Enabling a Healthier World

Lonza
Cell & Gene

Starting with the End in Mind:

Overcoming Challenges in Cell and Gene Therapy

In recent years, the benefits of cell and gene therapy have progressed far beyond experimental treatments to a rapidly growing global market. As of May 2021, there were 522 gene therapies available in the clinic with additional 1,745 in preclinical or clinical development (source: Pharmaprojects, Informa, July 2021). Likewise, there were 771 non-genetically modified cell therapies and more than 600 RNA therapies in development (preclinical to pre-registration).

For those working in such a rapidly growing field, whether as part of big pharma, small biotechs or as part of academic teams, what are the challenges being faced, what trends are being seen, and what are the future directions for cell and gene therapy?

Here we draw on insights from the **Lonza European Cell and Gene Therapy Workshop 2021**, where international experts shared their views and discussed the most pertinent issues.

Contents

Starting with the end in mind

As the field of cell and gene therapy has progressed from experimental research to creating a menu of established cell and gene therapies, many researchers are learning the hard way that not establishing a clear view of how their proposed therapy will be used in patients, makes later development stages very difficult and time consuming.

> "Starting with the end in mind is important for any therapeutic, but this is particularly true for advanced therapy medicinal products (ATMPs), such as cell or gene therapies, due to the complexity of their science, production and preclinical and clinical development. Developing ATMPs brings many unique and complex challenges, wherever you are on the path from discovery to commercialization."
>
> **– Michela Gabaldo, PharmD**

Contributors

Dr. Reuben Benjamin
Consultant Hematologist, King's College Hospital, London, UK

Dr. Vincenzo Di Cerbo
Lead Technical Scientist, Cell and Gene Therapy Catapult, London, UK

Michela Gabaldo, PharmD
Translational Project Management & Regulatory Affairs, Fondazione Telethon, Milan, Italy

Prof. Dr. Dr. Ulrike Köhl
Director of Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig, Germany

Dr. Rhys Macown
Lead Scientist, Cell and Gene Therapy Catapult, London, UK

Dr. Qasim Rafiq
Associate Professor, University College London, Department of Biochemical Engineering, London, UK

Michael Riedel, PhD
Senior Manager Business Development, Lonza Cell & Gene, Cologne, Germany

Contributed information has been provided during a roundtable discussion at the **Lonza European Cell and Gene Therapy Workshop 2021**. For more information about this event and Lonza's solutions for cell and gene therapy workflows:

Visit **www.lonza.com/products-for-cell-and-gene-therapy**

One particular minefield to navigate is the multilayer legislation that must be fulfilled. Currently, this is complex and not standardized between different pharmacopeia and different therapy types, which can pose numerous challenges. While many dream of commercializing a new cell-based therapy, it is easy to underestimate the hurdles on the path to success. Knowing from the outset which legislation you must fulfil can help streamline this process.

Of course, starting with the end in mind is vital when it comes to manufacturing too. During early-stages, scientists are not focused on material being available at GMP-compliant quality and tend towards accessible manual processes. However, as research scales up into manufacture, the production costs continue to accrue due to this reliance on manual processing.

> **"Talking to my early-stage clients... I learned that quite often academic, manually focused manufacturing processes are being used for clinical trial manufacturing. This is expected and understandable but manufacturing needs to be set up in a way so it can be scalable, cost effective and safe once the drug is approved for commercial manufacture"**
>
> **– Michael Riedel, PhD**

When it comes to the manufacture of cell and gene therapies, there are different approaches that can be taken. One is to use a centralized manufacturing unit, an approach often favored by the pharma industry. The other is de-centralized manufacturing, which is often the preferred route when therapies are developed by academic hospitals.

> **"I have experience of both a centralized manufacturing unit [where we have now produced more than 500 CAR-T cell products] and de-centralized manufacturing [running small clinical trials on university projects]. And, in my opinion, we need both in the future."**
>
> **– Prof. Dr. Dr. Ulrike Köhl**

There is a strong case for using centralized manufacturing due to the economies of scale this provides. On the other hand, de-centralized manufacturing at hospitals, benefits from researchers contributing innovative knowledge relating to genome editing (such as transposon and CRISPR mediated knock-in) in early clinical trials. However, the complexity of scaling up is frequently underestimated by many laboratories who are overly reliant on manual processes. In addition, they often do not appreciate the time and financial demands of GMP, including implementing a new way of working.

