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SPOTLIGHT

Decentralized and distributed advanced therapy manufacturing

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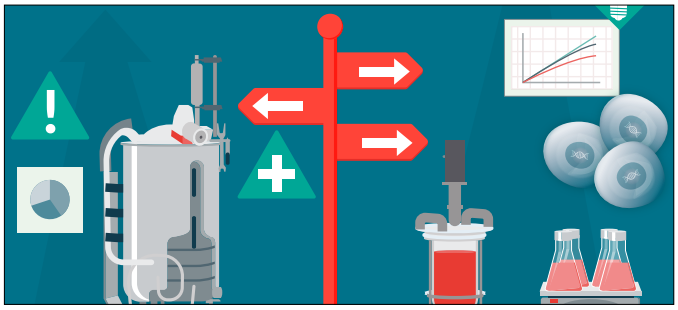

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

EXPERT INSIGHT

Enabling decentralized manufacture for cell and gene therapies

Francis Galaway

The MHRA put legislation for decentralized manufacture before the UK parliament in 2024. The statutory instrument amendment to Human Medicines Regulations 2012 (S.I.2012/1916) ('the HMRs') and the Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I. 2014/1031; 'the 2004 Regulations') will come into force on July 23, 2025. This legislation is in response to developments in technology that the MHRA considers challenging to regulate under the current legislation which is based upon a centralized manufacturing model. Traditionally, a medicinal product or investigational medicinal product is manufactured at a central factory site and distributed from there to administration sites. In the case of cell and gene therapies, this can involve patients travelling to a specialist care center both for cell or tissue sourcing and then for administration of the drug product. There is a growing burden on health care professionals at either end of the treatment requiring specialist knowledge and experience with personalized medicine. The manufacture of autologous therapies is challenging to synchronize with related treatment for the patient. The distribution model is also strained for cell and gene therapies by shipping between sourcing centers and the manufacturing site then back to a treatment center often across national borders and different regulatory regimes.

The new legislation attempts to address these practical problems for developers, manufacturers, patients, and healthcare institutions by providing another regulatory option to adopt new technology. It supports the safe development of medicines that need to be scaled out to manufacture and supply close to patients. It builds upon the existing regulatory framework and expectations for authorized, investigational, and unlicensed medicinal products.

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HUB AND SPOKE MODEL

The new regulatory framework allows for a license holder to adopt a 'hub and spoke' model for manufacturing a medicinal product or investigational medicinal product [1]. Provisions for unlicensed medicines and 'Specials' are also included. The 'hub'

is named as a control site in the legislation. It is responsible for ensuring the quality, safety, and efficacy of the product, interacting with the regulatory authority, and maintaining the master file that describes all the 'hub and spoke' activities. The 'spokes' are manufacturing sites located close to patients, which produce the drug product. They are supervised by the control site and listed in the master file. The 'spokes' can either be point of care (PoC) or modular manufacture (MM) units and can number in the hundreds. The decentralized manufacture framework has been divided into PoC and MM with provisions for each in the legislation. These are distinct models for decentralized manufacture (DM) but can often be referred to collectively as they share many regulatory expectations.

ELIGIBILITY

The applicability of the new regulatory framework to cell and gene therapies will largely depend on technological developments. It is to be used to supplement centralized manufacture in cases where the current model is not feasible.

To obtain a PoC manufacturer's license the applicant will have to justify to the MHRA that the product can only be manufactured at or near the place where the product is to be used or administered. This would typically be because the starting materials or finished product have a short shelf life (less than an hour) or for essential clinical reasons. The regulatory framework allows for a scenario in which the product needs to be manufactured in the same room as the patient such as an operating theatre.

To obtain a modular manufacturer's license the applicant will have to justify to the MHRA that, for reasons relating to deployment, manufacture in modular units is necessary. This could be because there is a clinical benefit or for public health requirements. The justification may feature improved efficacy or improved tolerability for patients when the product is manufactured in modular units at hospitals. An autologous therapy such as a CAR-T product with a prevalent indication has the potential to show improved benefit to patients if deployed in this way.

These two designations will be available for investigational medicinal products as part of clinical trial applications (CTAs), for marketing authorization applications (MAAs) and could be used for Specials manufacture. The PoC or MM manufacturing license can be added by variation to an existing MIA, MIA(IMP) or MS license which will trigger an inspection of the site.

