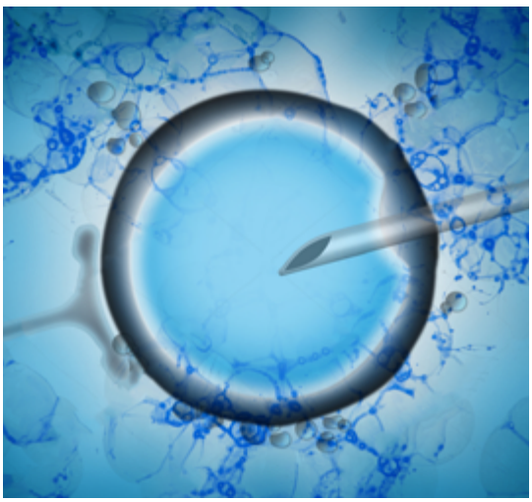
IS CELL & GENE THERAPY THE FUTURE OF MEDICINE?

At our Cell Series UK 2019, we sat down with an advisory group of leading experts to gain their thoughts on the state of the cell and gene therapy industry.

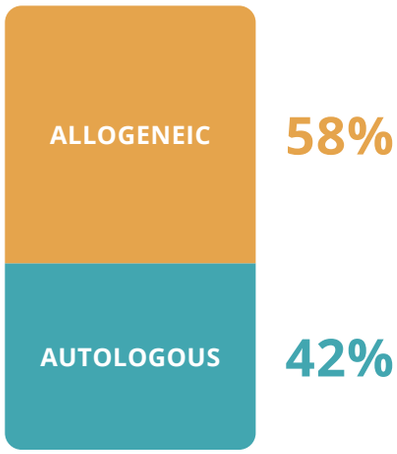
Cell and gene therapies are here – but are they here to stay?



The 21st century has brought with it numerous discoveries, mistakes and medical advances that have slowly transformed patient care. In some cases, these advances changed deep-seated beliefs in medicine; in others, they opened up possibilities beyond what doctors thought was possible years ago. With these discoveries came optimism that advances in medical science and technology could prove capable of solving all of our personal and global needs, whilst mistakes cast doubt on the safety and efficacy of these new modalities. It highlights the overwhelming pressure the pharmaceutical industry faces to deliver technologies and innovative therapies that offer hope to patients that currently have none, alongside the suspicion with which the world has come to view drug development, particularly in terms of safety and costing. This is particularly apparent when we consider cell and gene therapies, with our recent Cell & Gene Therapy Congress highlighting both the tremendous excitement about these therapies and the challenges faced by companies trying to develop them.

Cell and Gene Therapies are overlapping fields of biomedical research and treatment. The first aims to treat diseases by restoring or altering certain sets of cells, or by using cells to carry a therapy through the body. Cells are cultivated or

Which therapies have the biggest potential for success in the future?



modified outside the body before being injected into the patient, with cells originating from the patient (autologous cells) or a donor (allogeneic cells). Both autologous and allogeneic products have inspired a great deal of excitement, with the industry divided as to which strategy has more potential for the future – in a recent market survey we conducted, 58% of respondents believed allogeneic therapies to have the higher potential versus 42% choosing autologous products. Contrastingly, gene therapy aims to treat diseases by replacing, inactivating or introducing genes into cells – either inside the body (in vivo) or outside of the body (ex vivo).

Both cell and gene therapies are united in their transformative potential. Whilst conventional therapies typically relieve the signs and symptoms of a disease, cell and gene therapies have the potential to truly transform medicine by halting the progress of a disease or alleviating the underlying cause of a disease – they are therefore seen by many as truly curative. Moreover, the effect of treatment may be permanent after a single administration. This stands in contrast to the chronic nature of many conventional therapies, which must be taken by pill, injection or infusion on a continual basis.

For Jeff Galvin, CEO at American Gene Technologies, it is the vast number of diseases that could be cured by this development that is truly staggering.

