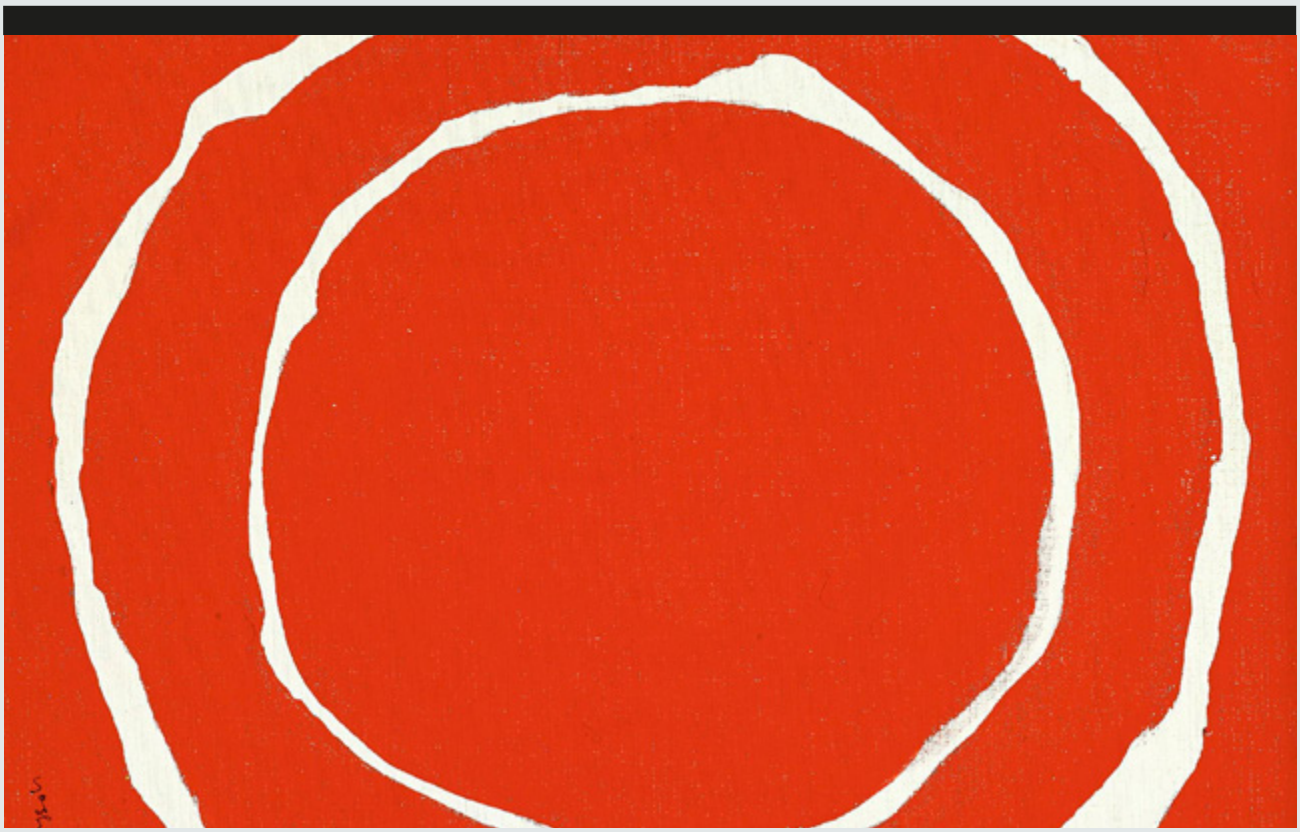
PHARMA BOARDROOM

InFocus

Cell & Gene Therapy



MAY 2020

In collaboration with: NOVARTIS

Contents

MAY 2020

The special report was produced by PharmaBoardroom.

Editor: Patrick Burton
Graphic design: Miriam León

In collaboration with Novartis International AG

Introduction

Cell and gene therapies are fast turning into a powerful engine of value creation for drug makers and represent a paradigm shift in the treatment of some of the world's most devastating and intractable illnesses. In the last five to ten years, for instance, we have witnessed innovative pharma investing deeply in high-risk frontier research involving stem cells and the harnessing of a patient's own immune system to attack the onset of a disease.

This has become most apparent in fields like oncology where ultra-expensive, yet thoroughly transformative CAR-T therapies are displacing classic treatments and swiftly going mainstream. This exclusive new E-book strives to interpret the disruptive impact of the gene revolution within medical science and examine its implications for payers, patients, healthcare providers and manufacturers.

On the industry side, CRISPR technology, rather like a pair of molecular scissors, is for the first time enabling drug developers to edit genes with unprecedented ease and precision, and as such is radically expanding the parameters of biological-based medicine. Cell and gene therapies are being integrated into conventional portfolios and bringing up fresh challenges to be surmounted in manufacturing, supply chain management, and the overall scale-up of this class of medicines.

On the institutional side, payers and care providers are going about the tricky task of financing and integrating these cutting-edge therapies: from the formulation of first-of-a-kind risk sharing models to the implementation of appropriate surround care. Also of note are the efforts to design an affordable off-the-shelf, gene edited, universal CAR-T cell.

Cell and gene therapy lies right at the heart of the new wave of personalized, precision medicine (PPM) being pioneered across mature pharma markets around the globe, and regulators are rethinking clinical trial and health technology assessment frameworks to adequately take into account the intricacies of these novel treatments, while, at the same time, mitigating possible ethical concerns around genetic modification.

What is clear is that the path towards greater adoption of cell and gene therapies cannot be walked alone. Inter-stakeholder collaboration and knowledge sharing, often in innovative new forms, will be of vital importance on the journey towards taking cell and gene therapies to the next level.

US FDA APPROVED CELLULAR & GENE THERAPY PRODUCTS

ALLOCORD (HPC, CORD BLOOD)
SSM Cardinal Glennon Children's Medical Center

CLEVECORD (HPC CORD BLOOD)
Cleveland Cord Blood Center

DUCORD, HPC CORD BLOOD
Duke University School of Medicine

GINTUIT (ALLOGENEIC CULTURED KERATINOCYTES AND FIBROBLASTS IN BOVINE COLLAGEN)
Organogenesis Incorporated

HEMACORD (HPC, CORD BLOOD)
New York Blood Center

HPC, CORD BLOOD
Clinimmune Labs, University of Colorado Cord Blood Bank

HPC, CORD BLOOD - MD ANDERSON CORD BLOOD BANK
MD Anderson Cord Blood Bank

HPC, CORD BLOOD - LIFESOUTH
LifeSouth Community Blood Centers, Inc.

HPC, CORD BLOOD - BLOODWORKS
Bloodworks

IMLYGIC (TALIMOGENE LAHERPAREPVEC)
BioVex, Inc., a subsidiary of Amgen Inc.

KYMRIAH (TISAGENLECLEUCEL)
Novartis Pharmaceuticals Corporation

LAVIV (AZFICEL-T)
Fibrocall Technologies

LUXTURNA
Spark Therapeutics, Inc.

MACI (AUTOLOGOUS CULTURED CHONDROCYTES ON A PORCINE COLLAGEN MEMBRANE)
Vericel Corp.

PROVENGE (SIPULEUCEL-T)
Dendreon Corp.

YESCARTA (AXICABTAGENE CILOLEUCEL)
Kite Pharma, Incorporated

ZOLGENSMA (ONASEMNOGENE ABEPARVOVEC-XIOI)
AveXis, Inc.

Source: FDA

JAPAN PMDA APPROVED REGENERATIVE MEDICINE PRODUCTS

BRAND NAME	GENERIC NAME	APPROVED IN
Collategene	beperminogene perplasmid	March 2019
HeartSheet	human (autologous) skeletal myoblast-derived cell sheet	September 2015
JACC	human autologous tissue for transplantation	July 2012
JACE* Initial Approval	human (autologous) epidermal cell sheet	October 2007
JACE Partial Change Approval	human (autologous) epidermal cell sheet	September 2016
JACE Partial Change Approval	human (autologous) epidermal cell sheet	December 2018
Kymriah	tisagenlecleucel	March 2019
Stemirac	human (autologous) bone marrow-derived mesenchymal stem cells	December 2018
Temcell	human (allogeneic) bone marrow-derived mesenchymal stem cells	September 2015

* This product was approved as a medical device under the previous regulatory framework.

Source: PMDA

LIST OF ATMPS APPROVED BY THE EMA

NAME	DEVELOPER	INDICATION	APPROVAL DATE	STATUS
Dectova	GSK	Influenza	March 2019	Approved
Luxturna	Spark Therapeutics	Retinal dystrophy	September 2018	Approved
Yescarta	Kite Pharma	Blood cancer	August 2018	Approved
Kymriah	Novartis	Blood cancer	August 2018	Approved
Alofisel	TiGenix	Perianal fistulas in Crohn's disease	March 2018	Approved
Spherox	CO.DON	Cartilage defects in the knee	May 2017	Approved
Zalmoxis	MolMed	Stem cell transplantation in high-risk blood cancer	June 2016	Approved
Strimvelis	GSK	ADA-SCID	April 2016	Approved
Imlygic	Amgen	Melanoma	October 2015	Approved
Holoclar	Chiesi	Severe limbal stem cell deficiency in the eyes	March 2015	Approved
Provenge	Dendreon	Metastatics prostate cancer	October 2013	Withdrawn in 2015
MACI	Vericel	Cartilage defects in the knee	July 2013	Withdrawn in 2014
Glybera	uniQure	Lipoprotein lipase deficiency (LPLD)	November 2012	Withdrawn in 2017
Chondrocelect	TiGenix	Cartilage defects	November 2009	Withdrawn in 2016

Source: European Medicines Agency

US FDA: PROVIDING CLARITY

Janet Woodcock
director, Center for Drug Evaluation and Research (CDER), US FDA

"It takes technology time to settle down once it gets into humans – it is not as easy as it seems. There is a lot for companies to do. It is not a slam dunk now.