The separation of decentralized manufacture into PoC and MM licenses is probably to the advantage of cell and gene therapies at this point in technological development. Currently, it is not apparent that cell and gene therapies could justify the PoC license on the basis of a short shelf life nor is there the standardized technology for rapid manufacture in a scenario such as the operating theatre. In future cells could be taken from a patient, manufactured into a medicinal product, and returned to that patient all during a single surgical procedure in a single room under the new legislation.

However, the need to scale out the manufacture of cell and gene therapy products is frequently apparent. The personalized nature of many of them precludes the traditional manufacturing approach with scale up during development. The new framework for MM facilitates scale out with a large number of smaller sites that can be redeployed all on the same MM license. These could be located within hospitals and healthcare clinics. If this will benefit patients through access to an innovative medicine with less burdensome treatment and better outcomes then the use of the decentralized manufacture can be justified to the MHRA. In future, the PoC license for manufacture close to the patient with immediate administration could become applicable to cell and gene therapies as

technology develops; the legislative framework is designed to accommodate such future scenarios.

REGULATORY EXPECTATIONS

The control site and all the spoke manufacturing sites must be GMP compliant. There is fundamentally no difference from current GMP expectations for ensuring safety and quality. However, the MHRA will not be inspecting every spoke site on a PoC or MM license. The primary mechanism of ensuring GMP compliance at every site listed on the master file will be through the control site and qualified person activities (which must be described in detail on the master file). The MHRA will conduct inspections as currently practiced at the control site and in a risk-proportionate manner with the spoke sites. This could mean that the first few spoke sites listed on the master file at the time of a clinical trial or marketing authorization application are inspected while further site additions are not inspected because the ability of the control site to ensure GMP compliance has been demonstrated. The control site will be responsible for knowledge transfer and training of staff at spoke sites.

All of the information on the control site and the spoke sites will be organized in a PoC or MM master file—collectively referred to as Decentralized Manufacture Master File (DMMF)—for the named (investigational) medicinal product. This follows the principles of the plasma master file system. The DMMF will list every manufacturing site but the clinical trial authorization or marketing authorization will only name the control site. This is to avoid the regulatory burden of potentially hundreds of sites in decentralized manufacture appearing on the authorization. The master file owner will be able to add, suspend, or remove spoke sites according to an authorized procedure without notifying the MHRA. The DMMF will list the activities of each site in detail. The key information it contains will also include: a description of the manufacturing, assembly, and release process at each spoke site; the arrangements for supervision and control by the license holder at each spoke site; the arrangements for reporting suspected adverse reactions from spoke sites to the control site. The DMMF will be submitted to the MHRA routinely for review. The MHRA will need to be notified of material alterations to the control site or spokes such as a change of location or named personnel.

The expectations for pharmacovigilance under a PoC or MM license are probably already familiar to those developing cell and gene therapies such as the need for follow up and registries. The pharmacovigilance system master file must have the details of the control site and spokes. A critical concern for cell and gene therapy products will be traceability. In the case of PoC manufacture, there will probably be no labelling of the product to facilitate immediate use. The added complication is handling the information coming in from all the spoke sites. At the time of a clinical trial or marketing authorization application, the MHRA will need to be convinced that the quality, safety, and efficacy of the medicinal product can be effectively monitored at all spoke sites.

Just as with the addition of a new manufacturing site in a conventional operation, the comparability of spoke sites to the control site will need to be demonstrated. The procedure for demonstrating comparability will be described in the DMMF. At the point of a clinical trial or marketing authorization application, the license holder will need to demonstrate comparability between all the manufacturing sites on the DMMF and the ability to add sites that manufacture comparable medicinal product. This is liable to be a difficult—but not insurmountable—challenge for cell and gene therapies. It will require an excellent understanding of the product and its manufacturing process

from early in development. The principles of an enhanced approach as described in ICH Q8 will be required both at CTA and MAA submission.

If the principles of an enhanced approach and quality by design are applied, then the challenges of product release should also be surmountable. The difficulties of a QP at the control site certifying batches for release from a spoke site—for immediate use in a PoC scenario—are not unique to cell and gene therapies. But they face additional challenges related to complex analytical procedures and sample constraints. The analytical methods will need to be fully validated at the control site. For spoke sites the manufacturer could justify a test method transfer using a comparator for which data is generated at the control and spoke site (the DMMF would need to describe a protocol for this). There will need to be greater reliance on in-process controls, surrogate assays, and retrospective quality control tests, together with real-time release testing. To justify these will need a firm grasp of the critical quality attributes and detailed risk analysis that uses the knowledge from an enhanced approach.