> *The drip drip drip of these miracle cures is about to turn into a steady stream, which is about to turn into a deluge. It's not like the older drug development modalities that will yield a couple dozen blockbusters. Imagine getting 1000 blockbuster drugs."*

The transformative nature of these therapies has led to a swell of investment and interest in this space, with the global market growing at an estimated CAGR of over 36% during 2019 – 2025 [Reference]. This is matched by the amount of activity taking place: the FDA had 500 active investigational new drug applications involving cell and gene therapies in 2018, whilst clinical trial results have been promising, including high rates of complete responses in cancer and reversing blindness caused by specific gene mutations. The FDA has also innovated approval pathways, such as the regenerative medicine advanced therapy designation. All of this serves to showcase how we have moved beyond theory; Novartis has three approved drugs

within this space, whilst there are seven approved drugs globally. Major drivers of this growth include the growing incidence of several chronic and terminal diseases, including cancer, the launch of new products, the increasing clinical evidence of safety and efficacy, favourable regulatory support in development of these drugs, and improved manufacturing expertise in these products. The commercial potential of these drugs is undeniable, with experts highlighting that there's a huge commercial viability in being able to create cures, rather than treatments of symptoms. Alongside this economic motivation for companies, there is though also a strong ethical component and a feeling of responsibility to do this for patients.

Challenges do of course remain, as is the nature of innovative therapeutic modalities, with these challenges framing the conversation at the congress in October.

To start: the vast majority of patients may not receive cell and gene therapies as stakeholders struggle with successful business models for approved medicines, with the delivery system designed for pills and biologics needing to be changed to accommodate cell and gene therapies. This reflects the price point of cell and gene therapies, which have six-figure price tags, reflecting the one-off nature of these drugs. It must be taken into account that this could work out lower than the long-term expenses of current forms of treatment, as clearly indicated when comparing to a repeat drug. The immuno-oncology medicine Pembrolizumab, for example, costs $9870 per dose, however the median treatment costs per patient average $145,233 (over 10.3 months) and a patient who enters durable remission for 2 years on therapy has an average treatment cost of $338,406 (over 24 months) based on average selling price and assuming dose of 200mg every 3 weeks [Reference].

While the price of cell and gene therapies is indicative of the immense value they provide to patients, healthcare systems and society at large as opposed to the cost of goods, the novel manufacturing processes necessary for these therapies makes scale-up to meet commercial demand a recurrent significant challenge. Manufacturers of cell and gene therapies must develop novel processes outside of the traditional norms to ensure fast, cost-efficient and scalable processes (see fig. 1). Indeed, when we asked experts in our survey as to the areas they anticipate major advances impacting cell and gene therapy, the top three answers related to

manufacturing: the technologies, automation and closed systems, and analytics (see fig. 2). There is a need for cGMP facilities and closed systems that operate through production line or device-based approaches, as opposed to current processes established in a lab for small-scale experiments, but current options are limited, with manufacturing organisations booked up months in advance.

With the challenges of the current manufacturing processes comes also the knowledge that any errors could have potentially dire consequences. This is something at the forefront of manufacturers' minds in a way that it is not for other therapies – with cell & gene therapies there is the pressure that delivering a batch quicker to the patient could potentially save their live, whilst any mistakes could prove fatal. The relationship between the patient and drug development is therefore never more apparent than in cell and gene therapies, with not just the manufacture of the drugs but the clinical delivery of these cell and gene therapies much more complex and multidisciplinary than pills or biologics. Cell therapy patients are likely to require complex care before, during and after therapy. Patients and families will likely incur significant out-of-pocket costs to go to a certified centre, stay nearby and manage a complicated life for a period of months or years.

They do so knowing the safety concerns that run at the heart of cell and gene therapies, the long-term implications of which must be studied to improve patient care. There are numerous unintended consequences to these

Fig. 1) What are the biggest challenges facing cell & gene therapy manufacturing?