Already at early stages of development, many organizations seek process development and manufacturing help from a CDMO. This support can vary from slight adaptations of the existing process to full revision in order to achieve GMP compliance. More established companies will often seek help to address particular technological bottlenecks or processing challenges. For others, greater focus may be put on scaling up or scaling out production. Regardless of the type of organization and their priorities, the importance of starting with the end in mind is becoming ever clearer.

Does the future lie in autologous or allogeneic therapies?

A common question in the cell and gene therapy space remains whether autologous or allogeneic approaches offer the best way forward, with both bringing their own benefits and disadvantages.

Certainly, autologous approaches have proven to be very successful. By using the patient's own cells, you eliminate a number of risks and possible rejection of the therapy. However, taking cells from an ill and possibly pre-treated patient can have an impact on the quantity and quality of the cells available, which in turn makes manufacturing the therapy more challenging. In addition, with autologous therapies, batch sizes tend to be small, which make such therapies more expensive to produce. Some in the industry propose that manufacturing autologous cell therapies in decentralized manufacturing centers close to the patient, would help drive costs down.

Alternatively, allogeneic therapies take cells from a donor and following modification, these are transplanted into potentially many patients. By using donated cells, each patient is spared the extraction process making allogenic cell therapies a gentler procedure. Furthermore, the cells derived for allogenic therapies are healthier and more tolerant of *ex-vivo* manipulations. However, to avoid rejection of the 'foreign' donor cells, immunosuppressants are delivered to the patients, and this can be a potential barrier to the broader adoption of allogeneic therapies. Additional methods of engineering allogeneic CAR-Ts are being explored to reduce the amount of immunosuppression required, so allogenic cell therapies may be better tolerated in the future with further technological advances.

> **"Ultimately we've seen huge success with autologous CAR-Ts and that will only improve over time. Yes, there is an issue about the current price point and the manufacturing strategies that we employ, but I think a lot of the cost of autologous CAR-T therapies at the moment on the market is down to the cost of development, not necessarily the cost to manufacture. The cost of manufacture will come down."**
>
> **– Dr. Qasim Rafiq**

Allogeneic approaches offer further financial benefits in terms of economies of scale akin to recombinant protein production. However, we're not likely to see autologous therapies being replaced by allogeneic therapies. They are going to remain the backbone of cell therapies for a long time to come. Many specialists feel that we will move away from that dichotomy of autologous versus allogeneic but will establish a sector that enables and supports both. It may be possible to develop allogenic "backbones" for cell therapies, and then personalize them with autologous modifications specific to the cancer type and patient genetics.

Is this the end for viral gene delivery methods?

Today's researchers have many different genetic material delivery options in their toolbox and while viral methods are generally considered to be 'tried and tested', there are many non-viral technologies that are gaining traction in the field. Drivers for exploring a non-viral approach are frequently costs for viral vectors and safety issues as well as a lack of flexibility in regards to the payload transported by viral vectors.

Several cell therapeutic approaches require quite complex transfection scenarios so having a range of transfection methods to turn to can be beneficial. Physical transfection methods including electroporation and Nucleofection® need to be mentioned here as well as chemical transfection methods. The latter include the use of nanoparticles, which have been in the spotlight most recently due to their use in COVID-19 vaccines.

> **"We have been seeing a massive traction in non-viral delivery technologies and recently we have been scoping a series of technologies present in the market. There is a list of over 50 different types of [non-viral] technologies available at the moment. The first approach taken by developers is often that of viral gene-delivery because: is the most established; there is more data available; and is the one people are most confident about. Nonetheless, I believe in the near future we will see a shift towards different types of gene delivery approaches."**
>
> **– Dr. Vincenzo Di Cerbo**

There remains an ongoing debate in the industry about whether viral or non-viral gene delivery methods offer the best solutions, but it is important to note that this isn't a one-size-fits-all situation as different non-viral delivery approaches may work differently depending on the type of payload or the cell type. For example, viral transduction suffers from a lack of flexibility when it comes to size of the payload, and some viral vectors may be unable to direclty deliver larger constructs, including some Cas proteins and transposases.