WORKING WITH CELL & GENE THERAPY DEVELOPERS

The MHRA will be publishing guidance documents (see list below) that cover the details of regulatory expectations in the new framework. It is important that cell and gene therapy developers and manufacturers contribute to the consultation process for this guidance. The requirements for the delivery of innovative cell and gene therapy medicinal products to the benefit of UK patients need to be captured in these documents. There is ongoing work to make institutions—principally the NHS—ready for these new types of medicines or new ways of delivering treatment to patients, such as the Advanced Therapy Treatment Centres (ATTC) network. PoC or MM will not be a success without institutional readiness. Developers have an important role to play in this through working with health care professionals and regulators. The MHRA is also coordinating with other regulators, principally through ICRMA, to align regulatory expectations for decentralized manufacture. The ICMRA will report in 2025 on three focus areas: terminology and definitions; GXP technical aspects; CMC aspects.

Guidance for decentralized manufacture that the MHRA will develop or has already published:

- Guidance to help interpret the new regulation: ***Human Medicines Modular Manufacture and Point of Care Regulations 2025***;
- ***Clinical Trial Authorisation (CTA)*** and ***Good Clinical Practice (GCP) Guidance***;
- Designation guidance: ***Decentralised Manufacture: The Designation Step***;
- Good Manufacturing Practice (GMP) guidance: ***Decentralised manufacture: UK Guideline on Good Manufacturing Practice (GMP)***;
- ***Decentralised Manufacture Master File Template Labelling Guidance***;
- Marketing Authorisation Application (MAA) guidance: ***Decentralised Manufacture: Marketing Authorisation*** **application;**
- Pharmacovigilance (PV) MA guidance: Decentralised Manufacture: ***UK Guideline of Good Pharmacovigilance Practices***;
- PV Early Access to Medicines Scheme (EAMS) guidance;
- PV Specials guidance.

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The MHRA has recently re-launched the innovative licensing access pathway (ILAP) [2]. Developers should use this and scientific or regulatory advice meetings with the MHRA to ascertain if the decentralized framework could help with the deployment of a cell or gene therapy [3]. It is important to check eligibility with the MHRA at this early stage when precedents are not available [4]. And it is important to inform the MHRA about new technology developments as part of the need to improve institutional readiness.

More generally the developers of cell and gene therapies will need an in-depth understanding of the product and its manufacturing process, leaning heavily into the paradigm that the process is the product. This will facilitate critical aspects of using MM to scale out, such as real time release procedures. It will also underpin future efforts to standardize and simplify the manufacture of cell and gene therapies. There are clinical trials taking place in the USA and EU that feature decentralized manufacture of cell and gene therapies [5,6]. But a clear regulatory framework is required to accelerate progress in the UK. With sufficient standardization and further technological development it may be possible to build on MM and have point of care manufacture of these complex medicinal products. This would be of great benefit to patients.

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DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

EXPERT INSIGHT

Point of care manufacture of ATMPs in the UK

Jackie Mulryne and Eleri Abreo

New legislation in the UK provides a flexible framework for the manufacture of cell and gene therapies at a patient's bedside.

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INTRODUCTION

The development and use of cell and gene therapies, including advanced therapy medicinal products (ATMPs), is accelerating in the UK, providing crucial treatment options for patients, often with debilitating and life-shortening diseases. These therapies may be targeted at individual patients and involve changing, replacing, or removing a patient's cells or genes. While such therapies present vast opportunities to provide innovative and highly personalized treatment options, they are also complex, costly, and time-critical to manufacture, which makes their use, and the conditions around such use, complicated.

Current difficulties

One area of particular difficulty is that such products often have a very short shelf life and require manufacture to take place at, or close to, the location where the patient receives treatment—this is known as point of care (PoC) manufacture. As these medicines are usually highly personalized to the individual receiving treatment, as is the case for autologous cell and gene therapies, this means that there may be multiple manufacturing sites for the product across different hospitals and clinics. Their supply therefore necessitates the *scale out* of manufacturing sites (adding more manufacturing sites), rather than the *scale up* of existing sites (increasing capacity to match patient need).

