In the Land of the Living Logistics

The supply of cell and gene therapies is a delicate operation – and easily broken, just like daisy chains.

Please click the circles to navigate

Introduction I

What it Takes to Bloom

Cell and gene therapies can live up to their potential – the field just needs to transform medicine as we know it.

When the first CAR-T cell therapy, Kymriah, was approved by the FDA in 2017, Commissioner Scott Gottlieb said that cell and gene therapies "hold out the potential to transform medicine." Words like "groundbreaking," "revolutionary," and "transformational" are often applied to new technologies. It's all part of the familiar hype cycle, where we overestimate the effect of a technology in the short run and underestimate the effect in the long run (Amara's law). And right now, it's possible that personalized medicine, including cell and gene therapies, are riding high on the "peak of inflated expectations" following the first CAR-T approvals.

It's true that the number of eligible patients for currently approved cell and gene therapies is miniscule when compared with the number of people who suffer from cancer or blindness (key areas for cell and gene therapy development) – and the field should brace itself for a spell in the "trough of disillusionment," as expectations fail to live up to the hype in the short term. But will the fall in visibility be followed by the "slope of enlightenment" and an eventual "plateau of productivity" described by the hype cycle of Amara's law?

Much will depend on whether or not researchers can find a way to selectively target solid tumors and expand the number of indications treated by cell and gene therapies. This, in the view of many researchers, is simply a matter of time. But there are additional, perhaps more challenging, problems that lie beyond the clinic; the field must rise to the challenges of commercialization, scale-up, logistics and cost.

Healthcare systems are set up to order, dispense, and pay for off-the-shelf products, but personalized medicines require new best practices and regulatory approaches. As things stand, it's difficult to imagine how apheresis centers and pharmacies would be able to cope with dozens of new protocols as more therapies reach the market.

Then there's the question of pricing and payment. Will payers and companies be willing to embrace new pricing and reimbursement models? And even if the industry develops new, closed systems for manufacturing cell and therapies – eliminating the need for complex and expensive logistics – how will regulators cope with the prospect of individual hospitals manufacturing therapies? How will they ensure compliance and prevent processes drift?

In short, the field of cell and gene therapies will have to transform medicine to succeed. I am optimistic, but only time will tell if the field can overcome the hurdles.

James Strachan
Deputy Editor

Advancing Therapies

A report highlights the acceleration of cell and gene therapy approvals worldwide

The International Society of Cell and Gene therapy (ISCT) has published a snapshot of advanced therapeutic approvals throughout the world (1). ISCT intends the report to be a "living document" – periodically updated and linked to a dedicated section of the ISCT website. Products authorized from 2015 to September 2018 represented 45 percent of all cell, tissue and gene therapy approvals worldwide – highlighting the growing number of marketing authorizations granted by regulators. The US had the greatest number of approved cell, tissue and gene therapies, with 16 (eight products included in this number, however, are based on cord blood hematopoietic progenitors for unrelated donor hematopoietic progenitor cell transplantation; similar products are available in most countries as cell transplants and not as marketed products).

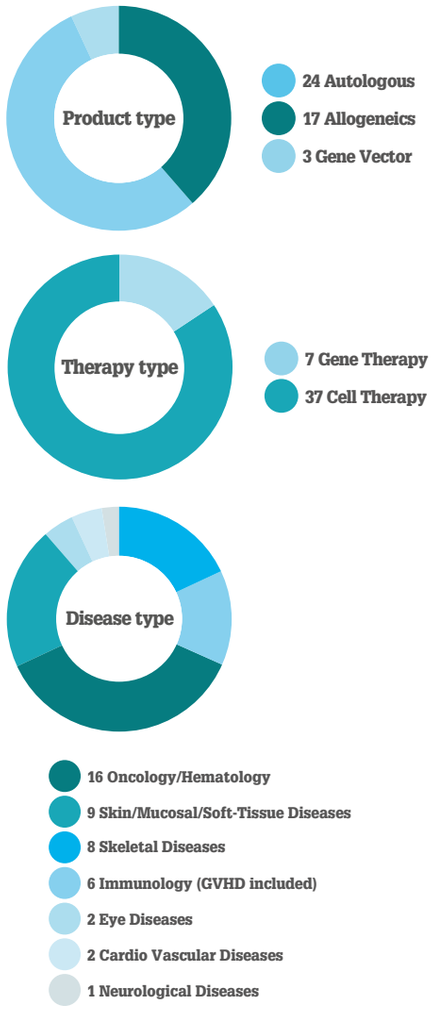
"The aim is to ultimately inform, by periodic snapshots, the scientific community, healthcare stakeholders and patient associations on authorized cell and gene therapies (CGT) as a way to increase communication around the approved therapeutic approaches charged with heightened expectations," said the authors of the report. "This article reflects the dynamic momentum around authorized CGTs coinciding with the parallel increase of unproven approaches where cells are delivered without appropriate and rigorous scientific and regulatory assessment and authorization."

Our infographic provides an overview of the key facts and figures.

Reference

1. *N Cuende et al., "Cell, tissue and gene products with marketing authorization in 2018 worldwide," Cytotherapy, 20, 1401–1413 (2018). PMID: 30366616.*

CELL THERAPY LEADS THE WAY



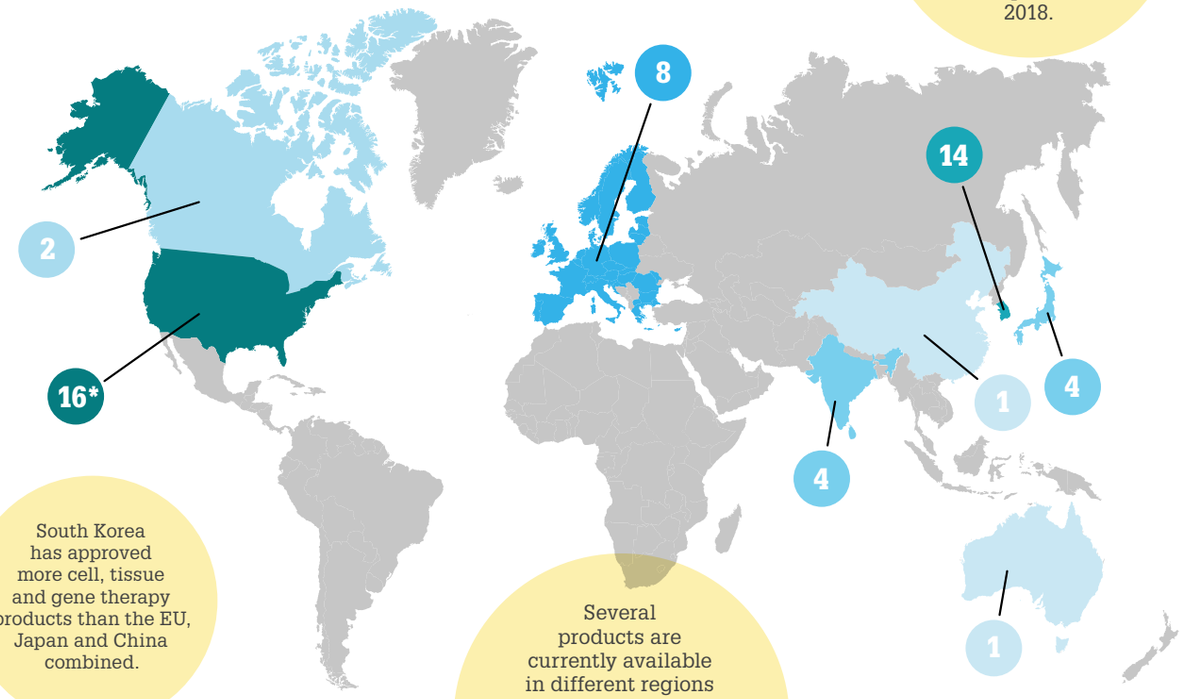
Of the 44 unique products, 37 are cell and tissue therapies (84%) and mainly autologous (55%).

More than 1/3 of the products are intended for the treatment of oncological or hematologic diseases.

Products authorized from 2015 to September 2018 represent 45% of all cell and gene therapy approvals.

GOING GLOBAL

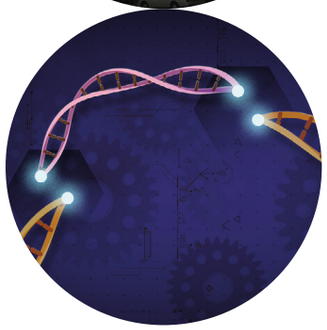
Cell, tissue, and gene products with marketing authorization by region



No cell/tissue/gene products have been authorized for marketing in Brazil, Hong Kong, Israel, Malaysia, Singapore and Taiwan, as of September 2018.

South Korea has approved more cell, tissue and gene therapy products than the EU, Japan and China combined.

Several products are currently available in different regions but have the same MA holder (Yescarta, Kymriah, Imlygic, RMS, Ossron/Ossgrow and Chondron/Cartigrow).



