major activities at the Agency in recent years include the establishment of the Orphan Drug Designation and Scientific Advice/ Protocol Assistance, the Qualification of Novel Methodologies and the Parallel Scientific Advice between Regulators and Health Technology Assessment Bodies. He is also the topic leader of the Adaptive Licensing project which was launched by the EMA in March 2014.

Netherlands
Stéphane Verdood - Vesalius

- Managing Partner at Vesalius Biocapital
- Founder of Value4Growth

Stéphane Verdood is a venture capitalist who led the merger and acquisition division of the accountancy group Arthur Andersen in Belgium from 1989 to 1995. He also founded and led Arthur Andersen's business consulting division in Belgium and Luxembourg and served on the European Board of Partners of Arthur Andersen. He was a founder and managing partner at Value4Growth, a specialised Life Science consulting firm supporting start-up companies in all aspects of company formation, product strategy and fund raising.

United Kingdom
Keith Thompson - Cell Catapult

- CEO Cell Therapy Catapult UK

Keith Thompson was appointed Chief Executive of the Cell Therapy Catapult, part of an Innovate UK Board initiative to improve UK economic capability by bridging the gap between academic invention and commercialisation, in May 2012. Keith joined the Catapult from the Scottish National Blood Transfusion Service where he was National Director, focusing on modernising the blood supply, and expanding the service into cell therapy. Prior to this, Keith held various senior domestic and international positions where he grew several biomanufacturing businesses to become global players.

Netherlands
Sander Van Deventer - Forbion

- Managing Partner at Forbion Capital Partners
- General Partner ABN AMRO Capital Life Sciences

Sander Van Deventer, MD, PhD, is a Managing Partner at Forbion Capital Partners and has served as venture partner at ABN AMRO Capital Life Sciences since 2004. Dr Van Deventer is also professor of translational gastroenterology at Leiden University Medical Centre and was co-founder of Amsterdam Molecular Therapeutics (now uniQure). Dr Van Deventer has also held positions on the advisory boards of the FDA and EMA and advised the Dutch government on several Advanced Therapy programmes.

United Kingdom
Alastair Kent - Genetic Alliance

- Director of Genetic Alliance UK
- Chair of Rare Disease UK

Alastair Kent OBE is the Director of Genetic Alliance UK – the national charity of over 150 patient organisations, supporting all those affected by genetic conditions. Alastair has worked in the field of genetic and rare disease healthcare for over 15 years. He represents the interests of patients on numerous platforms; he is the president of the European Genetic Alliances Network (EGAN), Director of the European Platform for Patient Organisations, Science and Industry (EPPOSI) and he sits on the Human Genetics Commission, the EU Committee of Experts on Rare Diseases and the European Medicine Agency's Committee for Advanced Therapies amongst others.

References

Caplan, A. I., & West, M. D. (2014). Progressive approval: a proposal for a new regulatory pathway for regenerative medicine. Stem Cells Translational Medicine, 3, 560–3. doi:10.5966/sctm.2013-0180

Couto, D. S., Perez-Breva, L., & Cooney, C. L. (2012). Regenerative Medicine: Learning from Past Examples. Tissue Engineering Part A, 120725085622009. doi:10.1089/ten.tea.2011.0639

Culme-Seymour, E. J., Davie, N. L., Brindley, D. a, Edwards-Parton, S., & Mason, C. (2012). A decade of cell therapy clinical trials (2000–2010). Regenerative Medicine, 7, 455–462. doi:10.2217/rme.12.45

Fisher, M. B., & Mauck, R. L. (2013). Tissue engineering and regenerative medicine: recent innovations and the transition to translation. Tissue Engineering. Part B, Reviews, 19(1), 1–13. doi:10.1089/ten.TEB.2012.0723

French, A., Suh, J. Y., Suh, C. Y., Rubin, L., Barker, R., Bure, K., … Brindley, D. a. (2014). Global strategic partnerships in regenerative medicine. Trends in Biotechnology, 32(9), 436–440. doi:10.1016/j.tibtech.2014.05.007