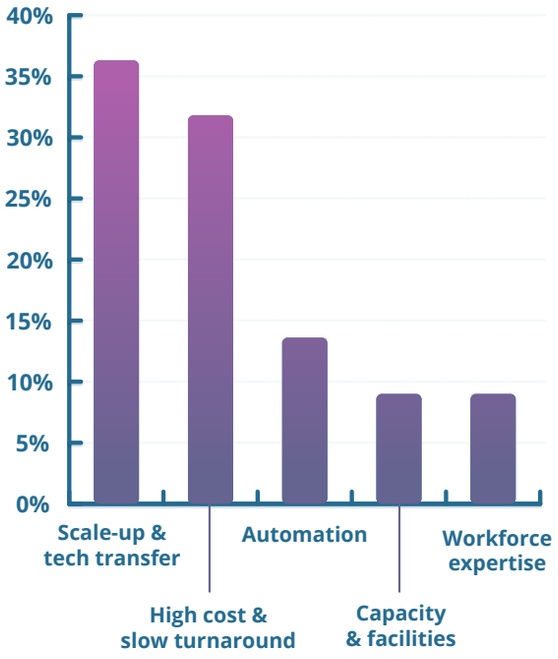
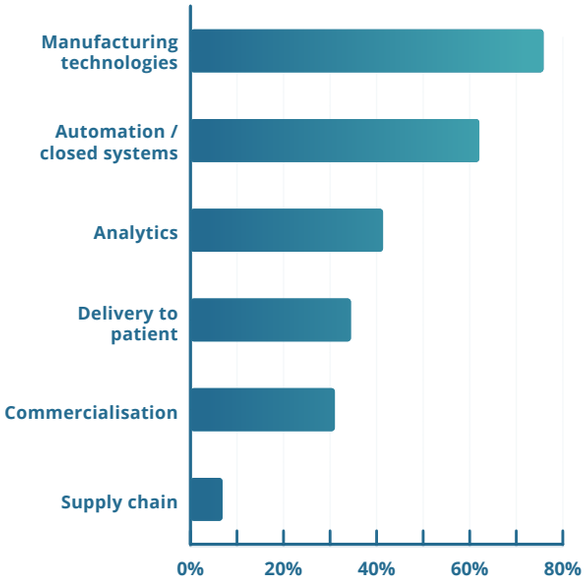


Fig. 2) In which areas do you anticipate major advances impacting cell and gene therapy development?



Source: Oxford Global's Cell & Gene Therapy Market Survey 2019, available as a free download on our Content HUB

Fig. 3) What are the five most pressing issues in cell & gene therapy development?

1. Safety
2. Analytics
3. Cost of Goods
4. Pricing
5. Automation

therapies, such as cytokine release syndrome associated with CAR T-cell therapies. Safety remains the most pressing issue in cell & gene therapy development (see fig. 3), and this extends beyond trials to approved products where there are questions as to the long-term consequences of cell and gene therapies. This is evidenced by current procedures necessitating gene therapy patients to be followed for 15 years, with the FDA also requiring follow-up for many types of cell therapies.

Considering these challenges, there are questions regarding whether the optimism around cell & gene therapies is well-founded. The expectation could simply be too high, particularly given the hope for patients that these therapies could bring desperately wanted cures. Companies must be careful not to overpromise in such a high-stake arena, where the excitement around cell and gene therapies is pushing the expectation extremely high.

It is without doubt, however, that it certainly not too optimistic to refer to these therapies as truly transformative, despite the challenges that must be addressed. This was at the heart of the presentations and discussions that took place at the Cell & Gene Therapy Congress, where it became clear that we are moving towards solutions that will have a lasting impact on this field. The progress that has been made was evident across the two days: from the opening address by Lothar Germeroth (Juno Therapeutics, A Celgene Company) on the progress of CAR-T cells to treat solid tumours, to opportunities in allogeneic CAR-T manufacturing as shown by Ricardo Baptista (Cellectis), to the panel discussion led by Jacquelyn Awigena-Cook (Celgene) on the future pathways for regulatory success. It is without a doubt an exciting time to be a part of the cell and gene therapy community as it builds on early approvals and proves its long-term viability.

Interested to learn more about the issues addressed above? We are delighted to share with you the presentation slides from Jeff Galvin's popular talk at the conference: HIV Cure And Immuno-Oncology – Powered By One Platform. This provides a broad view of gene and cell therapy and discusses how to reprogramme the human computer and repurpose cells for positive patient outcomes.

A THANK YOU TO OUR EXPERT SPEAKERS, CONVERSATIONS WITH WHOM INSPIRED THIS PIECE AND HELP US CONTINUE TO PROVIDE YOU WITH HIGH-QUALITY, INDUSTRY-LEADING EVENTS

Gabriele Proetzel, Director, External Neuroscience Innovation, Neuroscience Drug Discovery Unit, Takeda

Gabriele Proetzel, PhD is Director, External Neuroscience Innovation in the Neuroscience Drug Discovery Unit at Takeda Pharmaceuticals, based in Cambridge, MA. In her current role, she focuses on cell and gene therapy therapeutic approaches for neurological disorders. Prior industry appointments were at Scil Proteins, Deltagen Inc. and Boehringer Mannheim/Roche Penzberg. Before joining Takeda, Gabriele held the position of Associate Director of Technology Transfer at The Jackson Laboratory. Gabriele earned her Master degree in Life Sciences from the Ludwig-Maximilian University of Würzburg and a Ph.D. from University of Cincinnati, Ohio. She completed her postdoctoral training at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany.