News-in-Brief

Converting glial cells to neurons, more effective CAR-Ts, and groundbreaking IDAs… What's new in the advanced medicine field?

Manufacturing

- The US Center for International Blood and Marrow Transplant Research (CIBMRT) is collaborating with Novartis to track the long-term outcomes of patients treated with CAR-T cell therapies. The alliance will collect and examine real-world data about the use of Kymriah, and is encouraging all US centers to offer patient participation in the registry. "For decades, we collected research data about hematopoietic cell transplantation (HCT)," said Marcelo Pasquini, Senior Scientific Director at CIBMTR in a press release. "Previously, HCT was the only successful cellular therapy for cancer. We look forward to expanding into the field of targeted cellular therapies to help people with cancer."
- The UK government is investing £4.3 million in an effort to create more efficient and innovative methods for manufacturing medicines. Part of the funding has been awarded to UK gene and cell therapy group, Oxford BioMedica, which is developing a new digital framework initiative to streamline the production of next-generation medicines. In a press release, the group said the project aims to build "digital and robotics capabilities that are designed to drive improvements in analytical methodology, supply times and cost of goods." The UK government has also invested a further £3 million to support the work of Advanced Therapy Treatment Centres in rolling out new cell and gene therapies across the country's National Health Service.

Research

- Kymriah (tisagenlecleucel) is priced in line with its estimated long-term survival benefit among children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia, according to the results of a cost-effectiveness analysis. The international trio of researchers found that – given 40 percent of patients treated with tisagenlecleucel are expected to be long-term survivors, or alive and responding to treatment after 5 years – tisagenlecleucel had a total discounted cost of $667,000, with discounted life-years gained of 10.34 years and 9.28 QALYs (Quality Adjusted Life Years) gained. The researchers compared these results with the chemotherapy drug, clofarabine, which had a total discounted cost of approximately $337,000, with discounted life-years gained of 2.43 years and 2.10 QALYs gained. This difference resulted in an incremental cost-effectiveness ratio of approximately $42,000 per life-year gained and approximately $46,000 per QALY gained for tisagenlecleucel vs. clofarabine.
- A new gene therapy can convert glial cells into functioning neurons. Gong Chen, Professor and Verne M. Willaman Chair in Life Sciences at Penn State University, presented the findings at the annual meeting of the Society for Neuroscience in San Diego. Chen and his team were able to inject a neural transcription factor called NeuroD1 – a protein that activates neuronal genes and silences glial genes – within injured parts of the brain to infect glial cells. NeuroD1 then binds with the glial cell's DNA and activates the neuron genes, turning the glial cell into a functioning neuron. The team hope that the technology may be used to treat neurological disorders, such as stroke, Alzheimer's disease and Parkinson's disease.
- A new strategy to reduce the severe toxicities associated with CAR-T cell therapy? Researchers from the Mayo clinic said that by blocking the GM-CSF protein, which is produced by CAR-T cells and other cells using a clinical-grade antibody (lenzilumab), they can reduce toxicities in preclinical models. Presenting the results of their research at the 2018 annual meeting of the American Society of Hematology, the researchers said that they were able to use CRISPR to generate CAR-T cells that did not secrete the GM-CSF protein. Rosalie Sterner, a student working in the T Cell Engineering Laboratory of Saad Kenderian, said in a press release that the modified CAR-T cells were more effective than regular CAR-T cells.

Regulation

- The Biotechnology Innovation Organization (BIO) has called for flexibility in the design of gene therapy clinical trials following the publication of the FDA's Gene Therapy Draft Guidances. BIO said that the FDA should not "use otherwise limiting language such as those recommending specific number of treatment arms, utilizing different doses but the same product administration procedures, or the inclusion of a sham control group. Use of innovative clinical trial design can decrease unnecessary and unethical patient exposure to clinical procedures and experimental products while still advancing clinical development." BIO also questioned the scope of the draft CMC guidance and said some recommendations are unclear as to which stage of development they apply.
- The FDA has accepted Editas' Investigational New Drug (IND) application for their first gene-editing trial in 10-20 patients suffering from an inherited retinal degenerative disease called Leber Congenital Amaurosis type 10. Editas also collected a $25-million milestone payment from its partner Allergan. EDIT-101 is slated to be the first in-vivo CRISPR treatment tested in humans – Vertex and CRISPR's beta thalassemia treatment involves gene editing outside the body. The news comes six months after Editas suffered a manufacturing set back with one of its input materials failing a quality specification, after which the FDA delayed the IND approval.
- In more IND news, the first induced pluripotent stem cell (iPSC)-derived product has been cleared for clinical investigation by the FDA. Fate Therapeutics announced the news at the 60th American Society of Hematology Annual meeting, along with new preclinical data on the company's (iPSC) product platform and its iPSC-derived, off-the-shelf cell-based cancer immunotherapy pipeline.

Automation for Success

Current manufacturing processes for cell and gene therapies have limitations and challenges from quality, quantity, and efficiency perspectives. Companies must look at moving towards scalable, automated, computer-controlled, closed processes.

By Behnam Ahmadian Baghbaderani

The discovery of somatic cell reprogramming by Shinya Yamanka and the generation of human induced pluripotent stem cells (iPSCs) truly revolutionized the field of regenerative medicine and opened new opportunities in cell replacement therapies. Moreover, the development of new gene editing technologies and the development of cancer therapy applications based on chimeric antigen receptor (CAR-T) technology are truly exciting advances that could make personalized medicine readily available for large numbers of patients.

However, current manufacturing processes for the development of cell and gene therapy products pose numerous challenges:

- Quality. Existing open manufacturing processes require more stringent aseptic handling to prevent contamination, are carried out using 2D unit operations that lack appropriate in process control and monitoring methods, involve serum dependent processes (with lot-to-lot variability), and lack proper cell characterization strategies.
- Quantity. Existing processes include small unit operations with limited yield, and are lacking in flexibility and scalability (scale-up or scale-out depending on the application).
- Efficiency. Existing operations are often labor-intensive and require a large manufacturing footprint, which leads to significantly high manufacturing costs and overall treatment costs.

Robust and reproducible

There is much to be improved if the field is to deliver these therapies to larger numbers of patients. The development activities must be carefully designed to implement innovative technologies with appropriate in process control and monitoring analytical methods in the process, and establish a robust and reproducible manufacturing process. The development of automated, closed cell culture systems or transitioning from existing open, and manual protocols into scalable, computer-controlled, automated processes needs to be considered during early clinical development.

With respect to autologous applications, currently available automation technologies need to be further improved to scale-out and cover the entire manufacturing process, including selective isolation of specific population of cells, priming and activation, genetic modification (viral or non-viral manipulation), cell expansion, harvest and downstream processing. Currently, the majority of these unit operations are open and manual processes, which can increase the risks of manufacturing, cost of treatment, and, most importantly, affect commercial viability. The transition of these processes into automated unit operations can be done using an end-to-end approach or via a modular approach (step-by-step transitioning of the manual steps into automated unit operations).

Lonza's Cocoon™ system is an example of an innovative closed, automated system that can be used for manufacturing autologous cell and gene therapy products. The Cocoon™ system enables end-to-end automation through inter-linked unit operations under accurate and traceable manufacturing process. A key feature of the Cocoon™ is closed, disposable cassettes serving as culture chambers for both anchorage-independent and anchorage-dependent cells. The system has integrated pumps and sensors that process the cells and cell culture media /solutions and can maintain temperature and physiological gas concentrations at acceptable levels.

In the area of allogeneic cell therapy, there also exists great potential for improvements in scale up. Besides open and manual unit operations, these processes often use 2D cell culture systems that lack flexibility and scalability. Different 2D cell culture systems have been made available to increase the scale and address the yield and cell number requirements for cell therapy applications. However, even large-scale 2D cell culture systems have several disadvantages, including significantly high processing times, increased medium and material requirements, highly labor-intensive processes, increased manufacturing footprint, heterogeneity of the cells manufactured in multiple vessels, and, most importantly, a lack of in-process control and monitoring methods. To address these challenges and establish commercial ready processes, the industry needs scalable, computer-controlled 3D bioreactor technologies.

The iPSC challenge

Aside from logistic and regulatory challenges, there are several iPSC manufacturing challenges, including tissue sourcing, long manufacturing process, testing, and downstream directed differentiation. Reprogramming somatic cells into induced pluripotent cells is an example of a highly manual process, starting from the introduction of transcription factors into somatic cells, the reprogramming stage, and selection of iPSC colonies, expansion, and passaging of iPSCs. In addition to the openness of the processes, the efficiency of reprogramming is low and depends on the starting material, reprogramming method (viral or non-viral), and cell culture system used during the process. Finally, the nature of the iPSC manufacturing process and quality of iPSCs could affect the quality and yield of downstream directed differentiation process.