Previously, when we were all scared about recombinant technology, we had the Recombinant Advisory Committee. However, nowadays, researchers can raise humanized monoclonals in about a week if they have the antigen and can get a whole portfolio, and they know how to expand those clones.

Things have really changed from way back then when it was all laboratory mumbo jumbo and people didn't actually know how to do things reliably.

Gene therapy, regenerative medicine and cell therapy are all still in the phase where they need to work on safety and efficacy, which is very important for us."

Peter Marks
director, Center for Biologics Evaluation and Research (CBER), US FDA

"We have an important role in providing regulatory clarity to innovators. Our job as regulators is to set the bar in accordance with statutory authorities for the degree of uncertainty that we are comfortable accepting for our society in reaching product-approval decisions.

For cell and gene therapies, we have products that utilize a common set of technologies, for example, some of the vectors that I mentioned earlier. So, once we have established precedent and greater postmarket experience with the safety of these products, we may feel more comfortable with additional products that make use of the same underlying technologies. We don't think it is reasonable or that it provides any greater level of risk mitigation to expect innovators to reinvent the wheel with each new product when the underlying technologies are nearly identical.

In some ways, this can be likened to a razor-and-razorblade model. In instances where there is something that we have seen before—the razor—we might have an established set of expectations. We could then focus our attention on the razorblade: the unique and different aspects of a particular product compared to all the others that we have seen."

EUROPE

Maggie De Block

minister of social affairs, public health and asylum & migration, Belgium

"Many innovations reached the market faster than we expected which required an additional investment of approximately EUR 200 million in the medicines budget in 2019, specifically in oncology.

We are confronted with more advanced treatment options with high price tags while our resources are limited. It is a responsibility of all stakeholders to examine how to align innovative medicines with real unmet medical needs of our patients, hence the importance of horizon scanning. Additionally, the National Institute for Health and Disability Insurance (NIHDI) is examining new ways to reimburse expensive innovative treatments."

Catarina Andersson Forsman

director general, Swedish Medical Products Agency (MPA)

"The agency is prepared for this new wave of new treatments and technologies, but the MPA, as well as all other regulators, needs to seek the best tools to address the situation. We must develop a system to work more efficiently with real-world data. I am sure that the regulatory scene will evolve and be able to make correct determinations regarding new therapies. Expertise is another key component, and I see that the agency must continue to add experienced and talented people to the team.

Sweden would certainly like to be at the forefront of the changes, for example, we have discussed cell and gene therapies, but they have not evolved as fast as some of us thought. So, it is a balance between being prepared and having patience."

Niklas Hedberg

chair of the executive board, EUnetHTA, and chief pharmacist, Swedish Dental and Pharmaceutical Benefits Agency (TLV)

"It is a new area; therefore, there is not a wide range of experience to draw from [for HTA bodies]. The new therapies challenge the evidence predicament because we know that we will see several products that are authorized but still lack the traditional evidence that any HTA would like to see.

Regarding gene therapies, for example, companies cannot expect us to pay the whole cost up front with all the uncertainties that we have, given that we have needed to go beyond the traditional evidence predicament. This is due to the way research is being carried out and innovations that are being brought to the market and made available.

If this is something we are likely to see, then how do we handle the uncertainties with regard to the evidence predicament, the payment predicament and the uncertainty predicament? Furthermore, how do we follow up with real-world data? It is going to be interesting and challenging to solve all of these issues with integrity, with GDPR and with financing the registers."

HOW US HEALTHCARE CAN BETTER ACCOMMODATE CELL & GENE THERAPIES

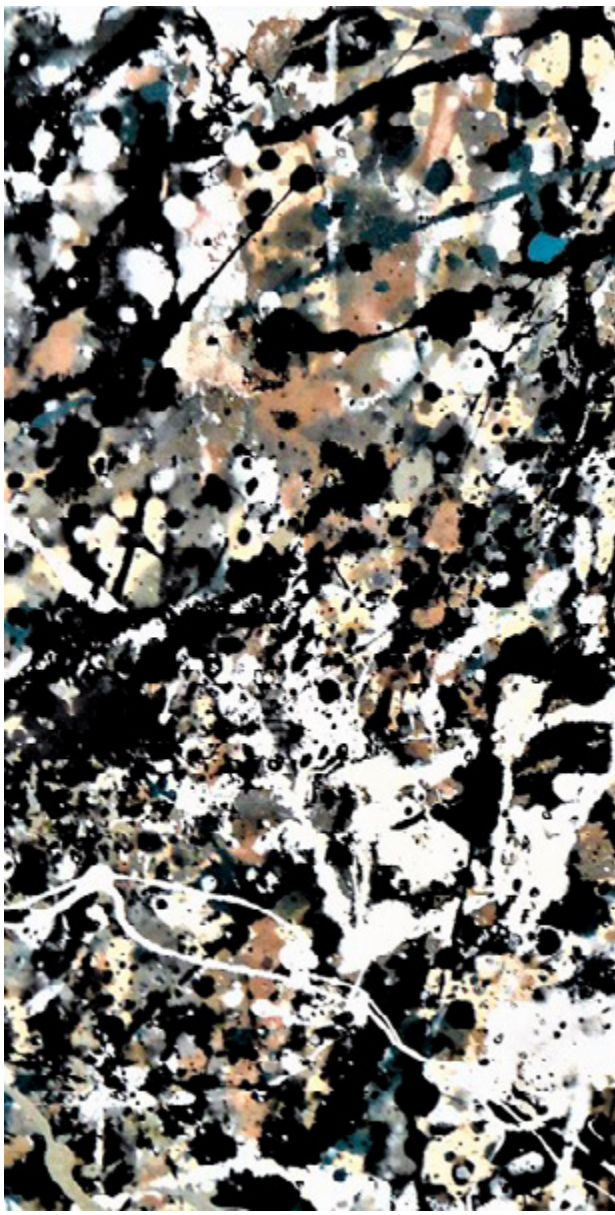
PhRMA's Anne McDonald Pritchett PhD highlights the remarkable development of cell and gene therapies in recent years and the three ways in which the US healthcare system can better accommodate them: creating manufacturing systems that take treatment timelines into account, a health system that values treatments based on patient outcomes, and new approaches to financing.

Anne Pritchett
senior vice president, policy and research, Pharmaceutical Research and Manufacturers of America (PhRMA)

It was only in the 1980s that scientists first began researching the potential of gene therapy to cure genetic disorders. Today, scientists and researchers at America's biopharmaceutical companies are developing nearly 300 cell and gene therapies to treat cancers, neurological diseases and more.

Gene and cell therapies use genes and cells to treat disease. This sounds simple, but the reality could not be more complex from a scientific and clinical standpoint. With gene therapy, the treatment involves making an addition to a gene or altering a gene. With cell therapy, cells are taken either from the patient themselves or a donor and may be genetically altered to treat disease. These treatments are often referred to together because the treatment may involve removing cells from the body, treating them with gene therapy, and then putting them back into the patient.

These new therapies have the potential to cure previously incurable diseases and to fundamentally alter the trajectory of many other life-threatening conditions, including many rare diseases. In fact, more than 70 percent of the gene therapies in development are for rare diseases.



> “THESE NEW THERAPIES HAVE THE POTENTIAL TO CURE PREVIOUSLY INCURABLE DISEASES AND TO FUNDAMENTALLY ALTER THE TRAJECTORY OF MANY OTHER LIFE-THREATENING CONDITIONS, INCLUDING MANY RARE DISEASES. IN FACT, MORE THAN 70 PERCENT OF THE GENE THERAPIES IN DEVELOPMENT ARE FOR RARE DISEASES.

Take sickle-cell disease as just one example which impacts approximately 100,000 Americans. The disease is life-threatening, due to potential complications from blocked blood vessels, which can include stroke, difficulty breathing, pulmonary hypertension and other organ damage. Today, scientists are exploring new ways to use established medicines and cutting-edge technologies such as RNA interference, gene-edited stem cell therapy and gene therapy. One therapy in the development could potentially be a one-time treatment for sickle cell disease – and this is just one of the nearly 20 sickle-cell disease therapies in development or in US Food and Drug Administration (FDA) review.

These therapies are the result of decades of research and are incredibly challenging to research, develop, manufacture and deliver to patients.

While these therapies reflect harnessing of the very latest scientific advances and many are potentially one-time curative treatments, our current healthcare system is not structured to handle potential one-time therapies. Additional challenges for the current healthcare system are that many of these therapies need to be delivered as early as possible to patients to provide maximum clinical benefit, which can be complicated by prior authorization policies for these therapies, and the challenges for insurance plans in estimating how many patients may need these therapies in a given year.

PhRMA and our member companies are focused on identifying ways to further evolve the US healthcare system to ensure continued headroom for these innovative therapies.

First, we need manufacturing systems that take treatment timelines into account. Biopharmaceutical companies are continuing to explore existing and new technologies to more efficiently and cost-effectively develop and manufacture cell and gene therapies, including exploring the feasibility of manufacturing therapies at the point of care.

Second, we need a health system that values treatments based on patient outcomes. Biopharmaceutical companies are increasingly exploring innovative-contracting arrangements in which payment reimbursement for new treatments is tied more closely to patient outcomes—research is showing that these types of contracts can reduce health system and out-of-pocket costs and improve patient access and health outcomes.