When it comes to clinical use, the cost of generating clinical grade viral vectors is significant. In fact, this cost can put it out of reach of those with budgets restricted by research grants – and this has the potential to limit clinical innovation. Furthermore, the huge treatment cost has an impact for the healthcare system and could limit the number of patients who can benefit.

> **"We had a lot of experience with TALENs and the transfection of TALENs in the construction of an off-the-shelf product that we were working with in a study. And I have to say that there's huge variability in the process; the batch-to-batch variation that we were seeing was enormous. So, in this case, there was a pharmaceutical company manufacturing the product, and they would go through several batches where the product failed QC and could not be used for the study."**
>
> **– Dr. Reuben Benjamin**

A further factor increasing viral vector costs is the small number of companies that have both the capacity and expertise to manufacture them. In 2017, the New York Times reported on the global lack of capacity with gene therapy companies booking viral vector manufacturers years in advance. However, an increasing number of companies Lonza included have invested heavily in this space with the likely effect being a normalization of cost over the next years.

The workshop panel agreed that a broad spectrum of different transfection technologies are needed, depending on the disease and depending on the treatment protocol.

A key role for automation

It is well recognized across all industries that automation brings a lot of benefits to manufacturing, and has been responsible for driving improvements in efficiency, quality, safety and cost-effectiveness. At the Lonza European Cell and Gene Therapy Workshop 2021, delegates showed that they overwhelmingly felt that automation was important for the future of manufacturing cell and gene therapies also.

To date, the unique challenges presented by cell and gene therapies have meant that scalability and automation have yet to be widely achieved. Many manual processes are still being employed for clinical manufacturing, especially in academia.

> "The evolution of advanced therapies and the advanced therapy space is very different to biologics. Biologics was always very industry or therapeutic company-driven whereas in this space it's very clinically and academically driven. And I think that is a strength in many ways because we have some fantastic innovation – but it also provides some barriers in terms of trying to adapt and scale a process that at this stage is clearly not scalable."
>
> **– Dr. Qasim Rafiq**

There are many ways in which automation can be considered for manufacturing ATMPs. At the most basic level, robotics and sample handing can be introduced into the process to replace some manual tasks, ideally focusing on those that cause the most variability of the product. At the opposite end of the automation spectrum is end-to-end automation, where robotic systems perform every task from sample preparation to final formulation. Offering something of a middle ground, an alternative manufacturing model is a modular system with some automation and some manual processes. Each model has its pros and cons, but in general, the more automation can be introduced into manufacturing, the more consistent a product is, and can be made at a cheaper cost. The ideal manufacturing workflow will also include advanced analytics and quality systems, so the manufacturing bottleneck is not simply moved downstream.

Beyond automation of the production process, it's important to also consider how we actually process information to make real-time decisions that support manufacture. Here, smart process development options include looking at different expansion technologies and establishing Quality by Design (QbD) principles. QbD has been used in biopharma production for 15-20 years and it provides a good framework for extending the design space.

> "Many in the industry have a passion, which I share, in using autonomous decision making, bringing in process analytical technologies – the on-line, in-line and at-line analytics – so we can not only remove the operator variability but also perhaps react to the variability and starting material and reduce how that variability is passed through to the final product."
>
> **– Dr. Rhys Macown**

> "For analytical assays, it is important to improve the throughput and to include assays that are on-line or at-line, really providing quick results... It is important to introduce automation in all steps to subsequently remove the analytical bottlenecks."
>
> **– Dr. Vincenzo Di Cerbo**

Automation coupled with data integration brings the opportunity to reduce costs by reducing process time – spending less time in the clean room and spending less time in manufacturing , spending less time with quality control reduces the costs significantly – and also by reducing reagent utilization and manpower. There is a significant role for automating in this space and further work will be needed to fully develop the systems that will truly support this.

Conclusion

The cell and gene therapy market has grown significantly over recent years, and this shows no sign of abating. New methods and technologies have been employed to develop unique therapies, and researchers have more tools at their disposal than ever. However, for companies to successfully commercialize cell and gene therapies, they need to be starting with the end in mind. Failure to do so can prolong development times and make scale-up and manufacture cumbersome, costly and difficult.