Produced by
the Medicine Maker

A wide range of strategies can be incorporated in the early clinical development phase to address these challenges: first, carefully selecting the starting somatic cells, reprogramming method, and cell culture system used for the generation and expansion of iPSCs; second, developing 3D bioreactor protocols for expansion and differentiation of iPSCs; and third, implementing appropriate in-process control and characterization methods in the entire manufacturing process. As a custom manufacturing organization offering cGMP manufacturing services around a variety of cell therapy products, Lonza set out to develop a cGMP-compliant human iPSC manufacturing process. We used a robust and reproducible, integration-free method that would allow one to develop a bank of well characterized iPSCs that can be used for differentiation into a wide range of clinically relevant cells.

Overall, the field of cell and gene therapy involves a wide range of autologous and allogeneic applications, each requiring specific process development approach (scale out vs. scale up). Different cell types will also have unique cellular characteristics (for instance, cell suspension versus cell attachment), requiring different unit operations to develop clinically viable product (for example, choice of gene modification technology or directed differentiation process), and may have distinct critical quality attributes (defined by identity, viability, functionality, and safety assays). Assay development and product characterization activities need to start concurrently with the process development and optimization activities to identify and establish the relationship between the Critical Quality Attributes (CQA) of the process with the critical materials attributes (CMA) and critical process parameters (CPP). Finally, different technological solutions covering a wide range of applications will be necessary to enable automation and allow scalable manufacturing, reduce the cost of manufacturing (through lowered footprint and manpower), and minimize the risk of failure through reduced contamination. This would allow us to move towards increased availability of treatment for a larger number of patients in a safe manner.

Behnam Ahmadian Baghbaderani is Global Head of Process Development, Lonza Cell and Gene Therapy. The author would like to thank Francesca Vitelli, Ryan Scanlon, Karen Magers, Eva Lindskog, Hadrien Piana, and Fatma Senkesen for their feedback and revisions.

Engineered AAV for Victory

While CAR-T therapies have created tremendous excitement in the field of the cell and gene therapy, gene therapy products will continue to play a significant role in improving the health of patients in the future. One thing that the growing gene therapy industry is in need of today is engineered viruses – and this will only continue.

Two years ago, Lonza recognized the potential of Luk Vandenberghe's (Harvard Medical School/ Massachusetts Eye and Ear, USA) in-silico designed synthetic adeno-associated viral vectors (AAVs) for the clinical development and commercialization of novel gene therapies. The Vandenberghe Lab initiated the work to develop antigenically distinct AAVs and to study the structure-function relationship of AAV. They chose a phylogenetic and statistical modeling approach called ancestral sequence reconstruction (ASR) to predict how the structure of the viruses has evolved, and came up with a series of protein sequences for AAVs that may have been ancestors of the current viruses. They then synthesized the ancient AAVs and found that one, Anc80, could efficiently transfer genes to various organs in animals.

Anc80L65 is a well-characterized single clone of the Anc80 variant pool and shows higher transduction efficiency and stability compared with other AAV vectors in liver, muscle, retina, cochlea, CNS, spine, heart, and kidney of rodent and non-human primate models. Anc80L65 has been commercially licensed by Selecta, Vivet and Akouos. A license with Solid Biosciences was also announced earlier in 2018 and other commercial licenses may have been agreed but not disclosed.

We are excited about the promise of newer Anc-AAVs, inferred by similar ASR methods. Overall, the Anc-AAV platform has generated considerable interest because it has superior expression to naturally occurring serotypes (including AAV8 & AAV9), a strong IP position, and a reduced prevalence of pre-existing neutralizing immune responses in target patient populations.

As we advance our methods for screening and interrogating the Ancestral library, we expect to have a powerful way to quickly and efficiently discover new Anc-AAVs that fit a given target vector profile. Watch this space!

A True Dawn

With all the hope and promise emanating from the cell and gene therapy field today, it's easy to forget that we've had false dawns in the past. But I'm convinced that 2017 was a true watershed year – a year I'll tell my grandkids about.

By John Rasko, Professor of Medicine, Central Clinical School Centenary Institute of Cancer Medicine & Cell Biology, University of Sydney, Australia.

For better or for worse, I became terribly excited by the potential of cell and gene therapies as a teenager, and I've been hooked ever since. I've spent 25 years of my clinical life focused on achieving the goals of the field, which is why the past few years have felt like a lightning bolt! It is actually happening. I will tell my grandchildren about the year 2017 – the year when cell and gene therapies became a reality and hit the mainstream.

And with all the excitement emanating from everyone involved in the field, it's easy to forget that we were almost here once before. In the year 2002, Alain Fischer and Marina Cavazzana-Calvo at the Necker Hospital in Paris used hematopoietic stem cells (HSCs) to treat severe combined immune deficiency (SCID). I can vividly remember attending international meetings at the time and watching people punching the air, high fiving each other, thinking they had used stem cells to successfully cure babies of a life-threatening predisposition to infection. But then a terrible cloud arrived because a quarter of those babies went on to develop leukemia – the insertional mutagenesis challenge. And although those problems have largely been overcome – we've changed the vector system and matured the safety of those technologies – it was a huge setback for the field as people began asking serious questions about the safety of gene therapy as a whole.

It's taken us around 15 years to recover. Of course, in retrospect, people had been working on CAR-T cell therapy for a decade, but it doesn't really hit home until a major regulatory agency like the FDA acknowledges that this is something that should be offered to patients because it works and is safe. We've gone far beyond the fleeting success of 2002 and that's why everyone in the field is so ecstatic.

But we must also accept that the field faces huge challenges – both scientific, logistic and economic. On the clinical side, non-Hodgkin's lymphoma is, of course, a horrible disease and it's amazing that we now have a potentially curative therapy, but the condition is fairly rare. How can we apply the insights we've gleaned in recent years to much larger clinical challenges? Solid tumors, colorectal cancers, breast cancers, lung cancer – these are massive public health problems that compete with cardiovascular disease as the biggest killers in the developed world. Translating CAR-T technology or immunotherapies to solid tumors will require a massive moonshot-like investment. It is up to us to go to governments and explain that the technology is here and can deliver for patients, but that we need more before we can make the potential difference to health that we could make.

I see some particularly encouraging signs from the UK with their Catapult centers – that's the kind of investment we need, if the field is to reach its full potential. Australia has also embarked on an ambitious project called the Medical Research Future Fund, which is a sovereign fund set up in 2015 set to reach $20 billion by 2020-21, whereby the interest accrued will be used to fund medical research. By 2020, it will provide approximately $1 billion per year in medical research funding, effectively doubling Australia's investment in health and medical research. We need more investments of this nature, and we, as scientists and physicians, must ensure we are making the case for cell and gene therapies.

We will also have to come to terms with the logistic and manufacturing challenges of allogeneic therapies. Do we have a centralized model with centers of excellence, or a decentralized model of nodes and spokes? This question remains unresolved today – and the answer will perhaps depend on the geography of individual countries. Of course, everyone agrees that the ultimate goal is to have an off-the-shelf technology that will not cause graft versus host disease. Imagine being able to prescribe a vial from liquid nitrogen storage without the need for manufacturing to be conducted at individual sites – all closed and automated.

And then we must face up to costs. How do we pay for these therapies? What innovative pricing and reimbursement models are required? Encouragingly, there are signs that drug manufacturers are open to new kinds of models where payment is dependent on the therapy continuing to deliver therapeutic benefit over time.

These are the major hurdles the field must overcome, but 2017 has set essential foundations. You will not find a hematologist today who believes that CAR-T won't find a place in the treatment of acute lymphoblastic leukemia and non-Hodgkin's lymphoma. It is a huge step and shows that cell and gene therapies are here to stay. And I cannot describe how excited I am about the future of the field.

Command and Control Your Bioprocess

The stem cell industry needs to embrace bioprocess control systems to develop consistent, high quality, and commercially viable bioprocesses.

By Philipp Nold, Infield Application Specialist, Eppendorf AG Bioprocess Center.

The challenge in stem cell bioprocessing – as in any industrial bioprocesses – is developing a commercially viable process that delivers products in high, consistent quality. It's fair to say, however, that the protocols for stem cell expansion and differentiation are often significantly less mature than in biologics bioprocessing.

If we consider the medium composition, for example, cell-based therapy manufacturing requires xeno-free media to meet regulatory demands and allow process standardization. It also requires growth factors or chemical substitutes for them – at an affordable price. Another challenge is keeping commercial-scale manufacturing in mind during early-stage process development. David Courtman from the Ontario Institute for Regenerative Medicine hit the nail on the head when he said, "If I make a drug, it's a chemically defined product and I know exactly what it is. […] In contrast, cell therapy products are really only defined by their process because the product can never fully be characterized. So the better you are at defining your process, the better you are at getting a standardized product and meeting regulatory approval" (1). Courtman's words underline the importance of comprehensively understanding your process.