Third, we need to continue to explore new approaches to financing these medicines. Just as there won't be one size fits all gene and cell therapies, there is not a one-size-fits-all approach to payment. Biopharmaceutical companies and payers are exploring a range of creative approaches from innovative contracting arrangements that can include value-based arrangements, extended payment plans, and annual subscription plans.

As stated by the FDA, some of these therapies “are almost certainly going to change the contours of medical practice, and the destiny of patients with some debilitating diseases”—it is critical that we work together to develop a coverage and payment system that can ensure timely patient access, manage short-term affordability challenges, and continues to foster the development of these new treatments.

Emanuele Ostuni
head of cell and gene therapy for Europe, Novartis Oncology

IN IT FOR THE LONG RUN

Emanuele Ostuni, Novartis Oncology's head of cell and gene therapy for Europe, gives an overview of the introduction of the company's CAR-T therapy to Europe, the work still to be done to get this product to more patients who need it across the continent.

Novartis' CAR-T product has been on the market for nearly two years now. Can you walk us through the journey it took to get to the first approval from the EMA and uptake by major European 5 markets? What lessons have you been able to draw from this process?

EMANUELE OSTUNI (EO): There are two words that come to mind: collaboration and learning.

We pioneered the therapy and the approval but had to do this by collaborating with many stakeholders. This journey started in 2012 with the University of Pennsylvania where the scientific and medical foundations for Novartis were laid when Emily Whitehead, a 6-year-old child, terminally ill with treatment-resistant leukaemia, was successfully treated with the CD19-CAR-T therapy that later on Novartis licensed in. Today, she is a healthy and happy teenager!

When we started the clinical trial program, we had to collaborate very closely with physicians and patients as well as manufacturing partners. As the therapy became more broadly used were learned together how to treat patients in a real-world setting, sharing information, and updating guidelines.

Throughout the journey we needed to collaborate with manufacturing partners, supply chain partners, patient organisations, regulators, policymakers and payers – jointly we were building an understanding how to manage the complexity of the therapy on the one side and a sustainable access scheme on the other side. As with all pioneering journeys, we have to constantly be alert to learn from our steps and course-correct where necessary.

CAR-T therapies are still very new and to some degree represent uncertainty for physicians and patients, high prices for payers, and safety and efficacy concerns for regulators. How are you attempting to find answers for these issues?

EO: Novartis' CAR-T is a one-time therapy with a multi-year impact. In the beginning, many were not familiar with this new paradigm. We had to innovate collaboratively, learning what was and what was not working from other parties in order to deliver the therapy to patients in dire need of therapeutic options. Transparent collaboration with our partners in a learning mode is key to address these challenging questions without obvious answers.

A part of safety concerns relates to the uniqueness of the therapy. As a patient's own cells are the basis of

the medicine, a so-called "chain of identity" is of paramount relevance. If ever two batches are incidentally interchanged, and patient A would receive patient B's cells, both are likely to die. So even something seemingly simple like the look of a product label becomes a significant question. For traditional therapies, the name of the product would suffice. But for Novartis' CAR-T, a patient's full name and date of birth become part of the batch ID – in Europe, this raised hitherto unknown data privacy challenges which we had to manage collaboratively with regulators.

Not surprisingly, the pricing conversations were complex. While payers consistently recognised the value of the product, they were not used to the concept of a one-time therapy with multi-year effect. Most of today's innovative therapies are for chronic disease management and payers are used to reimbursing over a period of time. Since every healthcare system has its own, unique aspects and we realized that cell and gene therapies are often a magnifying lens to existing problems and that we could not take the same approach in every system. Therefore, we collaborated with each payer to find solutions that matched their needs, as long as they could recognize the value of the therapy.

In addition, there were other new challenges that required that we and the systems adapt to match the situation. For example:

1. Given their complexity, today's commercial CAR-T therapies are only licensed for administration in specialized treatment centres. These hospitals are trained and qualified by Novartis. One of our biggest learnings was that clinics – which are usually clients "only"- become "suppliers" for pharma companies. They collect and provide the cells that are starting material for the final product. This fundamentally new relation requires specific regulations and a new, collaborative mindset.
2. Internally, we had to create new roles to appreciate all these different challenges, for example the experts who train and qualify the treatment centres or those who accompany the product ordering process throughout the whole manufacturing journey. We also had to develop an IT platform that allows physicians to place orders. Over the course of time, we have worked closely with physicians to continuously improve that platform. We are still working on that to make sure it meets our needs.

CAR-T therapies are administered once but give the hope of a long-term cure. Have you yet managed to gather any post-administration data to show whether this promise will hold true?

EO: The word 'cure' has to be used carefully. It is a one-time treatment with multi-year impact and evidence of the sustained efficacy is growing.

Our clinical trials have selected data from up to 24 months and there are now separate studies that go up to 48 months.

Looking at trial results after two years, the product is effective in 40 percent of lymphoma patients and in 66 percent of paediatric patients. Those clinical trial data are now complemented by real-world studies. So far, the curves of the clinical trial data and the curves of the real-world evidence (RWE) seem to match. Also, the medicine's safety profile seems to improve in the real-world setting – probably due to the fact that physicians are learning how to work with this therapy and are more comfortable managing the side-effects.

We also have an obligation to track our CAR-T patients for 15 years after administration. That has started both in the US and Europe where we just announced a collaboration with the EBMT on building a registry and will continue.

What are your priorities in cell and gene oncology for the next two to three years?

EO: There are multiple tumour types that may be treated with cell therapies and CAR-T. We are expanding the number of haematology malignancies that we fight with the existing CAR-T as well as rapidly evolving and innovating the manufacturing platform for our currently approved and other CAR-T products. Novartis has invested a tremendous amount in establishing multiple manufacturing sites all over the world in order to be able to provide the therapy for years to come and for all patients globally. Another priority is innovating the manufacturing process to make it faster and more efficient.

We are in this for the long run. We are looking to reduce side-effects, increase safety and efficacy, and finally expand to solid tumours so that we can provide solutions to more patients.

OUTCOMES-BASED REIMBURSEMENT FOR CAR-T IN THE EU5

In 2018, the European Medicines Agency (EMA) approved the first two chimeric antigen receptor (CAR)-T cell therapies (Kymriah® and Yescarta®) for marketing authorisation for the treatment of certain rare and severe cancers.

2019 was milestone year as Novartis and Gilead managed to obtain reimbursement for these therapies in many key countries. The Health Economics and Market Access team at the Cell and Gene Therapy Catapult provides an overview of the reimbursement and funding schemes used for Kymriah® and Yescarta® in the five major European markets (France, Germany, Italy, Spain and the United Kingdom, i.e. EU5), as per the final quarter of 2019.

Kymriah® and Yescarta® launched with relatively uniform list prices across the EU5 (see table below). The reimbursement schemes used for these therapies appear to show an increased willingness both on the part of manufacturers and European healthcare system decision-makers to move beyond the more traditional reimbursement approaches (e.g. simple discounts) to payments conditional on a treatment's success.

Across the EU5, early engagement with Health Technology Assessment (HTA) bodies and National Health Service (NHS) stakeholders is key, not only for securing reimbursement, but also for preparing the institutional readiness to adopt these therapies. Both Kymriah® and Yescarta® rely on highly complex requirements in terms of the care pathway, clinical infrastructure and skill of the clinical staff in order to be delivered successfully to patients. Meeting these requirements is challenging for hospitals, and manufacturers should work closely with healthcare providers to ensure the appropriate clinical infrastructure and processes are in place in preparation for the successful and timely adoption of complex therapies like CAR-Ts and to ensure the best possible health outcomes for patients treated in the real-world setting.

SUMMARY OVERVIEW OF LIST PRICES, REIMBURSEMENT SCHEMES AND KEY OUTCOMES ASSOCIATED WITH THE REIMBURSEMENT OF CAR-T CELL THERAPIES IN EU5

	FRANCE	GERMANY	ITALY	SPAIN	UK
REIMBURSEMENT SCHEME	Coverage with evidence development	Outcomes-based rebates	Outcomes-based staged payments	Outcomes-based rebates	Coverage with evidence development
DETAIL	Annual HTA reassessments based on longer-term follow-up data from pivotal trials, and post-launch data collection from use in French patients	Rebates linked to individual patient outcomes	Payments in three instalments linked to individual patient outcomes	Payments in three instalments linked to individual patient outcomes	Future price reassessment based on longer-term follow-up data from pivotal trials, and post-launch data from use in UK patients
KEY OUTCOMES CONSIDERED	Several (survival, remission status, disease progression, adverse events)	Survival	Specifics not disclosed	Complete response Survival	Survival Post-treatment requirement for sterm cell transplantation and/or use of immunoglobulins
LIST PRICE	Kymriah: €320,000 Yescarta: €327,000	Kymriah: €320,000 Yescarta: €327,000	Kymriah: €320,000 Yescarta: €327,000	Kymriah: €320,000 Yescarta: €327,000	Kymriah: €320,000 Yescarta: €327,000

This is an abbreviated version of an open-access article originally published by the Cell & Gene Therapy Catapult here https://ct.catapult.org.uk/case-study/car-t-cell-therapies-and-use-outcomes-based-reimbursement-five-major-european-countries

*Using average annual exchange rate for 2018: £1 = €1.1305

CRITICAL CHALLENGES & INNOVATIVE RESPONSES IN MANUFACTURING

Deloitte's Omkar Kawalekar, Hussain Mooraj, and Amit Agarwal examine the evolution and future of cell and gene therapy manufacturing and the areas in which biopharma firms need to invest in order to succeed in this emergent field.