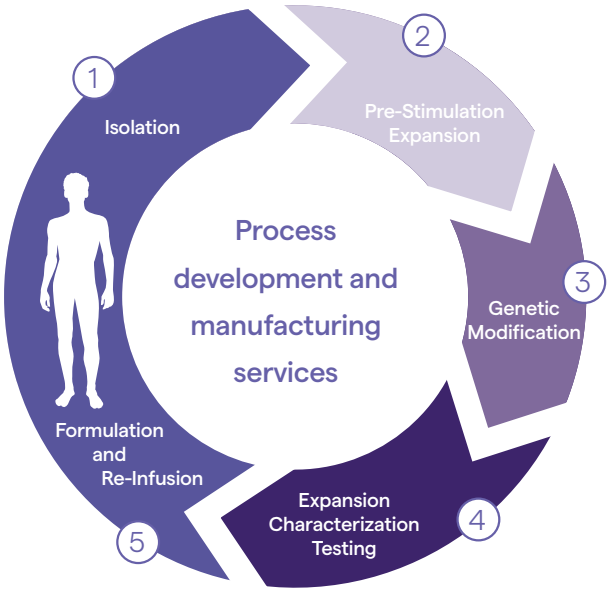
This is an important part of the work Lonza takes on when partnering with customers – helping our customers to set up a workflow early on that will be scalable and quality controlled to meet strict regulatory requirements at a later stage. We can advise on automated manufacturing solutions, data integration and provide workflow solutions for almost any step in the ATMP workflow from development to commercial manufacturing.

Given the pace of developments in the cell and gene therapy space, the market is seeing constant change, and new challenges will continue to arise. Communicating and sharing knowledge across the industry is vital and we would like to thank all the speakers at the **Lonza European Cell and Gene Therapy Workshop 2021** for openly and passionately sharing their expertise. To keep the conversation going, stay tuned for future events.

For more information on overcoming the challenges you may experience in your cell and gene therapy commercialization journey, download our ebook.

'The Cell and Gene Therapies Journey from Translation to GMP Production and Commercialization'.

Your partner for accelerating your cell and gene therapy



lonza.com/products-for-cell-and-gene-therapy

2, 4
TheraPEAK® Media and Reagents

3
TheraPEAK® Nucleofector® Products

2 – 4
The Cocoon® Platform

4, 5
Endotoxin testing solutions

4, 5
MODA® Solutions

1 – 5
Cell and gene therapy development and manufacturing services

PD, T
Primary cells and tissues for Process Development (PD) and Training (T)

Contact us

North America

Customer Service: + 1 800 638 8174 (toll free)
order.us@lonza.com
Scientific Support: + 1 800 521 0390 (toll free)
scientific.support@lonza.com

Europe

Customer Service: + 32 87 321 611
order.europe@lonza.com
Scientific Support: + 32 87 321 611
scientific.support.eu@lonza.com

International

Contact your local Lonza Distributor
Customer Service: + 1 301 898 7025
Fax: + 1 301 845 8291
scientific.support@lonza.com

Lonza Walkersville, Inc. – Walkersville, MD 21793

All TheraPEAK® Products are produced according to applicable GMP standards and follow the USP/EP guidance for cell and gene therapy raw materials. It is the end user's responsibility to ensure full compliance with local regulations in terms of safety assessments and effective removal prior to patient exposure.
All trademarks belong to Lonza, registered in USA, EU or CH or to third party owners and used only for informational purposes. The information contained herein is believed to be correct and corresponds to the latest state of scientific and technical knowledge. However, no warranty is made, either expressed or implied, regarding its accuracy or the results to be obtained from the use of such information and no warranty is expressed or implied concerning the use of these products. The buyer assumes all risks of use and/or handling. Any user must make his own determination and satisfy himself that the products supplied by Lonza Group Ltd or its affiliates and the information and recommendations given by Lonza Group Ltd or its affiliates are (i) suitable for intended process or purpose, (ii) in compliance with environmental, health and safety regulations, and (iii) will not infringe any third party's intellectual property rights. The user bears the sole responsibility for determining the existence of any such third party rights, as well as obtaining any necessary licenses. For more details: www.lonza.com/legal.

CT-SP010 12/21

lonza.com/products-for-cell-and-gene-therapy