Understanding can be broken down into a number of parameters – for example, medium pH, oxygen tension, physical forces, growth substrate, and concentrations of nutrients and metabolites – and their impact on cell growth and fate. The good news is that cultivation in bioreactors opens up new possibilities for process monitoring and control compared with conventional cell culture flasks. In bioreactors, you can easily control dissolved oxygen (DO) concentration, for example, and achieve conditions resembling those of the stem cell niche in vivo.

Other difficulties can arise from the sheer number of experimental conditions to be tested. Parallel mini bioreactor systems can be of help, as they reduce the number of process runs needed, while saving precious resources like media and supplements. Another challenge is sensor technology; measuring certain parameters online, such as pH and dissolved oxygen, is well established, but analyzing additional parameters that tell us more about nutrient and metabolite concentration or the cells' state are not yet routine. Flexible bioprocess control software that allows integration of external sensors can greatly help here.

The most important factor is understanding which parameters have the greatest influence on the results, how they play together, and what the optimal setpoints are. In traditional experimental approaches one factor is changed per experiment, but this does not deliver information on interdependencies between variables. A Design of Experiments (DoE) approach involves simultaneously changing several factors. DoE allows a wider range of parameters to be covered, unravels interdependencies, and gives hints for meaningful follow-up experiments. A great advantage of a DoE approach is that only the experiments that are really needed are done, and so resources are saved. Multivariate analysis (MVA) is a statistical technique used to analyze data that arises from more than one variable, which helps to maximize the amount of information gleaned from the available data. DoE is a useful complement to multivariate data analysis, as it generates data tables that contain an important amount of structured variation.

Another technology that may play a significant role in cell therapy bioprocessing is perfusion technology. This is a hot topic today in protein production as it can deliver more product for a given bioreactor volume and therefore can save lab space and enhance flexibility. Plus, product quality profits through a more constant cellular environment and product harvest. Kropp and coworkers demonstrated the potential of perfusion technology for the cultivation of human induced pluripotent stem cells (2). The authors compared the expansion of cell-only aggregates when using different feeding strategies; and, in perfusion mode, glucose and lactate levels, pH, and DO were much more homogenous throughout the cultivation period, compared with a conventional repeated batch process. Importantly, the cell yield was almost 50 percent higher. I believe that gaining more cells in shorter time will help in translating the process for successful therapeutic applications. One can also imagine that perfusion processes are suitable for smooth transitions of media; for example to change growth factor concentrations in the course of cell expansion and differentiation.

Overall, successful stem cell bioprocess development needs comprehensive process understanding, which in turn requires bioprocess control systems that allow for process monitoring and control. Advanced methods for experimental design and data analysis, like DoE and MVA, can also help to gather important data and transform them into actionable insights.

The protocols for stem cell bioprocessing may be behind other fields, but the technology available today will make a big difference.

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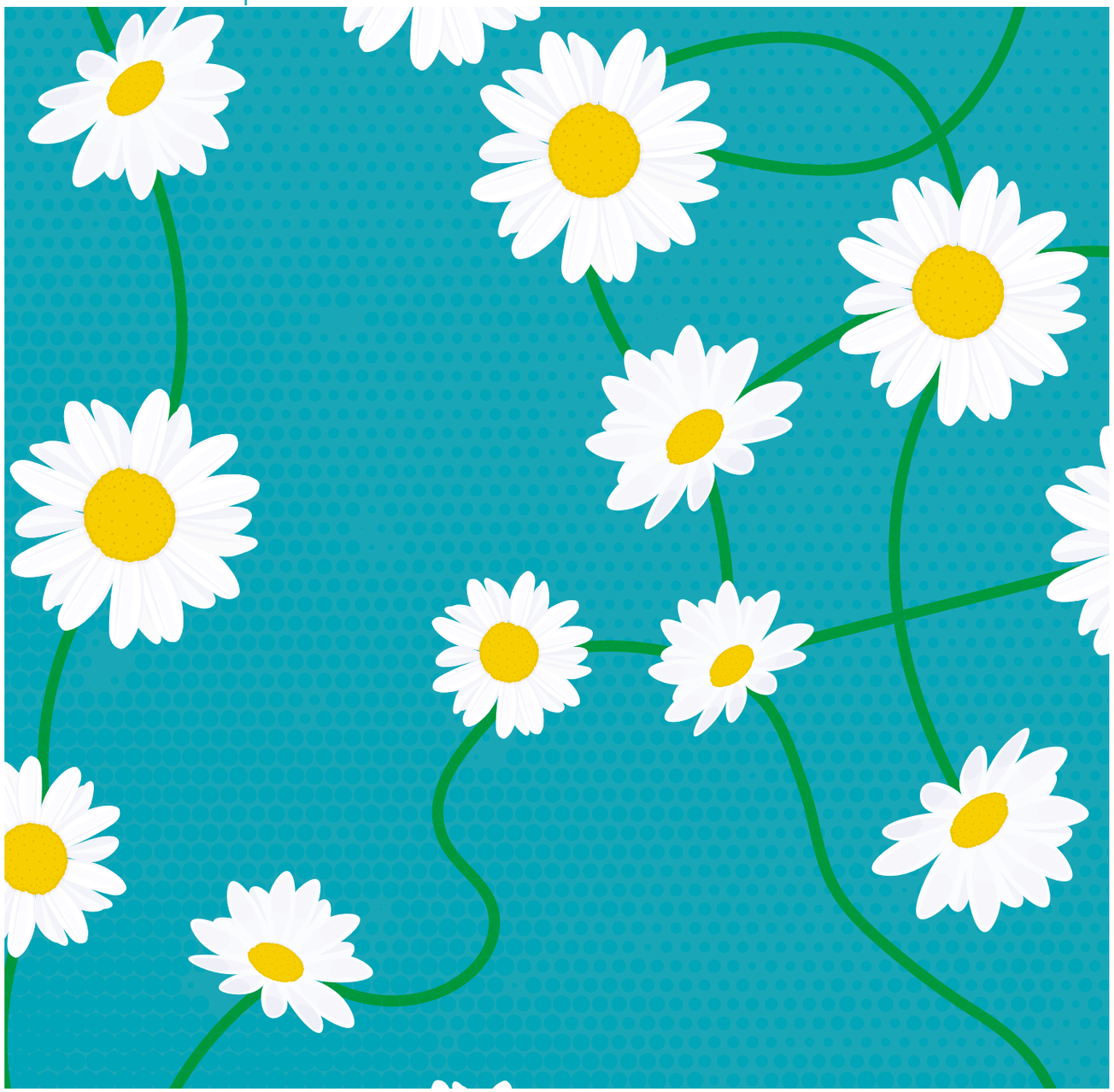
2. *Kropp et al., "Impact of Feeding Strategies on the Scalable Expansion of Human Pluripotent Stem Cells in Single-Use Stirred Tank Bioreactors", Stem Cells Transl Med, 5, 1289–1301 (2016). PMID: 27369897.*

In the Land of the Living Logistics



Ideal drug manufacturing and logistic processes are closed and automated to eliminate the risks associated with human intervention and manual operations, but most cell and gene therapies are not yet at this stage. Here, we discuss the problems of handling living, breathing cells in transit, and ask a big question: are healthcare systems ready for cell and gene therapies?

By James Strachan

In The Medicine Maker, we often discuss the challenges of scaling up and commercializing biologic drugs, such as monoclonal antibodies. Identifying the right set of conditions to get the highest titer possible, while ensuring there's enough "wiggle room" should anything deviate, isn't easy. But at least the cells are, in theory, identical, and there are established precedents to build processes upon. Cell and gene therapies are a whole new kettle of fish: every process is different because the cells are different, and companies are often inventing processes from scratch.

Developing and delivering cell and gene therapies necessitates the handling of living, breathing cells in transit – sometimes across great distances. You have to know exactly where your cells are at all times, who they belong to, and who has handled them. Often, you'll have to coordinate the activities of multiple clinical centers too: condition the patient, book the bed, align your clinicians, and get the delivery in all at the right time. One mishap could mean a seriously ill patient missing their treatment, and the loss of hundreds of thousands of dollars' worth of product.

Welcome to the world of cell and gene therapy logistics! Here, four esteemed experts in the field explore the challenges in more detail.

Meet the Experts

Matthew Lakelin
Chief Scientific Officer, TrakCel

Heidi Hagen
Chief Strategy Officer and Co-Founder, Vineti

Phil Vanek
General Manager, Cell and Gene Therapy Strategy, GE Healthcare

Simon Ellison
Cell & Gene Therapy Service Director, World Courier

What are the main challenges of translating lab-scale therapies into industrial-scale therapies?

Matthew Lakelin: Until fairly recently, cell and gene therapies were developed without scale-up (or scale-out) in mind. Starting material and the final therapy would always be transported fresh, with a limited shelf life, and there would be little time available to move the starting material into the manufacturing environment, and then get the therapy to the patient. This system wasn't practical for much larger patient populations, scattered across a country – or even around the world. And that's why developers have to think about cryopreservation – not just for autologous therapies, but also for starting materials. By nature, these therapies involve many manual steps, with several technical specialists and potential points of failure, so developers are having to think about manufacturing and logistics during development of the therapy itself.