Cell and gene therapies (CGT) are the next evolution of personalized health care. These products are potentially curative in nature, highly tailored for specific disease indications/individual patients, and have shown promising efficacy in disrupting existing therapy paradigms.

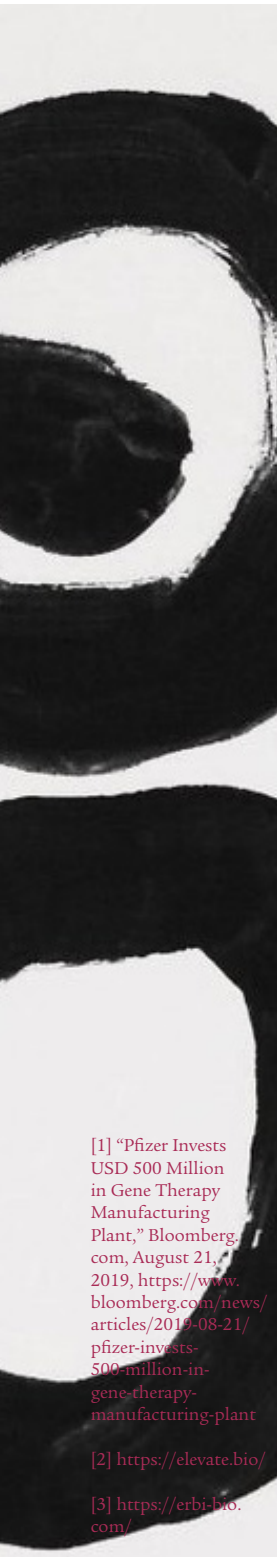
Working closely with CGT companies over many years, we have learned that a crucial component of CGT's success is reliable, consistent, and scalable manufacturing—something that continues to be complex and challenging. Our clients have discussed challenges such as reliable raw materials supply, end product yield, consistent quality, scalable manufacturing, and value chain complexity. While the problems are well-understood by market players the solutions have been harder to come by. Here, we shed light on a few concepts that can help redefine how we should think about CGT manufacturing.

CAPACITY IS KING

Investing in sufficient and reliable manufacturing capabilities is vital to successful CGT production and launch. We have seen companies making large capital investments—sometimes up to USD 500 million[1]—to build their own manufacturing facilities. We also have seen companies at the opposite end of the spectrum. Some organizations continue to invest in partnerships with external contract manufacturing organizations (CMOs) and spending almost as much in leasing suites for long-term capacity, even if they are not being used. This has placed a massive capacity constraint on the supply of GMP-grade materials (sometimes leading to a 12-15-month wait time for the supply of critical CGT materials, such as viral vectors). In our conversations with several CGT company senior executives, they expressed regret for not investing in sufficient manufacturing capacity years ago. Having control of your own CGT manufacturing capacity has become one of the biggest rate-limiting steps in being able to launch and grow revenues. Therefore, CGT companies small and large should re-evaluate their manufacturing strategies and plan future investments accordingly.

RETHINK YOUR PARTNERSHIPS

CGT organizations are exploring new ways to build and control manufacturing network capacity at more affordable costs. We have observed the emergence of risk- and space-sharing models to spearhead innovation from modestly funded start-ups by increasing capital investment efficiency, lowering risks, and shortening time to market. One such example is ElevateBio,[2] which has built a centralized facility and supporting capabilities including highly skilled talent, manufacturing



infrastructure, and processes to provide CGT companies a commercialization launchpad. Such models are financially attractive to companies that do not have the capital to build their own manufacturing facilities. An alternative approach is to decide which part of the value chain companies should build versus buy. Several CGT clients have decided to outsource/partner for the final drug product manufacturing while investing in manufacturing capacity for the critical raw materials (e.g., viral vectors). This type of configuration allows the company to lessen the risk of single product failures in the clinic because the raw materials can be used in multiple portfolio products.

> “THE AIM IS TO CREATE A HIGHLY MATRIXED ORGANIZATION THAT IS SUPPORTED BY A FLEXIBLE, INTEGRATED TECHNOLOGY INFRASTRUCTURE THAT CAN HELP STANDARDIZE PROCESSES FOR CERTAIN CAPABILITIES AND BUILD PRODUCT-SPECIFIC PROCESSES FOR OTHERS.

ONE FOOT IN TODAY, ONE FOOT IN TOMORROW

Many big pharma companies struggle to position new CGT offerings within traditional monolithic operational models, which favour supply chains built around products, are push-based, and are heavily reliant on inventory. CGT manufacturing—especially individualized therapies—requires a clinically connected value chain that is built around patients, highly agile, and usually pull-based. We see multiple models emerging, including establishing standalone business units, absorbing CGT in therapeutic franchises, or a blend of the two. Leading organizations in this space have assembled cross-functional teams to design operating models centred around patient and clinical staff pain points. The aim is to create a highly matrixed organization that is supported by a flexible, integrated technology infrastructure that can help standardize processes for certain capabilities and build product-specific processes for others. Companies cannot ignore the necessities of today; however, they should consider developing bi-modal operating models to accommodate the CGT value chains of tomorrow.

POINTS TO PONDER

Invest early in your manufacturing strategy. Take into consideration the level of upfront investments you want to make versus your risk appetite for capacity constraints. If cash-strapped, consider the option of building your own pilot manufacturing facilities to support early-phase clinical investigation for multiple CGT assets and perfect your processes. Identify leading candidates early and then negotiate with manufacturing partners for successful advancement.

Design your value chain to win. There is no one-size-fits-all CGT operating model. Design your value chain from an outside-in, patient-oriented perspective. The enabling digital core and its components (systems, databases, and tools) should provide end-to-end value chain visibility and an opportunity for broad interconnectivity.

Embrace risks and push the envelope. Even in today’s uncertain times, human nature drives us to find opportunities in crisis. Embrace risks and invest in future-focused technology, such as fully automated/robotic manufacturing modules, to prepare for continued unpredictability, spur innovation, and deploy CGT to patients in need. Erbi Biosystems,[3] Invetech,[4] and MultiplyLabs,[5] for example, are developing cutting-edge robotic systems for industrial-scale manufacturing.

[1] “Pfizer Invests USD 500 Million in Gene Therapy Manufacturing Plant,” Bloomberg.com, August 21, 2019, https://www.bloomberg.com/news/articles/2019-08-21/pfizer-invests-500-million-in-gene-therapy-manufacturing-plant

[2] https://elevate.bio/

[3] https://erbi-bio.com/

[4] https://www.invetechgroup.co

[5] https://multiplylabs.com/techn

TAKING CAR-T TO THE MAINSTREAM

André Choulika, chairman and CEO of Cellectis, discusses how UCART will revolutionize cell therapy as a universal gene-edited solution as opposed to the current therapies on the market which uses a patient's own re-engineered T-cells.

What are the points of differentiation between TALEN® engineered UCART and existing therapies already on the market and what will ultimately make your technology more competitive?

ANDRÉ CHOULIKA (AC): CAR-T has been a paradigm shift in oncology treatment, transforming the way patients face the disease. However, we see the difficulties today of trying to bring these products to market. Even on the patient end, some individuals cannot be treated with CAR-T therapy because they do not have the raw materials in their body – the T-cells. In addition, the pricing of these therapies is also a barrier. Nevertheless, I believe CAR-T is a transformative innovation that will revolutionize oncology in the future to come.

Our goal is to shift the CAR-T therapies available today on the market into real frozen pharmaceutical products by harvesting T-cells from healthy donors, which can be gathered from the leftovers of blood donation and engineering them into cancer-fighting cells. Cellectis is working to develop this concept of off-the-shelf, gene edited UCART cells – universal CAR-T. These cells could become a standardized treatment for all patients in the same way that a traditional pharmaceutical drug is used.

Marketed CAR-T therapies have come at a staggering price. We understand as an "off-the-shelf" product, UCART could be more affordable – is this the case?

AC: UCART will absolutely be a more affordable option compared to the treatments that are currently on the market today. This is not a personalized therapy, so we are able to produce hundreds of dosages at a time to treat a wide patient base. Furthermore, Cellectis is providing a high quality, GMP-compliant product which is not the case of today's CAR-T therapies. Today's manufacturers have to deal with the resources they have and create treatments on individual bases – this costs hundreds of thousands and they can only market for half the price. Of course, we cannot offer a generic price, but we expect to be able to deliver a price point that is in line with the standard of other oncology treatments.

What reimbursement structure do you ultimately have in mind for the products you are developing?

AC: Gene therapy treatments today are essentially autologous and classified as personalized medicine. On the other hand, UCART is a gene therapy for all patients that hospitals all over the world can keep in their inventories and utilize like a normal pharmaceutical. Yes, the therapy will be more expensive than some other drug options, but it will fit into the traditional reimbursement scheme. Due to its universal benefits and cost savings, I believe UCART can still be affordable to healthcare systems despite being priced slightly higher than current solutions on the market. For example, if the death toll in the US can be reduced by one percent, the savings potential for the entire healthcare system would be close to USD 350 billion.

André Choulika
chairman & CEO, Cellectis

> "IF THE DEATH TOLL IN THE US CAN BE REDUCED BY ONE PERCENT, THE SAVINGS POTENTIAL FOR THE ENTIRE HEALTHCARE SYSTEM WOULD BE CLOSE TO USD 350 BILLION."

CAR-T'S PAIN POINTS

William Wei Cao, chairman and CEO of Chinese CAR-T firm Gracell shares what he sees as the four big challenges facing the global CAR-T industry.