Ginn, S. L., Alexander, I. E., Edelstein, M. L., Abedi, M. R., & Wixon, J. (2013). Gene therapy clinical trials worldwide to 2012 - an update. The Journal of Gene Medicine, 15(2), 65–77. doi:10.1002/jgm.2698

Guthrie, K., Bruce, A., Sangha, N., Rivera, E., & Basu, J. (2013). Potency evaluation of tissue engineered and regenerative medicine products. Trends in Biotechnology. Elsevier Ltd. doi:10.1016/j.tibtech.2013.05.007

Gore, M.E. "Adverse effects of gene therapy: Gene therapy can cause leukaemia: no shock, mild horror but a probe". Nature Gene Therapy (2003) 10, 4–4. doi:10.1038/sj.gt.3301946

Hourd, P., Ginty, P., Chandra, A., & Williams, D. J. (2014). Manufacturing models permitting roll out/scale out of clinically led autologous cell therapies: Regulatory and scientific challenges for comparability. Cytotherapy, 16(8), 1033–1047. doi:10.1016/j.jcyt.2014.03.005

Jaklenec, A., Stamp, A., Deweerd, E., Sherwin, A., & Langer, R. (2012). Progress in the Tissue Engineering and Stem Cell Industry "Are we there yet?." Tissue Engineering Part B: Reviews. doi:10.1089/ten.teb.2011.0553

Ledley, F. D., McNamee, L. M., Uzdil, V., & Morgan, I. W. (2014). Why commercialization of gene therapy stalled; examining the life cycles of gene therapy technologies. Gene Therapy, 21(2), 188–94. doi:10.1038/gt.2013.72

Li, M. D., Atkins, H., & Bubela, T. (2014). The global landscape of stem cell clinical trials. Regenerative Medicine, 9, 27–39. doi:10.2217/rme.13.80

Moran, Nuala. Tale of two biotech stars, Science Business. 09 July 2014. <http://www.sciencebusiness.net/news/76627/Tale-of-two-biotech-stars> 03 March 2015.

Macpherson, J. L., & Rasko, J. E. J. (2014). Clinical potential of gene therapy: Towards meeting the demand. Internal Medicine Journal, 44, 224–233. doi:10.1111/imj.12366

Plagnol, A. C., Rowley, E., Martin, P., & Livesey, F. (2009). Industry perceptions of barriers to commercialization of regenerative medicine products in the UK. Regenerative Medicine, 4, 549–559. doi:10.2217/rme.09.21

Schachter, B. (2014). Therapies of the state. Nature Biotechnology, 32(8), 736–741. doi:10.1038/nbt.2984

PAS 84:2012 (2012) Cell therapy and regenerative medicine. Glossary, BSI Standards Limited, ISBN: 9780580749049

Council Directive 2001/83/EC on the Community code relating to medicinal products for human use (2012) OJ L311/67

Committee for Advanced Therapies (2014), Reflection paper on classification of Advanced Therapy Medicinal Products, EMA

Council of Europe (2013). European Pharmacopoeia. vectors for human use. 8th ed

Schwartz, S. D., Hubschman, J.-P., Heilwell, G., Franco-Cardenas, V., Pan, C. K., Ostrick, R. M., Lanza, R. (2012). Embryonic stem cell trials for macular degeneration: a preliminary report. Lancet, 379(9817), 713–20.

Stem Cell Research Products – Opportunities, Tools and Technologies. AboutPharma 26 May 2014. <http://www.aboutpharma.com/blog/2014/05/26/stem-cell-research-products-opportunities-tools-and-technologies/>. 03 March 2015.

Trainor, N., Pietak, A., & Smith, T. (2014). Rethinking clinical delivery of adult stem cell therapies. Nature Biotechnology, 32(8), 729–735. doi:10.1038/nbt.2970

UK Cell Therapy Catapult. The Cell Therapy Catapult UK Clinical Trial Trials Database as of April 2014. April 2014. <https://ct.catapult.org.uk/documents/10588/11348/

ebe-biopharma.eu