Phil Vanek: Yes, these therapies are different in that they're "manufactured" in laboratory settings, often involving flasks and disposable plastics, with many individual components and combined unit operations – very different to a large-scale GMP facility! To bridge the gap between a laboratory set up to GMP facility, companies must think about the most efficient and optimal means of bringing equipment and people together in a process that requires less skilled labor and results in lower risk. And that typically means more sophisticated equipment that is able to integrate the disparate steps.

Heidi Hagen: I believe there are four main challenges. The first is data management across the value chain. Cell and gene therapy success relies on secure data management as much as it relies on the physical management of the cell products. These types of therapies involve a wide array of data across a variety of stakeholders that must be retained and integrated for the sake of patient safety, customer service, regulatory compliance and product quality.

The second consideration is scale-out versus scale up. In traditional off-the-shelf therapies, the production process is developed and scaled up into larger mixing vats or bioreactors. This, combined with process optimization, provides an increase in production yield and requires only a limited number of manufacturing lots annually for thousands of patient doses. Autologous cell therapies, in contrast, are individual lot runs per patient and thus cannot scale up, but rather must be scaled out. The cell therapeutic manufacturers increase their production by adding more workstations to perform individual lot runs. Overall, the production systems and tools in the industry are still quite immature, but optimization of unit operation efficiencies and application of new process technologies should enable some scale up ability within the same footprint. However, there will be inherent limitations because of the minimum of a one-to-one ratio of lots-to-patient.

Third, companies must use operational systems that work globally. As described above, an increased volume of production will be enough of a challenge for companies. Globalizing these therapies exaggerates the challenges while adding other unique language, financial, and regulatory factors. To find solutions, the company must manage unique workflows, product labeling, and data requirements for each geographical region, while also ensuring that the data privacy requirements are met for those individual regions. Also, the product may move across borders and thus proper maintenance of the Chain of Identity (COI)/Chain of Custody (COC) becomes more challenging with greater risks involved.

Finally, cost and misaligned analytical technologies provide another major challenge. Because of the individualized nature of cell therapy production and the need to handle living, breathing cells in transit across sometimes great distances, these therapies are inherently expensive to produce – resulting in high price tags. Added to the manufacturing costs are the quality control tests and oversight of the product. If the production tools for cell therapy are considered to be lagging and immature compared with the groundbreaking science of these new cell therapies, then the analytical tools are even further behind. The tests for these single lot products primarily measure surface changes on the cell membrane and secretion of well-defined proteins rather than evaluating and quantifying the genetic modifications within the cell after production. The analytical tools must catch up so that the real changes to the cells can be measured and done so in an automated and in-line fashion.

Simon Ellison: There is a need to think about what future logistics platforms are going to look like, as early as possible within clinical development. A robust logistics platform connects patients to therapies, but without it critical shipments (e.g. donation) can

be delayed (e.g. tied up in customs). This envisioning of future challenges is key to successful evolution from lab to industrial scale.

What are the main logistic challenges associated with cell and gene therapies – particularly CAR-T and other autologous therapies?

ML: The challenge with cell and gene therapies is that you can build a system that works perfectly: where all the handovers involve individuals who understand that they may be dealing with a patient's last chance for life. But if you've got members of staff on holiday or a new courier driver, that's when things can go wrong. And one mishap could mean a gravely ill patient missing their treatment. It's not easy, but you must build clusters of understanding throughout the entire supply chain.

Another challenge arises because the supply model for these therapies tends to have one centralized manufacturing site, fed by multiple clinical centers, which means you must coordinate activities between the different clinical centers and standardize their approaches for taking starting material. This task is not easy, there will always be biological differences between patient's starting material, but a key challenge is how to engineer out differences in starting material arising from the supply chain.

Thirdly, maintaining chain of identity/custody is a key consideration in cell and gene therapy logistics, which becomes more challenging when increasing the number of patients being treated. This is important for autologous therapies where there's a risk of graft versus host disease if there's any cross-contamination. Regardless of whether you use an electronic system or a paper-based system, it needs to be robust and able to ensure and record that each patient received the correct therapy.

PV: I agree; these are autologous or personalized medicines, connected to an individual, which means there needs to be absolute fidelity in the ownership of that sample – from the point of sample collection (whether it's apheresis or another starting material) all the way through the various manufacturing steps to eventual administration. You need to know at all times to which patient a sample belongs to as well as when, where and who touched a product and what they did to it. Getting it wrong can be extremely risky for the patient, as Matthew mentioned.

HH: Complexity is a central challenge for cell and gene therapy logistics, especially when you consider the fact that the patient and healthcare provider are part of the supply chain. The production of the final product involves coordinating healthcare providers, the patient, the cell collection process, the transport, the manufacturing, and product administration in often tight timelines. And even when the timelines can be interrupted using a freezing method, and thus simplifying parts of the value chain, the patients who are receiving these products are very sick and also have very complicated treatment schedules, where the administration of the cell therapy must be done within certain time periods of other medicines being administered

Cells are the critical raw material and have complex biological processes that are not entirely understood by science. The entire supply chain requires specialized materials to maintain cells at their optimum and defined temperature and within the tolerances considered acceptable for product quality and safety. Some of these steps can be quite lengthy and certain unit operations can take days and/or weeks to complete and must also be done by well-trained professionals. Every cell therapy process is unique and the companies in the industry are still trying to find the "best mousetrap." These therapies can sometimes cause severe side effects (for example, cytokine release syndrome) that require qualified medical personnel trained to be available for post treatment.

Finally, the coordination of value chain participants and activities is inherently difficult. The addition of real-world issues, such as scheduling patients into crowded apheresis sites, inclement weather, timeline changes due to patient health issues, and reimbursement data requirements increase the complexity to new levels. For small patient numbers and limited production volumes, it is complex, but with larger volumes in phase III clinical trials and beyond, the complexity and opportunity for error rises exponentially.

SE: The main challenge is that the entire healthcare supply chain is set up to land everything on a pin head. You're conditioning the patient, doing the screening, booking the bed, aligning your clinicians, getting the delivery in – perhaps via international shipment – of a critical sample, all at a specific time. It only needs one of those things to change – for example, a patient is too sick to start their conditioning or for less serious conditions, the patient is late for their apheresis, or for a storm hits and delays flights – and it can alter the entire supply chain.

How can improvements be made to the supply chain?

ML: I think we need to develop a standard protocol for the collection of starting material, as it would make it much easier to open new clinical centers; staff would already be familiar with the protocol rather than having to be retrained. It would also help companies developing therapies as they would have a starting point, rather than having to reinvent starting material collection protocols for each therapy. Clearly, some of the more established companies may be resistant to such an idea, given that they've spent a lot of time and money developing and then training their procedures – and they may argue that those processes are part of their intellectual property. But standardization would be great for the industry and, more importantly, expedite access to these therapies to larger patient populations.

"One mishap could mean a gravely ill patient missing their treatment. It's not easy, but you must build clusters of understanding throughout the entire supply chain."

PV: As cell therapies are scaled up and out, you have to introduce inbound and outbound logistics, often involving a manufacturing site that isn't located at the clinical center, which means every unit operation along the way has to scale. For a typical CAR-T process, an apheresis center may be handling tens if not hundreds of patients a week and as the process becomes more industrialized, it could become a major burden for the apheresis center. Having new standards and tools available to the apheresis center so that the process can be streamlined and simplified presents a major opportunity for improving cell therapy logistics.

And on the distribution side, as the therapy gets manufactured, packaged and cryopreserved for distribution back to the clinical center, there's another opportunity for better integration. By which I mean, integration of standards: making custody management software and approaches connect to all of the steps in the process, with complete custody and identity management.

HH: We also need better process characterization. These are

"You're conditioning the patient, doing the screening, booking the bed, aligning your clinicians, getting the delivery in – perhaps via international shipment – of a critical sample, all at a specific time."

When the logistics go wrong

By Matthew Lakelin, CSO, Trakcel

I know of one case where a company was using date of birth and initials to verify the identity of the patients as part of their traceability network. They happened to have two patients with the same date of birth and initials. And one patient received the other patient's treatment and became seriously ill as a consequence. You might say they were unlucky, but I would say they should have engineered out the mistake by having additional identifiers in their system.

Another interesting example is where a company lost around £800,000 worth of treatment because a parcel containing the drug substance (autologous, genetically manipulated cells) was left behind a reception desk over a weekend. The problem? The usual staff-member who dealt with deliveries was on holiday and the temporary replacement wasn't aware of the importance of the delivery and treated it like an Amazon parcel. This story demonstrates that the final mile is really important and companies must have the right systems in place.

complex biological entities (cells) in new types of processes. And although the industry in general is building its knowledge of this new class of therapy, we have a lot of work to accomplish before we truly understand what we are doing both at a cell functionality level and at a molecular/genetic level with these processes. It will be difficult to truly industrialize and/or optimize these processes until we understand the key attributes and know how to control them in the production processes.