William (Wei) Cao
founder, chairman & CEO, Gracell

Today, we see that there are four core problems – pain points – for the CAR-T industry globally. If we can resolve even just one of them, then Gracell would have achieved something incredibly meaningful.

The first obstacle is the significant cost of CAR-T therapies. In the US, we are looking at a price tag of USD 400,000 – 475,000 just for the CAR-T drug itself and adding the associated medical services can take the whole cost up to USD one million. This is exorbitant, even for US patients. In the biotech industry, sometimes there is a gap between scientific breakthroughs and real market needs.

In the US, the healthcare system is bloated at 25 percent of GDP. In China, the national GDP is already half of the US, and healthcare spending is only six percent. The public healthcare system simply cannot afford to fund therapies costing USD 1 million per patient! Not even CNY one million (USD 150,000) is feasible in developing markets like China. We have done some market research in a number of first- and second-tier cities and we estimate that the maximum price for patients to bear out-of-pocket is CNY 400,000 (USD 60,000). Therefore, we think cost is the first pain point of the industry.

> "IN THE US, WE ARE LOOKING AT A PRICE TAG OF USD 400,000 – 475,000 JUST FOR THE CAR-T DRUG ITSELF"

The second obstacle is the length of the process. For instance, the 'vein to vein' time (time from when cells are extracted to when they are infused back into the patient) for CAR-T products approved in USA is around 30 to 50 days. Considering how fast a disease like acute B-cell lymphoblastic leukaemia (B-ALL) progresses, that is a very long time for patients to wait. Then you have to factor in potential failures with the manufacturing processes.

The third obstacle is patient relapse. So far, figures suggest that after six to 12 months, up to 50 percent of patients, including those in complete remission, will relapse.

The last obstacle is that thus far, CAR-T's efficacy in solid tumours has been pretty low. This is a huge area of unmet need; the market size of solid tumours is ten times that of blood cancers.

Therefore, Gracell's focus now is to work on four platforms to resolve these four core problems – the cost, the manufacturing process, the relapse rate, and the efficacy in solid tumours – in the global CAR-T industry.

THE CELL & GENE THERAPY MARKET: COMING INTO ITS OWN

David H. Crean, managing director for Objective Capital Partners, highlights the latest trends in the cell and gene therapy market for investments and deal activities.*

Taking into account the global picture of gene and cell therapy R&D, the United States is a strong leader, generating overwhelmingly more journal articles and patents than any other country. Other significant contributors include China, Japan, Germany, South Korea and the United Kingdom.

Three sectors have been identified as areas of significant future promise: stem cell therapies, chimeric antigen receptor (CAR) T-cell therapies and gene editing technologies.

DEAL MAKING AND INVESTMENT ACTIVITIES

Top mergers and acquisitions (M&A) deals, Venture Capital (VC) investments and partnerships point to a growing number of cell & gene therapy deals. Big pharmaceutical companies and other large companies are paying significant sums not only for therapeutics but also for manufacturing capabilities. The top market players are actively investing in research for developing cell and gene therapy. Moreover, key players operating in the market are focused on adopting strategies such as M&A, in order to gain access to innovative products and expand their product offerings in the potential markets (e.g., planned acquisition of Celgene Corporation by Bristol-Myers Squibb Company). The players are offering new and improved products, in order to address the critical unmet needs of patients. It is no surprise then that the investment outlook in cell and gene therapies for the near term is positive.

KEYS TO SUCCESSFUL INVESTMENTS IN CELL & GENE THERAPY

Three primary qualities that investors and partners are seeking in their cell and gene therapy portfolios include: strong management team, solid and differentiated technology, and existing financing to advance the company. Management teams that know how to pivot, or adopt an agile mindset as the business evolves, are extremely attractive to investors. The underlying technology has to be a game changer. A platform that can create repeatable quality assets is critical because it provides more breadth and depth to the investment.

Investments in the area, however, are not without their challenges. Manufacturing is the most important barrier in cell and gene therapy right now. Manufacturing becomes question numbers one, two, and three when you are beginning to know a cell and gene therapy company. Not surprisingly, industry has taken note, with several cell and gene therapy players building out their own manufacturing and/or booking manufacturing slots with certain contract development and manufacturing organizations (CDMOs) and contract manufacturing organizations (CMOs). Since the start of 2019, there have been at least three major acquisitions of contract manufacturers: Hitachi Chemical's purchase of apceth, Danaher's USD 21.4 billion takeover of GE Healthcare's biopharma business, and Thermo-Fisher's USD 1.7 billion

acquisition of Brammer Bio. It is important for potential investors and companies to understand the manufacturing setup, how scalable the processes are, and what is being done in process development. As I was once told "the product is the process and the process is the product".

CDMOS INVESTING MORE IN CELL AND GENE THERAPY CAPABILITIES

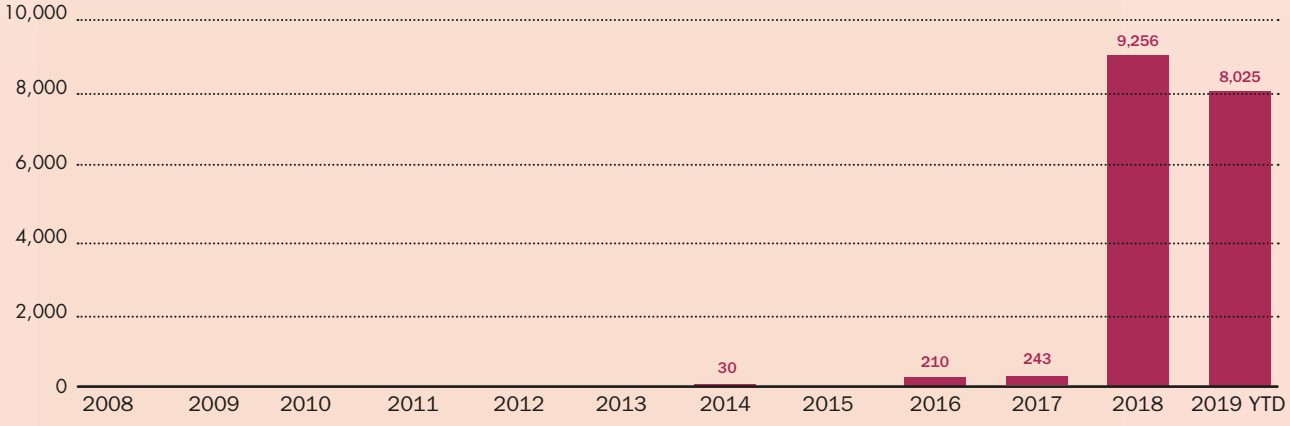
This year has also seen two major deals among CDMOs for cell and gene-therapy manufacturing. In April 2019, Catalent agreed to acquire Paragon Bioservices, a Baltimore, Maryland-based contract provider of viral vector development and manufacturing services for gene therapies, for USD 1.2 billion. Paragon has specialized expertise in adeno-associated virus (AAV) vectors, the most commonly used delivery system for gene therapy as well as capabilities in GMP plasmids and lentivirus vectors. The company provides GMP development and manufacturing services for recombinant viral vectors, vaccines, hard-to-express recombinant proteins, and oncolytic viruses from research and process development to GMP manufacturing for clinical trials and commercial launch.

In March 2019, as mentioned previously, Thermo-Fisher Scientific agreed to acquire Brammer Bio, a CDMO of viral vector manufacturing for gene and cell therapies. Brammer Bio is on track to deliver USD 250 million of revenue in 2019 and expects to continue to exceed the projected market growth rate of 25 percent over the mid-term. Upon completion of the deal, Brammer Bio will become part of Thermo Fisher's pharma services business within its Laboratory Products and Services Segment.

TRANSACTIONS

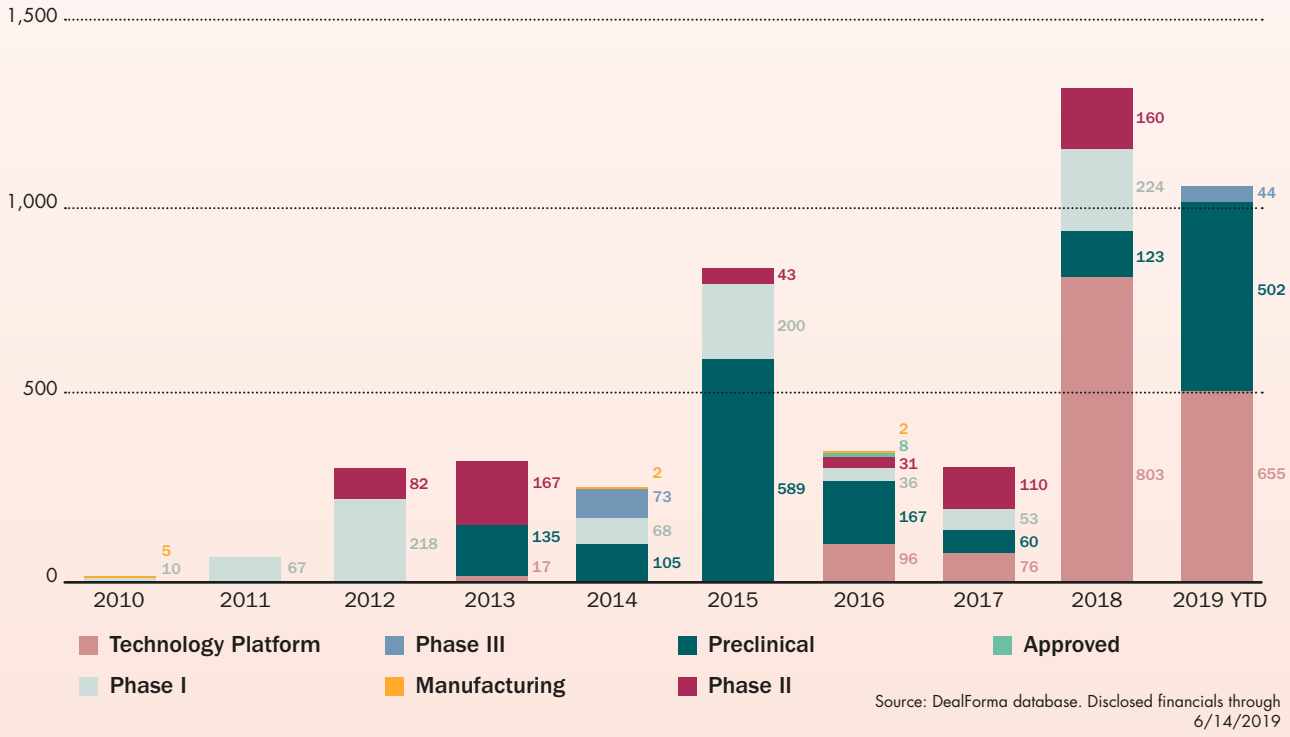
DealForma provided data over the past 10 years, as the number of deals, R&D partnerships and M&A buyouts steadily have gained steam, spiking in 2018 and potentially on track to maintain the surge in 2019. The upfronts and totals for the dollars on deals so far in 2019 is already close to the 2018 mark, underscoring a new phase of negotiations as the major players step up to gain a piece of the late-stage and commercial action. Deals over the span of the last decade have been structured with payouts on the back end. Corporate deals accounted for 114 of the 256 deals done since 2008. But when it comes to M&A, the money arrives up front: 27 acquisitions provided USD 18 billion up front with a total deal value of USD 20 billion.