Curtis Rambaran, Senior Director & Cardio-Renal Category Lead, Daiichi Sankyo

Dr Curtis Rambaran is a physician/scientist who received his medical degree from the University of the West Indies, Trinidad and completed his residency in Internal Medicine in Yorkshire, United Kingdom (UK). In 2009 he joined the Translational Medicine team at GlaxoSmithKline leading first in human/experimental medicine studies for novel compounds before acting as the medical governance lead for the LATITUDE-TIMI 60 Phase 3 CV outcome study. In 2015, he became the European Head of Translational Medicine/Clinical Pharmacology at Daiichi Sankyo, UK and in 2016 he relocated to the East coast USA as Senior Director CV Therapeutic area at Daiichi Sankyo Inc (DSI). He is currently the DSI Cardio-Renal category lead providing clinical leadership for stem cell CV programs including iPSC and MSC therapies for Heart Failure. He is also global clinical lead for rare disease programs of high unmet medical need and is the DSI representative on the Cardiac Safety Research Consortium (CSRC).

Jeff Galvin, Chief Executive Officer, American Gene Technologies

Jeff Galvin is the CEO and Founder of American Gene Technologies™ (AGT). He earned his BA degree in Economics from Harvard in 1981 and has more than 30 years of business and entrepreneurial experience including founder or executive positions at a variety of Silicon Valley startups. Several of his companies were taken public and/or sold to public companies, including one in the medical technology arena that was sold to Varian, the leading maker of linear accelerators used in cancer therapy. Following his startup experience, he retired to become an Angel Investor in real estate and high tech. He came out of retirement to found and fund AGT after meeting Roscoe Brady at NIH.

Paul Lammers, President & Chief Executive Officer, Triumvira

Dr. Lammers, MD, MSc, joined Triumvira Immunologics as President, CEO, and Director in January 2018. Before joining Triumvira, Dr. Lammers served as President/CEO/Director at Mirna Therapeutics. Previously, he served as President of Repros Therapeutics and also 6 years as Chief Medical Officer and Head of US Product Development for EMD Serono (Merck KgA). During his early industry tenure, Dr. Lammers also held various executive and senior management positions in clinical development, medical affairs, and regulatory affairs. Dr. Lammers currently serves as Lead Independent Director of Salarius Pharmaceuticals, on the Board of Directors of ImmunoMet, and as a Member of the Product Development Advisory Committee of CPRIT.

Marina Tarunina, Research Director, Plasticell

Dr. Marina Tarunina, Research Director at Plasticell Ltd, is an experienced scientist with a broad knowledge across different aspects of stem cell therapy development and commercialisation. She plays a major role in driving internal R&D and external scientific collaborations on stem cell technologies. She joined Plasticell 12 years ago and was involved in the development of Plasticell's main technological platform CombiCult® and its multiple applications in different areas of stem cell biology. Prior to joining Plasticell she worked as senior scientist at Inpharmatica Ltd focusing on drug discovery in the therapeutic area of metabolic diseases. Her academic career includes postdoctoral fellowships at Ludwig Institute for Cancer Research and Marie Curie Research Institute.

Mythili Koneru, Senior Vice President, Clinical Development, Marker Therapeutics

Mythili Koneru, M.D., Ph.D. is Senior Vice President of Clinical Development at Marker Therapeutics, a clinical-stage company specializing in the development of T cell-based immunotherapies for treatment of hematological malignancies and solid tumors. In this role, she is responsible for clinical development strategy, clinical study design, and medical oversight of the Company's therapeutic product candidates. Dr. Koneru joins Marker Therapeutics from Eli Lilly and Company, where she served most recently as Associate Vice President of Immuno-Oncology. In her previous role, Dr. Koneru designed early-stage clinical trials for hematologic and solid tumor malignancies and was instrumental in developing clinical trial protocols, serving as medical lead for trial conduct. Prior to Eli Lilly, Dr. Koneru completed her oncology fellowship in the laboratory of Dr. Renier Brentjens at Memorial Sloan-Kettering Cancer Center, where she developed adoptive T cell therapies in both leukemia and solid tumor malignancies in early phase clinical trials.