Better analytical methods that go beyond cell expression/phenotypes and cytokine release of cell populations to the genomic level would also go a long way. We need better methods that interrogate the cells beyond the membrane. The most common means of analyzing a cell and measuring changes is via fluorescence-activated cell sorting (FACs) – also known as flow cytometry. FACs can determine what cell markers are expressed and how that expression may shift after certain manipulations. We need better and more real-time methods of measuring how a process may modify the genetics of the cells and how that relates to the cells' phenotype, metabolism, and biological functions.

SE: There's a lot governments can do to improve the infrastructure in place to deliver cell therapies. The UK's Advanced Therapy Treatment Centers (ATTCs) are good examples of this. The four centers will cover the majority of the UK population; and the idea is to bring clinicians from various NHS trusts, academics, as well as companies like GE and Trakcel, together to solve the challenges associated with manufacturing and distributing cell and gene therapy products. By putting the key stakeholders in a room, the hope is that the knowledge gained can be applied across the NHS and also internationally.

A key barrier to building a seamless supply chain is the lack of communication between silos. Things can work seamlessly in the manufacturing center, within the courier and in the hospital ward, but the real risk arises during the transitions. That's where the ATTCs may be able to bring people together to create seamless supply chains.

Another important concept that the industry needs to adopt is "logistics by design." Building on the quality by design approach that is an established part of the process development mindset. Developers really need to be thinking about how they're going to industrialize and commercialize their therapy as early as possible – as well as working with technical partners to make it a reality.

Where can technology help?

HH: I think digital management via cloud-based software platforms could bring great improvements. We need more tools to enable all the stakeholders to have easy access to their part of the process, as well as to allow for planning upcoming production and managing capacity. Further, paper processes are costly and error prone; not only are they ill-suited for this complex supply chain, but there is a limit to their effectiveness even at low volumes – and yet, some companies still use them.

ML: Indeed they do. It may seem obvious that introducing an electronic system is the way to go, but I know of at least one autologous therapy developer that uses a paper-based system for managing their patients. Each time their therapy is approved for use at a new treatment centre they have to increase the number of administrators. It isn't scalable and eventually eats away at your budget, as well as slowing down development because of the time spent recruiting specialist administrators.

If you're using a paper-based system, you'll have multiple documents feeding into a central location from the various treatment centers. Having a single technological solution that centralizes that documentation will make document control much easier and reduce the chance of administrative errors. From a compliance perspective, it will also allow you to demonstrate that the people managing the patients have been trained and you're only one mouse-click away from their profile showing what they can and can't do or sign for. From a traceability perspective, an electronic system with barcodes reduces the risk associated with transcription errors. Electronic

systems significantly reduce the number of admin staff required.

PV: Technology can help us make the unit operations more closed and thus less risky. For example, a clinical lab will have technicians, who use flasks and biosafety cabinets to perform manual manipulations. This is a completely open and labor intensive process where the technician could make a mistake. Not only that, but the technician will be required under GMP to record what they've done at every step of the process, which requires a significant amount of, often manual, data entry. Technology can help reduce the amount of human intervention – or touch points – involved in the process.

Do healthcare systems have the infrastructure in place to effectively deliver cell and gene therapies?

ML: There are some complex processes associated with administering or dispensing cell therapies. For example, it's important to get cryopreservation right because there's a risk that you might lose a half a million dollar treatment if you thaw the cells too quickly – or too slowly. There will need to be more pharmacies and staff able to cope with these complexities and accommodate the growing demand for cell and gene therapies.

HH: The majority of the medical centers that are approved to order (set up as an authorized prescriber by the therapeutic companies) and administer cell and gene therapies are motivated to use these products and want to be seen as leaders in the healthcare system. However, it appears that only about half of them have set up their own internal teams with defined procedures that enable the easy referral of qualified patients from other medical centers, proper data transfer to the order systems, patient support, and claims reimbursement procedures after infusion. Best practices for these internal medical centers are developing and should mature as these types of products begin to be more broadly administered and in greater volumes.

PV: Are they ready at the scale they're operating at today? Yes. Would they be ready for a sudden influx of new therapies? Not immediately. I do not think apheresis centers would be able to adhere to different specific procedures for a large number of different therapies, nor would clinical centers be able to cope with 10 or 20 different protocols on how to prepare samples for administration. As the number of therapies grows, standardization, as Matthew said earlier, will become increasingly important.

Infrastructure around the globe

By Heidi Hagen, Chief Strategy Officer and Co-Founder, Vineti

As noted in the main discussion, different parts of the world may need to approach cell and gene therapies differently. The US conducts product approval and medical practice under one set of laws; the FDA has legal authority, while the interstate trade and labeling considerations are decided at the federal level. This alignment streamlines the product development and commercial launch process. However, the country is large, which creates a challenge for individual therapies; the product may need to be transported a great distance or to rural areas in short time frames. Because of this issue, and the current CAR-T side effect protocol, there is a geographical bias in the distribution map. In the US, reimbursement is also complex and driven by each individual payor.

The EMA, on the other hand, is a cooperative agency that approves products for all nation states, but local nation states have their own language, regulatory, labeling, and reimbursement requirements beyond the original EMA approval. So, upon approval of the MAA (Marketing Authorization Application), therapeutic companies must still navigate the individual country regulations and sometimes obtain additional approvals.

In Europe, therapeutic companies typically take a tiered and prioritized effort to where they will conduct clinical trials or launch commercially. The higher prioritized countries are those that are early adopters with strong KOLs and a favorable reimbursement process for new and innovative therapies (typically, Germany, France, the Netherlands, Italy, and Spain are top) and other countries (for example, the UK, Greece, Norway) will be at the bottom of the priority list or not considered targets at all. So, geography bias also exists in Europe, but for different reasons.

In China, the CFDA usually mirrors the FDA in compliance policies and inspection principles. Reimbursement is a standard process and, as with other processes in the country, is overseen by the government. The country is often considered the most progressive innovator in the field, and perhaps the most daring too. The large population of China and their penchant for being early adopters are motivators for both Chinese companies and global companies to develop cell therapy products there. It is considered a current hotspot for cell therapies, and as China does not accept such products from outside of its borders, the company and the manufacturing facility must reside within the country.

Do you have an opinion on the centralized versus decentralized debate?

ML: The decentralized model is difficult from a regulatory perspective. To obtain local competent authority licensing for advanced therapy GMP manufacturing is challenging; so having a manufacturing facility located at each hospital is unfeasible at present, the complexity is exacerbated because for the decentralized model to be cost-effective these facilities must be able to manufacture several different ATMP products.

But the landscape may be different in ten years' time. There are technologies being developed where you can attach vessels containing starting material to a closed system manufacturing unit and with the correct reagents and viral vector two weeks later you get a therapy. In a perfect world, closed automated systems like this could be distributed to every specialist hospital in a country, which would remove the need to transport starting material and drug products over long distances. And it would also require a fundamental shift in the way regulators think about

these products. Perhaps the automated units would have to be licensed and approved as medical devices, with the viral vector classified as a medicinal product. Each individual hospital would then need a license to manufacture and you'd also need to monitor and compare manufacturing at all sites to prevent process drift, where different facilities might produce increasingly different products over time. So, there are a lot of hurdles to overcome, but decentralized manufacturing could solve a lot of logistical problems in the long-term.

PV: Philosophically, I'm agnostic as both models can work. It depends on the indication and the number of patients being treated. It doesn't make much sense to have multiple small centers producing only one or two types of therapies. But if the number of therapies rises significantly, a central facility might not be able to cope. It comes down to the scale of production.

HH: Centralized manufacturing of cell therapy products must exist with the industry in its current state. These products are still being scientifically characterized and understood, and this will continue for some time until there is a much larger database from a larger volume of production.

The earlier point about process drift is a good one. And I think decentralized manufacturing will only take off when the quality and safety of these products can be easily assured without complex procedures being performed by specialized personnel. And when the average medical technician in a medical center can reproducibly perform the manufacturing process in an aseptic manner with the proper in-line quality control tests. The manufacturing processes, the equipment, the characterization data and the analytical methods must mature to the level of "plug and play" before decentralized manufacturing can occur safely and reproducibly in medical centers.

SE: It's an interesting question and reminds me a lot of the autologous or allogeneic debate when I first got involved in the industry. It turned out that both were viable depending on the indication, patient population and geographical spread. I think the same will prove to be true regarding centralized and decentralized manufacturing models. A very important factor is the logistics platform. If you've got a cryopreserved inbound donation and a cryopreserved outbound donation, then it's possible, in theory, to treat patients across the globe from a centralized facility. But if you've got a fresh donation coming in then you might have less than 24 hours of viability. Such a constraint necessitates a more local, decentralized approach.