TOTAL DISCLOSED UPFRONT CASH & EQUITY IN CELL & GENE M&A (USD M)



Source: DealForma database. Disclosed financials through 6/14/2019

VENTURE TOTALS BY STAGE OF COMPANY AT TIME OF FUNDING - GENE TX AND VECTOR TECH (USD M)



Source: DealForma database. Disclosed financials through 6/14/2019

Since 2010, DealForma has also tracked 120 venture seed and venture rounds in gene therapy, with USD 5 billion raised. Half of that has arrived in the last 18 months. And over USD 3 billion went to companies with only a platform technology or preclinical work – with nothing in the clinic.

FINAL THOUGHTS

Since 2010, DealForma has also tracked 120 venture seed and venture rounds in gene therapy, with USD 5 billion raised. Half of that has arrived in the last 18 months. And over USD 3 billion went to companies with only a platform technology or preclinical work – with nothing in the clinic.

Unlike conventional biologics which have been commercialized for nearly three decades, the first approvals for cell and gene therapies in the United States came only recently in 2017. As such, the market for these next-generation therapies are still emerging, and this developing and evolving industry is currently a hot area for companies looking to grow and investors.

Although it is viewed as an active investment area, it is a sector that needs appropriate diligence before investing due to the need for maturing and scale in infrastructure, people with experience and expertise in this area, raw material availability and manufacturing and analytical technologies. There is a growing robust clinical pipeline, with several products expected to come to market in the short term and many in late-stage clinical development.

As such there is strong investor interest expected this year and next. Overall, positive regulatory environments across the globe are fuelling interest in working with sector stakeholders to promote patient access to safe and effective therapies.

* This article was originally published on PharmaBoardroom.com in June 2019

PROPELLING STEM CELL RESEARCH FORWARD IN APAC

Rita Huang introduces the TMU Research Center for Cell Therapy and Regeneration Medicine's innovative research projects within the emerging space of stem cell treatments, how the Center is collaborating with the biopharmaceutical industry, and why Taiwan can cultivate a leading regional role in this field.

What are some of the key research projects that the TMU Center for Cell Therapy and Regeneration Medicine is undertaking?

RITA HUANG (RH): We are focused on developing the systemic safe use of stem cell products. Some of the key projects we are working on include diabetes, diabetes foot ulcers, severe burns, stroke, multiple sclerosis, and acute lung injuries.

Speaking about tumour risks, there is one possibility that the stem cells will initiate a tumour themselves or the stem cells will promote tumour growth. Currently, how to identify the specific cell products that will promote or suppress the tumour is still not well analszed. TMU is now working to perform gene profiling and preclinical studies to determine the tumour promotion ability of different MSCs in various cancer types. We also study the underlying mechanisms to determine how diabetes and ulcers can be treated.

Additionally, we have another project studying the effect of system stem cell therapies on radiation. When exposed to radiation, it kills the bone marrow in the body. However, in our research, we have seen that system stem cell therapy can raise the survival rate to up to 60 percent. The Research Center for Cell Therapy and Regeneration Medicine is also collaborating with TMU's dental school on a study that uses small blood stem cells in dental implants which is very promising for Taiwan's ageing population.

In what ways does TMU collaborate with the industry to develop the center's research and bring it to the clinical trial and translation phase?

RH: In TMU we also have a business department that will help the researchers have their IP rights and build connections with the translational industry. We encourage our professors to have their own spin-off companies. In TMU we already have spin-offs for a small molecule drug and medical devices, and we soon plan on having our own cell therapy company. Not only will we collaborate with the industry here in Taiwan, but also internationally.

The Research Center for Cell Therapy and Regeneration Medicine already collaborates with several companies from China, Japan, and the US in the areas of immunotherapies and degenerative diseases.

Internationally, we cooperate with five US universities and one US company, four Taiwanese companies, a Korean university and hospital, two top Japanese universities, and both Hong Kong University and the Duke University-National University of Singapore Medical School.

Yen-Hua (Rita) Huang
dean, Office of Research and Development; director, TMU Research Center for Cell Therapy and Regeneration Medicine, Taiwan

The Taiwanese government has placed a high focus on biomedicine and innovation as drivers in transforming the country's economy and scientific positioning. Do you believe that cell therapy and regenerative medicine is an area where Taiwan can be a regional or even global leader?

RH: Although Taiwan is very small, we highly emphasize the rights of our patients. In Taiwan, transparency is very important and all institutions working with stem cells must report all outcomes. Taiwan's role in the region will be to establish a highly regulated, safe usage of stem cell therapies which will make us the leader in this area.

FRESH APPROACHES: ONCOLYTIC VIRUS

GeneMedicine's Chae-Ok Yun, with over 20 years of experience developing oncolytic virus (OV) technology, introduces her firm's approach to gene therapy, the benefits and opportunities it brings, and its complementarity to other technologies such as CAR-T.

Yun introduces the approach thusly: "Recent breakthroughs in targeted cancer therapeutics and cancer immunotherapy have become a promising treatment strategy for cancer patients who respond poorly to conventional cancer therapies. Despite their relative success, tumour recurrence and metastasis are eventually observed even in patients who initially responded well to targeted therapeutics. The major limitation of currently commercialized cancer immunotherapeutics is that only a small subset of patients show a good response toward immunotherapy. These apparent limitations in advanced cancer therapeutics necessitate the development of novel therapeutics that can address these unmet needs of cancer patients."

She continues, "To this end, the OV, which replicates and selectively destroys cancer cells, can be a promising alternative. Importantly, oncolytic virus-mediated destruction of cancer cells induces a systemic antitumor immune response which is capable of destroying metastasized cancer cells at distal sites, making

> “ONCOLYTIC VIRUS IS NOT NECESSARILY A COMPETITOR OF STANDARD THERAPIES THAT ARE ALREADY PRESENT IN THE MARKET SUCH AS CAR-T OR CHECKPOINT INHIBITORS”

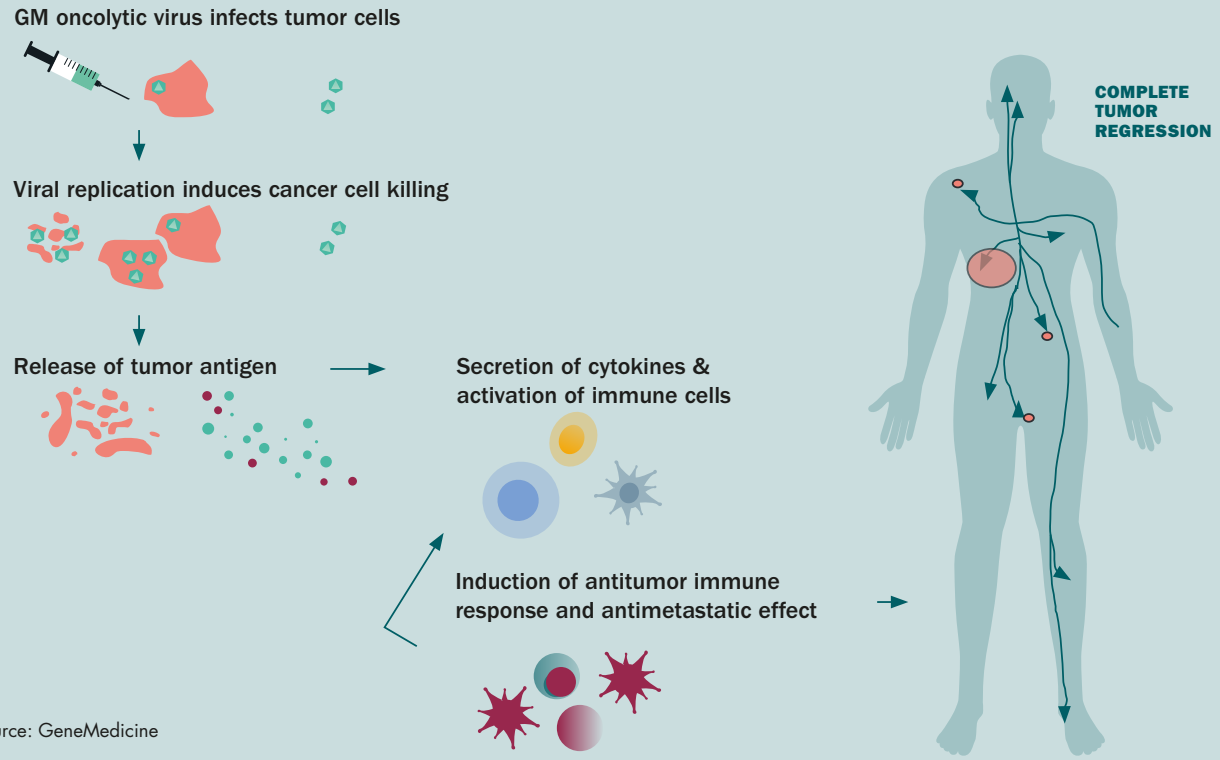
oncolytic viruses promising next-generation cancer therapeutics. Additionally, OVs in combination with conventional cancer therapeutics (chemo- or radiotherapy) as well as cancer immunotherapeutics can elicit a synergistic antitumor effect.”