On the Cusp of Curing Disease

Welcome to the M Lab™ Collaboration Centers – where customers can use non-GMP lab spaces to operate equipment, evaluate processes and receive real-time technical support without disrupting production.

With Elizabeth Goodrich and Ranjeet Patil

What is your role at the M Lab™ Collaboration Centers?

Elizabeth Goodrich: I lead the Application Engineering team worldwide, and most of our projects are run in the M Lab™ Collaboration Centers. We don't work in product development, but we do work with products that are already launched to develop best practices and other useful information that we can deliver to customers to help them streamline their own process development efforts. Often, customers come into the M Lab™ Collaboration Centers so that we can address their specific concerns – they can also learn more about our products and test out different processing strategies. These labs are situated in nine different locations worldwide, so we can reach customers wherever they are.

Ranjeet Patil: I lead the vaccine and viral therapies group, which works with customers in a consulting capacity. Many customers come to the M Lab™ Collaboration Centers to look at our systems and hardware to get a feel for what would be a good fit for them. Gene therapy products are attracting a great deal of attention so my group talks to customers in this area.

What are the biggest needs of gene therapy manufacturers?

RP: There is now rapid growth in the pipeline and this translates to a need for speed. Speed to market is nothing new, but it resonates with gene therapy customers for a few different reasons. Firstly, many companies are targeting rare diseases – and, in many cases, patients won't have long to live without treatment. Secondly, many of these drug programs qualify for expedited approvals and other companies may be chasing the same targets. You may not have a viable business because there isn't a large population to go after if your competitor is first to market.

Given that companies want to get to market fast, many decide not to invest in a physical footprint and instead look for a CMO, but

capacity at such companies is extremely limited given how many people are developing gene therapies. On the other hand, even if a company wanted to expand and have their own manufacturing capacity, it is extremely challenging to build and effectively operate spaces suitable for gene therapy manufacturing. Infrastructure for any kind of viral process is significantly more expensive than for other classes of biopharmaceuticals. Although there is clarity on the clinical aspects of the process, the manufacturing aspects are challenging because there is no template approach – every process is different and regulatory guidance isn't straight forward.

What do the M Lab™ Collaboration Centers offer to customers?
EG: Many of the companies working on gene therapies are small – perhaps even virtual – so they have limited human and laboratory resources at their disposal. The M Lab™ Collaboration Centers can be an extension of their resources, giving them relevant tools to work with and a place where they can test new processing options.

We also have a full suite of single-use products available in the centers for customers to evaluate. Single use is a great option for gene therapy manufacturers because there is a huge need for sterility and eliminating the potential for cross contamination. Again, the M Lab™ Collaboration Centers are spaces where customers can visit to see what technology is available, receive hands-on experience, and test to see what will work for their process.

Finally, we offer a wide range of training for equipment, process strategies, and manufacturing strategies under different types of operating conditions. The M Lab™ Collaboration Centers can be used by the process development team to train new hires, and we also see training being delivered to manufacturing operators. If speed to market is critical, you don't want to have a product approved and then have a delay in getting the product manufactured. There have also been instances where customers come to us and we work side by side with them to create and test their process.

And how have customers responded to the M Lab™ Collaboration Centers?
RP: Feedback from customers has been excellent. Many developers of gene therapies are still in small research labs (many have been spun out of academia) – and the teams often under-estimate the real difficulties of manufacturing a therapy at scale. At the M Lab™ Collaboration Centers, the customer brings their understanding of their product and expectations for scale, and we contribute our expertise in each unit operation and our holistic understanding of the implications of certain processes for commercial scale manufacturing.

How is MilliporeSigma preparing for the future?
EG: Gene therapies could dramatically change world health, and will also cause a shift for companies like ourselves. We need to contribute product and application expertise to ensure that these therapies are manufacturable to high safety and quality standards. This also needs to be done in a cost-efficient manner so that patients can access these important treatments.

RP: Product and technology innovation is very important to MilliporeSigma. We are looking at purpose-built tools for gene therapy manufacturers, such as more productive cell lines, more efficient downstream tools, and the biosafety testing services to consistently satisfy regulatory expectations. We are also working to understand how we can become a better business partner for gene therapy developers, as well as other players in the ecosystem, such as other CMOs.

Elizabeth Goodrich is Director of Global Applications Engineering within Manufacturing Sciences and Technology, and Ranjeet Patil is Segment Head, Vaccines and Viral Therapies, both at MilliporeSigma.

Heading to the Clinic

With Michael Mercaldi, Ph.D, Director Purification Process Development at Homology Medicines.

Homology Medicines is a gene therapy and gene editing company that was started based on the discovery of 15 novel adeno-associated viruses (AAV) naturally found in human hemopoietic stem cells (AAVHSCs). This set of novel serotypes enables the selection of optimal AAVHSC capsids for genetic medicines that exhibit differentiated biodistribution, lower immunogenicity and enhanced potency compared to other AAV serotypes. We have discovered that AAVHSCs can perform nuclease-free gene editing in addition to gene transfer. The gene editing capability of these AAVs was shown to harness the mechanism of homologous recombination, the body's natural DNA repair process. This is different than other gene editing technologies (i.e., CRISPR, ZFNs, etc.), which require a nuclease to cut the DNA and, in doing so, promote another DNA repair pathway called non-homologous end joining, or NEHJ, a more common yet error prone process. Homologous recombination-based gene editing has shown to be highly efficient and precise, and utilizes a single component system (i.e., one vector, one construct), making it a more straightforward method.

Currently, we are moving toward the clinic with our lead gene therapy construct, HMI-102. HMI-102 is designed to treat and potentially cure phenylketonuria (PKU) in adult patients.

There are many challenges in the gene therapy space. Leveraging the industry's experience with proteins (mAbs) is a great start to manufacturing gene therapies, but it's insufficient, and in some cases provides counter-productive directions. Unlike mAbs and recombinant proteins, where there is a 30 to 40-year bedrock of understanding on how to efficiently and effectively design and produce these therapies, the industry is only just beginning to learn how to do this with AAVs. To this, we feel that the big drivers to advance the field are to increase upstream and downstream productivity, develop more in-depth analytical methods, and to drive development of more specific AAV raw materials and equipment.

At Homology, we are building our own internal process development and GMP manufacturing capabilities and to this point we understand that it requires collaboration among Homology and key partners to solve the challenges in this field. We decided to visit the M Lab™ Collaboration Center this year to work with MilliporeSigma on developing some of our platform manufacturing processes for our AAV therapies. We found MilliporeSigma to be extremely helpful with identifying equipment and consumables that we are testing and may want to implement in our new facility. Their expertise and openness toward collaboration has been very valuable for us as we build out our pipeline and capabilities.

Revolutionizing Medicine – While Learning "Novartian"

Sitting Down With... Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy, Perelman School of Medicine, University of Pennsylvania, USA.

How would you characterize the cell and gene therapy field when you first entered it?

When I finished my graduate work, there wasn't really a cell and gene therapy field to speak of. We had to build one from the ground up. During my postdoctoral fellowship, I was asked to create a lab that would grow T-cells for an immunotherapy trial with HIV. There wasn't a roadmap, but we managed to figure it out and eventually treat 10 patients with their own expanded T-cells – increasing CD4 counts and CD4 ratio in immune function. We then used the technology to grow T-cells in other settings – namely, cancer and post-stem cell transplant.

How did your career progress from there?

In the late 1990s, a company called Cell Genesys performed the world's first Chimeric Antigen Receptor (CAR)-T cell trials. They found that, using an older ex vivo T-cell culture method, T-cells could enter the body but would subsequently disappear. They came to us because of the work I had done in creating an efficient and potent way to stimulate and grow T-cells. We worked day and night, and eventually published the first anti-viral vector clinical trial in humans for HIV in 2000. Around that time, we went to the University of Pennsylvania to do clinical trials in cancers. We had two avenues we could pursue. One was to try and increase the number of tumor specific T-cells – and we found that we could combine vaccination and adoptive transfer of T-cells to increase immune function via that pathway; the other was to obtain the gene vector for the CD4 zeta CAR that Cell Genesys had used in their HIV patient trials. In early 2004, the latter line of investigation sparked an application to a small philanthropic organization called the Alliance for Cancer Gene Therapy to begin the pre-clinical work for a CAR-T trial in cancer targeting CD19.

The work culminated in treating the first three patients with CAR-T cells in 2010. But it was another 15 months before we were able to treat the fourth patient because of a lack of funding. We were so far from conventional thinking in research funding and we were rejected by the NIH several times.

While this was going on, we also continued to work on HIV. A company called Sangamo Therapeutics came to Carl June with the idea of editing genes using zinc finger nucleases. I clearly remember the moment when Carl came into my office and told me about the idea, which was crazy given the company's low gene editing efficiency in preclinical to date. But we gave it a shot to see if we could substantially increase the gene editing efficiency to make it work. These studies led to the first ever gene editing trial in humans. Since then, we've continued to do first-in-human trials, lentivirus, gene editing – and we're currently doing the first CRISPR trial outside of China.