Yun is keen to point out that OV is complementary to other cell and gene therapy approaches. “OV is not necessarily a competitor of standard therapies that are already present in the market such as CAR-T or checkpoint inhibitors,” she asserts. “OV works synergistically with those technologies and, if used together, can significantly enhance therapeutic efficacy. We have a lot of proprietary data, as well as data from other companies, demonstrating that potential.”

“Companies that have developed checkpoint inhibitors have already conducted Phase II clinical trials in combination with the oncolytic herpes virus launched on the market. They have already finished Phase II clinical trials and have reported that when they combine checkpoint inhibitors with the virus, the efficacy is significantly enhanced.”

Chae-Ok Yun
founder, CEO & CTO, GeneMedicine

ONCOLYTIC VIRUS TECHNOLOGY



Source: GeneMedicine

CAR-T: A POTENTIAL TREATMENT SOLUTION FOR HIV?

Professor Stéphane De Wit, head of the Department of Infectious Diseases at St Pierre University Hospital in Belgium outlines the potential of innovative new treatment nodes such as CAR-T in HIV treatment.

Stéphane De Wit
head, Department of Infectious Diseases, St Pierre University Hospital

You have talked about CAR-T, a technology mainly associated with oncology, as one of the avenues to fight HIV. How realistic is this considering not only the cost but also the implementation difficulties associated with this technology?

STÉPHANE DE WIT (SDW): Let me first clarify, that I am absolutely not a specialist in the CAR-T area and that I have no experience in this technology. That being said, CAR-T is really one of the new fields that has opened in the last two to three years with regards to HIV.

There are trials on the way, and we will probably be cooperating on some of them in the near future. The goal here is to find a cure. But it is only one of the avenues, one of the strategies that we need to explore. I am a firm believer that the solution will come from a global approach and through a combination of different solutions.

If CAR-T was the absolute and ultimate solution it would probably already have been shown. I do believe CAR-T will be part of the solution within a multistep process, with different points of action and very precise sequences of intervention. Maybe the first could be the kick and kill strategy [where the "reservoir" of dormant HIV cells that can survive for years without replicating but have a very strong memory are targeted]. This strategy "activates" – kicks - those sleeping cells by removing the locks that keep them dormant and killing them once they are activated. The process is then replicated until the reservoir is emptied – Ed.] and then you could use different approaches such as CAR-T.

> "I AM A FIRM BELIEVER THAT THE SOLUTION WILL COME FROM A GLOBAL APPROACH AND THROUGH A COMBINATION OF DIFFERENT SOLUTIONS."

However, this is a very complex technology that you cannot obtain simply as a medication. This does raise serious questions of feasibility, accessibility and cost. At this stage, we don't know what the frame will be. We are at the very beginning of the process. Despite all these questions it remains one of the new approaches with extremely promising perspectives in HIV, for the simple reason that when talking about HIV, we are talking about T-Cells. Since the disease is directly present in T Cells, CAR-T seems very promising.

GLOBAL APPROVALS OF REGENERATIVE MEDICINE PRODUCTS

CELL-BASED IMMUNOTHERAPY PRODUCTS


USA

ALLOCORD (HPC, CORD BLOOD)
SSM Cardinal Glennon Children's Medical Center


INDIA

APCEDEN
APAC BIOTECH
APCeden is an autologous monocyte-derived mature dendritic cell vaccine. It was approved in India in 2017 for the treatment of prostate cancer, ovarian cancer, colorectal cancer, and Non-Small Cell Lung carcinoma.


USA

PROVENGE
DENDREON
Autologous Cellular Immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. BLA approved by the US FDA in 2010.


SOUTH KOREA

IMMUNCELL-LC
GC PHARMA
A medicine for anticancer cell immunotherapy, made with T-lymphocyte incubated and activated after extraction from the blood of a patient. Conditionally approved in South Korea in June 2007.


SOUTH KOREA

CREAVAX RCC
JW CREAGENE
A dendritic cell based vaccine intended to treat metastatic renal cell carcinoma for which nephrectomy can be performed. Approved in South Korea in 2007.


USA, EU, CANADA

YESCARTA
KITE PHARMA/GILEAD
Yescarta is a CAR T-cell therapy product indicated for the treatment of B cell malignancies such as non-Hodgkin lymphoma, acute lymphoblastic leukemia, mantle cell lymphoma, chronic lymphoid leukemia and diffuse large B-Cell lymphoma. Approved by US FDA in October 2017. Approved by the EC in August 2018. Approved by Health Canada in February 2019.


USA, EU, CANADA, JAPAN

KYMRIAH
NOVARTIS
Kymriah is a CAR T-cell therapy product indicated for the treatment of acute lymphoblastic leukemia, chronic lymphoid leukemia and diffuse large B-cell lymphoma in patients up to 25 years of age, as approved by US FDA in August 2017, and the treatment of adult patients with relapse/refractory (r/r) large B-cell lymphoma, as approved by US FDA in May 2018. It was also approved for these indications by the EC in August 2018, and by Health Canada in September 2018. It was approved in Japan for the treatment of ALL in February 2019.

GENE THERAPY PRODUCTS


USA, EU, AUSTRALIA

IMLYGIC
AMGEN
IMLYGIC is a weakened form of Herpes Simplex Virus Type 1, which is commonly called the cold sore virus, indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. Approved by EMA in December 2015, US FDA in October 2015, Australian TGA in June 2016.


JAPAN

COLLATEGENE
ANGES
A gene therapy consisting of an intramuscular injection of plasmid (DNA) coding for Hepatocyte Growth Factor (HGF), intended to grow blood vessels, for the treatment of critical limb ischemia.
Approved in Japan in February 2019.


USA

ZOLGENSMA
AVEXIS, A NOVARTIS COMPANY
Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy. Zolgensma was approved by the US FDA for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA), including those who are pre-symptomatic at diagnosis, in May 2019.


EU

ZYNTEGLO
BLUEBIRD BIO
Zynteglo is an ex-vivo lentiviral based gene therapy used to provide a functional copy of the the **β**-globin gene into a patient's hematopoietic (blood) stem cells. Approved by the EMA in May 2019.


EU

STRIMVELIS
GSK
Strimvelis is an ex-vivo stem cell gene therapy which uses retroviral vector encoding adenosine deaminase gene transfer into hematopoietic stem/progenitor cells. Strimvelis is indicated for the treatment of adenosine deaminase severe combined immune deficiency. Approved by the EMA in May 2016.

CHINA

GENDICINE
SHENZHEN SIBIONO GENETECH
A recombinant adenovirus engineered to express wildtype-p53 (rAd-p53), designed to treat patients with tumors which have mutated p53 genes. Gendicine is the first gene therapy product approved for clinical use in humans, approved in China in 2003.

USA, EU

LUXTURNA
SPARK THERAPEUTICS
LUXTURNA is an adeno-associated viral vector gene therapy indicated for the treatment of RPE65-mediated inherited retinal dystrophies. Approved by US FDA in December 2017; approved by the EMA in November 2018.

CELL THERAPY PRODUCTS

SOUTH KOREA

QUEENCELL
ANTEROGEN
An autologous mesenchymal stem cell for the treatment of connective tissue disorders. Approved in South Korea in 2010.

SOUTH KOREA

CUPISTEM
ANTEROGEN
An autologous adipose derived mesenchymal stem cell treatment
to reduce inflammation and regenerate damage joint tissues, indicated for the treatment of Crohn's fistula. Approved for marketing by South Korea's Food and Drug Administration in July 2012.

SOUTH KOREA

KERAHEAL
BIOSOLUTIONS
An autologous keratinocyte based cell therapy for the treatment of 2nd degree burns. Approved in South Korea in 2006.

SOUTH KOREA

KERAHEAL-ALLO
BIOSOLUTIONS
A hydrogel-type allogeneic keratinocyte therapy product for the treatment of second-degree burns. Approved in South Korea in 2015.

USA

HPC CORD BLOOD
BLOODWORKS
Approved by the US FDA in January 2016 for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

EU

HOLOCLAR
CHIESI FARMACEUTICI
Holoclar is a cell therapy based on autologous cultures of limbal stem cells. It regenerates a functional corneal epithelium allowing recovery of visual acuity. Holoclar is indicated for the treatment of moderate to severe limbal stem cell deficiency due to ocular burns. Granted conditional marketing authorization by the European Commission in February 2015.