How has the cell and gene therapy field changed over the years?

Just look at the number of delegates at the International Society of Cell and Gene Therapy (ISCT) annual meeting every year, and at publications like Time Magazine featuring Carl June as one of 2018's top 100 most influential people. The field has certainly percolated beyond a small niche group of investigators. Years ago, we would go to conferences and our sessions would be on the last day in a room nobody could find. The attitude of the scientific community at that time was, "That's kind of cute, but we'll continue doing what will actually impact patients." Things have changed following the first approvals, but it's still early days. Really we're at the "Model T" stage of this technology, and it will take time to automate and for it to be more widely accessible.

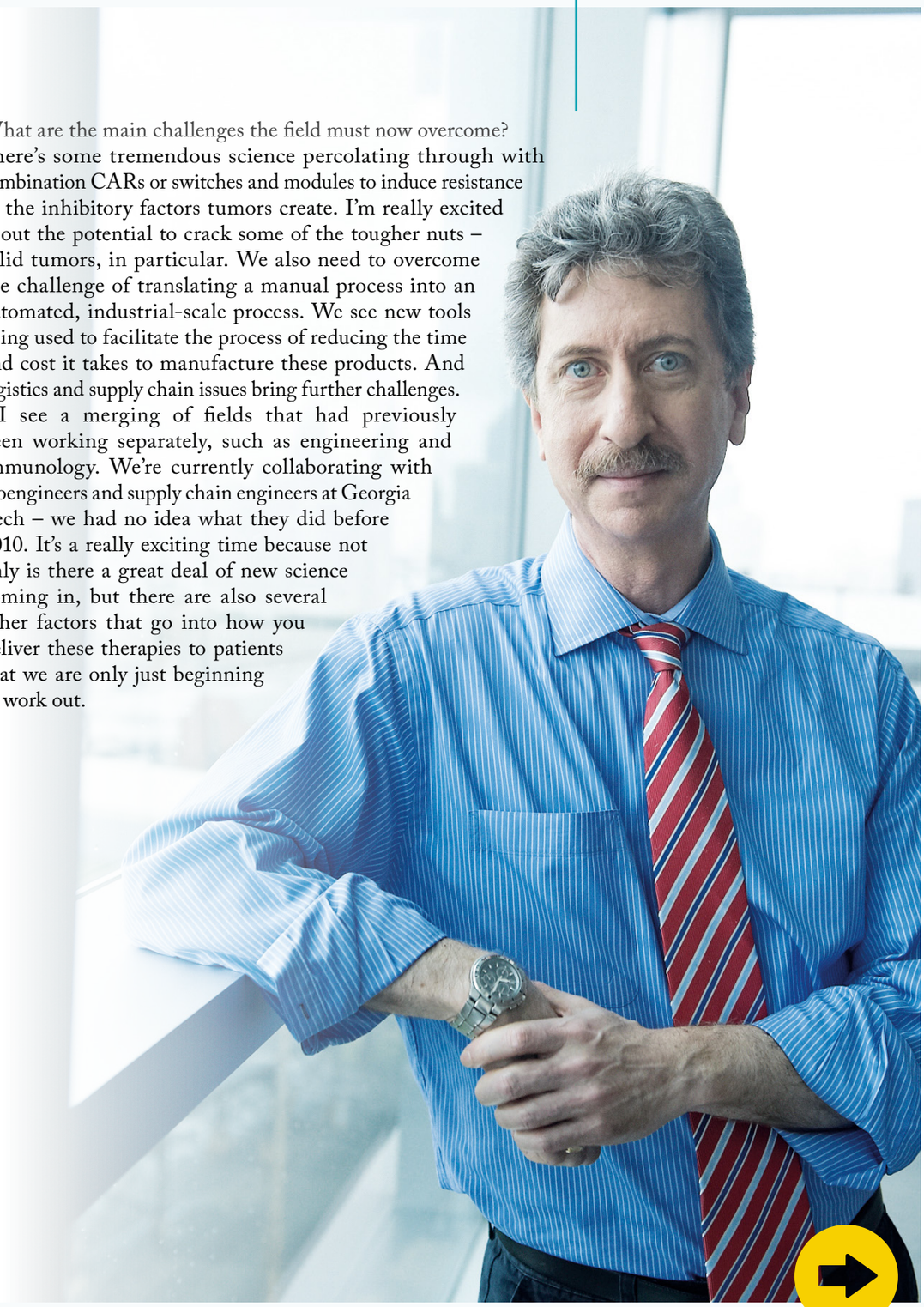
What have you learned through working with big pharma companies?

I learned how to speak Novartian! There's a way of doing things and a kind of language that you must use with big pharma. But we also taught them what a T-cell is, and what dosage means if you're administering a dividing drug – the pharmacokinetics are very different compared with something like Gleevec. It's been interesting in that respect. Back in 2010, we were speaking to a number of different entities of all shapes and sizes, but we felt that Novartis, with their experience in oncology and global clinical and regulatory expertise, was ethically the best choice to develop the therapy fastest with patient access in mind.

What are the main challenges the field must now overcome?

There's some tremendous science percolating through with combination CARs or switches and modules to induce resistance to the inhibitory factors tumors create. I'm really excited about the potential to crack some of the tougher nuts – solid tumors, in particular. We also need to overcome the challenge of translating a manual process into an automated, industrial-scale process. We see new tools being used to facilitate the process of reducing the time and cost it takes to manufacture these products. And logistics and supply chain issues bring further challenges.

I see a merging of fields that had previously been working separately, such as engineering and immunology. We're currently collaborating with bioengineers and supply chain engineers at Georgia Tech – we had no idea what they did before 2010. It's a really exciting time because not only is there a great deal of new science coming in, but there are also several other factors that go into how you deliver these therapies to patients that we are only just beginning to work out.



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The emergence of cell therapy as a frontline treatment for challenging diseases, including cancer, is rapidly changing the healthcare landscape. Our Cell Therapy business provides the tools, technology and processes to enable customers from pharmaceutical manufacturing as part of our Cell Processing segment, to clinicians and technicians in our Cell Banking and Point of Care business segments. We are investing in the field for the long-term, and partnering with pharma, biotech and clinical researchers. GE brings expertise in quality, global distribution, research and development and regulatory that will transform cell therapy from small-scale treatment to a globally-accessible personalized medicine.

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At Lonza Pharma & Biotech we provide contract development and manufacturing services that enable pharma and biotech companies to bring medicines to patients in need. From the building blocks of life to the final drug product, our solutions are created to simplify your outsourcing experience and provide a reliable outcome, at the time when you expect it. Our extensive track record includes commercialization of pioneering therapies and manufacturing of a wide variety of biological and chemical drugs. We continuously invest to solve not just the current, but also the future challenges. Together, we can bring your next medicine to life.

www.pharma.lonza.com

Lonza

Pharma & Biotech

MilliporeSigma is skilled in the art of GMP viral vector production and technology innovation, having manufactured viral vectors for over 20 years. We have produced more than 500 lots of drug substance from preclinical through Phase 3 and commercial production. Our M Lab™ Collaboration Centers are non-GMP labs that allow gene therapy manufacturers to operate equipment, evaluate processes and receive real-time technical support without disrupting production. Customers can explore our comprehensive portfolio of products and learn how these cutting-edge technologies can help them quickly reach their process goals.

Our BioReliance® Testing services employ the broadest range of vector types to speed progress of gene therapy development. Full characterization, potency, analytics, safety, and stability testing combine to ensure safe therapies for patients awaiting treatment. Our expertise and regulatory knowledge are key in helping developers gain regulatory acceptance of CMC.

MilliporeSigma's unique range of products and services for viral and gene therapy production and testing help tackle the industry's commercialization challenges.

Visit our M Lab™ Collaboration Centers:
www.emdmillipore.com/mlabs

Learn more about our Gene Therapy and Viral Vaccine Contract Manufacturing:
www.bioreliance.com/us/services/biomanufacturing-services/gene-therapy-viral-vaccine-contract-manufacturing

Explore our BioReliance® Testing services:
https://www.bioreliance.com/us/services/biopharmaceutical-services

MilliporeSigma

Sartorius Cell & Gene Therapy Manufacturing Solutions

• Single-use bioprocess technologies
• Integrated scalable solutions
• Intelligent equipment and analytics

As a trusted global solution provider within the biologics industry, Sartorius is well positioned to support the development and manufacture of your cell and gene based therapies. We understand the need for technology and service solutions that provide process automation, integrity, standardization and are supported by a robust supply chain.

Our extensive portfolio of upstream and downstream products for both cell and virus production enable the development of comprehensive workflows from research through to commercial production. This portfolio can be applied to both allogeneic and autologous advanced therapies.

Our robust single use systems, intelligent equipment, bioanalytics, and testing capabilities can help accelerate the development of your advanced therapies.

Contact us to see how we can help support your process development and manufacturing goals.
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