USA

CLEVECORD/HPC CORD BLOOD
CLEVELAND CORD BLOOD CENTER
Approved by the US FDA in 2016 for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

SOUTH KOREA

NEURONATA-R
CORESTEM
An autologous bone marrow mesenchymal stem cell therapy approved in South Korea in 2014 for the treatment of ALS.

SOUTH KOREA

CELLGRAM-AMI
FCB PHARMICELL
An autologous intracoronary bone marrow-derived mesenchymal stem cell injection for the treatment acute myocardial infarction. Approved for marketing by South Korea's Food and Drug Administration in July 2011.

USA

LAVIV (AZFICEL-T)
FIBROCELL TECHNOLOGIES
LaViv is an autologous fibroblast-based cell therapy. Approved by the US FDA in January 2011 for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.

JAPAN, CANADA, NEW ZEALAND

TEMCELL
JCR PHARMACEUTICALS CO LTD, LICENSEE OF MESOBLAST LTD
TEMCELL is an allogeneic mesenchymal stem cell product indicated for the treatment of acute radiation injury, chronic obstructive pulmonary disease, Crohn's disease, graft-versus-host disease, Type I diabetes and myocardial infarction. Fully approved by the Japanese Ministry of Health, Labour and Welfare in October 2015 and conditionally approved in Canada & New Zealand (also known as Prochymal).

USA

HPC, CORD BLOOD
MD ANDERSON CORD BLOOD BANK
Approved by the US FDA in June 2018 for use in unrelated donor hematopoietic progenitor cell transplantation procedures.

SOUTH KOREA

CARTISTEM
MEDIPOST
A cellular therapeutic agent containing allogeneic human umbilical cord blood-derived mesenchymal stem cells, indicated for the treatment of knee cartilage defects such as traumatic articular cartilage, degenerative arthritis and rheumatoid arthritis. Approved for marketing by South Korea's Ministry of Food and Drug Safety in January 2012.

JAPAN

STEMIRAC
NIPRO CORP
A mesenchymal stem cell therapy approved in Japan in December 2018 for the treatment of spinal cord injury.

SOUTH KOREA

CURESKIN
S. BIOMEDICS
An autologous dermal fibroblast cell-based therapy approved in South Korea in 2010 for the treatment of depressed acne scars.

USA

HEMACORD / ALLOCORD / HPC CORD BLOOD
SSM CARDINAL GLENNON CHILDREN'S MEDICAL CENTER
The US FDA's only approved stem cell product to-date, a cord blood-derived product used for specified indications in patients with disorders affecting the body's blood-forming system. For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment. Approved in 2011, name change to HPC Cord Blood in 2013.

INDIA

STEMPEUCEL
STEMPEUTICS RESEARCH PVT
An ex-vivo cultured adult allogeneic mesenchymal stromal cell therapy for the treatment of Critical Limb Ischemia. Conditionally approved in India in 2017.

SOUTH KOREA

KALODERM
TEGO SCIENCES
An allogeneic cell therapy for deep second degree burns and diabetic foot ulcers. Approved in South Korea for burns in 2005 and diabetic foot ulcers in 2010.

SOUTH KOREA

ROSMIR
TEGO SCIENCE
Autologous cell therapy approved in South Korea in 2018 for the treatment of under eye wrinkles.

EU

ALOFISEL
TIGENIX
An allogeneic stem cell therapy to treat complex perianal fistulas in patients with Crohn's disease. Received EU marketing authorisation in March 2018.

TISSUE-ENGINEERED PRODUCTS

USA

EPICEL
VERICEL
A permanent skin replacement product grown from a patient's own skin cells. The autologous keratinocytes are co-cultured with irradiated murine cells to form cultured epidermal autografts (CEA). Epicel is indicated for treatment of deep dermal or full thickness burns. Epicel has been used in the U.S. and other countries since 1988; approved in the United States in 2007 as a Humanitarian Use Device (HUD) under a Humanitarian Device Exemption (HDE).

SOUTH KOREA, INDIA

OSSRON
RMS
An autologous bone cell implantation for the treatment of bone defects in patients caused by degeneration, drugs, intense physical stress, diet, genetics, obesity, smoking, alcohol or disease. Approved in South Korea in 2009, approved in India in 2017.

USA

MACI
AUTOLOGOUS CULTURED CHONDROCYTES ON A PORCINE COLLAGEN MEMBRANE / VERICEL
An autologous cellularized scaffold product, indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.
Approved by the US FDA in December 2016.

USA

OMNIGRAFT
INTEGRA
An advanced bilayer dermal regeneration matrix for the treatment of diabetic foot ulcers. Approved by the US FDA in 2016.

USA, EU, CANADA, SINGAPORE

CARDIOCEL
ADMEDUS
A cardiovascular scaffold which facilitates endogenous stem cells and other cells to regenerate and repair damaged tissue for the treatment of cardiovascular abnormalities. Marketed in the U.S. under 510(k) clearance as of 2014; marketed in Europe under CE Mark as of 2013; received medical device license in Canada in 2014; approved in Singapore in 2015.

EU

SPHEROX (FORMERLY CHRONDOSPHERE)
CO.DON AG
A product containing spheroids of human autologous chondrocytes for use in cartilage defects. Marketed in Europe as of 2017; marketed in Germany since 2007.

EU

RENOVACELL
AVITA MEDICAL
An autologous cell harvesting device that enables a to create a regenerative epithelial suspension using the sample of the patient's skin for the treatment of skin discoloration. Marketed in Europe as of 2016.

EU

VERGENIX FG
COLLPLANT
A device composed of homogenous human recombinant type I collage for use in wound treatment. Marketed in Europe as of 2016.

EU

VERGENIX-STR
COLLPLANT
A matrix made of collagen type I for use in the treatment of connective tissue disorders. Marketed in Europe as of 2016.

EU

REGENERCEL
AVITA MEDICAL
An autologous cell harvesting device that enables a to create a regenerative epithelial suspension using the sample of the patient's skin for the treatment of ulcers. Marketed in Europe as of 2015.

USA

AURIX
NUO THERAPEUTICS
A biodynamic hematogel composed of platelet-rich plasma gel prepared from a small sample of a patient's own platelets and plasma as a catalyst for healing indicated for the treatment of wounds. Marketed in the U.S. under Section 361 for the Platelet Rich Plasma and under 510(k) clearance as of September 2007.

SOUTH KOREA

HYALOGRAFT 3D
CHA BIO&DIOSTECH CO LTD
A cell therapy which cultivates autologous skin fibroblasts in 3D scaffolds formed of hyaluronic acid derivatives for the treatment of diabetic foot ulcers. Conditionally approved in South Korea in July 2007.

SOUTH KOREA

HOLLODERM
TEGO SCIENCES
A cultured epidermal autograft composed by culturing autologous keratinocytes. It is transplanted to the wound and aids in regeneration of the dermis and develops into new skin. Holoderm is indicated for the treatment of skin disorders such as burns, vitiligo, nevi and scars. Approved in South Korea in 2002.

JAPAN

HEART SHEET
TERUMO BCT
An autologous skeletal myoblast preparation approved in Japan in 2015 for the treatment of patients with serious heart failure.

USA

TRANSCYTE
ORGANOGENESIS
A tissue-engineered skin substitute made from a nylon mesh and a silastic semi permissible and biocompatible layer for the treatment of Epidermolysis Bullosa. Approved by the US FDA in 1998, acquired by Organogenesis from Shire in 2014.

USA

APLIGRAF
ORGANOGENESIS, INC. & NOVARTIS AG
A bi-layered living skin substitute made from a dermal layer of human cells (fibroblasts) in a bovine type I collagen and an overlying cornified epidermal layer of living human keratinocytes. Apligraf is indicated for the treatment of chronic venous leg ulcers and diabetic foot ulcer. Approved by US FDA in July 1998 and June 2000, respectively.

USA

DERMAGRAFT
ORGANOGENESIS
A dermal substitute used to help in the wound closure of diabetic foot ulcers. It is made from human cells (fibroblasts), placed on a dissolvable mesh material. Organogenesis acquired Dermagraft from Shire in 2014. Approved by US FDA in September 2001.

JAPAN

JACC
J-TEC
A combination product of autologous cultured chondrocytes and collagen gel approved in Japan in 2012 for the alleviation of clinical symptoms of traumatic cartilage defect or osteochondritis dissecans of the knee.

JAPAN

JACE
J-TEC
An epidermal cell sheet produced from keratinocytes isolated from a patient's own skin tissue, approved in Japan in 2007 for use in patients with deep dermal and full-thickness burns covering 30% or more of the total body surface area; approved in Japan in 2016 to treat patients following the excision of giant congenital melanocytic nevi to facilitate the closure of the wound.

AUSTRALIA

ORTHO-ACI
ORTHOCELL
Ortho-ACI is an autologous chondroctye-based cellularized scaffold to treat symptomatic defects of the articulating cartilage of the joints, predominately the knee and ankle. Approved in Australia 2017.

EU

NOVOCART 3D
AESCULAP BIOLOGICS
The product consists of three-dimensional collagen-chondroitin sulphate scaffolds with embedded autologous chondrocytes in a cell suspension. Marketed in the EU for for articular cartilage repair since 2003.

Source: https://alliancerm.org/available-products/

We are present in more countries than anyone else.
We speak directly with healthcare leaders and pharmaceutical executives.
We are ready to share their insights and experiences with you.

PHARMA
BOARDROOM
www.pharmaboardroom.com