The manufacture and supply of these PoC products does not easily fit within the current UK legal framework relating to the development, manufacture, and supply of medicinal products, which focuses on medicinal products supplied under the standard model of factory-based manufacture. Notably, the manufacture of medicinal products is based on certification and inspection of each manufacturing site in compliance with GMP, which is impractical where there

are multiple individual hospital sites producing medicines at a patient's bedside. The current lack of a specific and clear framework for PoC manufacture has deterred many companies from manufacturing and bringing such products to the UK market. PoC medicines are, therefore, commonly provided as unlicensed medicinal products, referred to as 'specials' in the UK, which makes them incompatible with manufacture or delivery at-scale, and importantly, makes them harder for patients to access.

UK solution

The UK government has recognized this difficulty and the need for a legal framework to enable the proper and safe manufacture and use of these therapies in a bedside manner, whilst assuring appropriate quality, safety, and efficacy measures are maintained. The aim is to set out a framework to provide care that is flexible and tailored to individuals' needs and to increase the availability of novel advanced therapies across the UK.

INCOMING LAW ON PoC MANUFACTURE

On January 23, 2025, following consultation with numerous regulatory bodies, a new statutory instrument was enacted by the UK Parliament. Publicized as the first of its kind, The Human Medicines (Amendment; Modular Manufacturer and Point of Care) Regulations 2025/87 (the PoC Regulations [1]) are set to come into force on July 23, 2025. Further, the Medicines and Healthcare products Regulatory Agency (MHRA) has published a range of supporting guidance with additional details for companies seeking to take advantage of the new regime (Figure 1) [2].

The PoC Regulations define two sets of products as follows:

- **Point of care medicinal products** ('PoC medicinal products'), which are medicinal products that, for reasons relating to method of manufacture, shelf life, constituents, or method or route of administration, can only be manufactured at or near the place where the product is to be used or administered (which may include ATMPs derived from autologous therapies, blood products, and 3D printed products); and

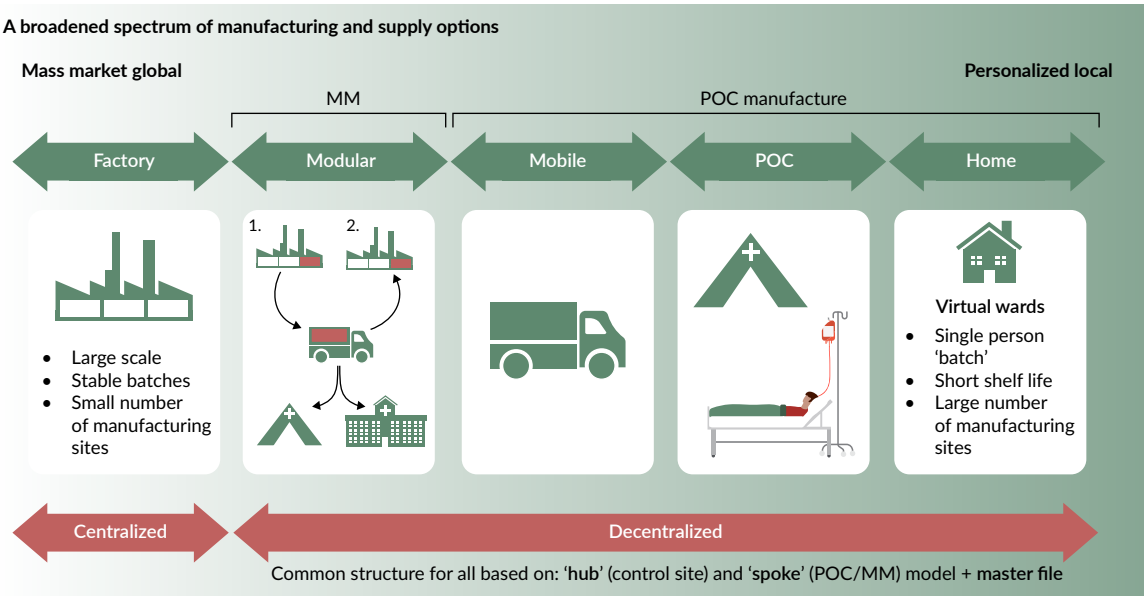
- **Modular manufacture medicinal products** ('MM medicinal products'), which are medicinal products that, for reasons relating to deployment, MHRA determines it necessary or expedient to be manufactured or assembled in a modular unit (which may include personalized cancer immunotherapy and manufacture of vaccines).

Below we set out an overview of the key concepts introduced by the PoC Regulations. Amendments have been made to both the Human Medicines Regulations 2012/1916 ('Human Medicines Regulations'), which set out a comprehensive regime for the authorization and regulation of medicinal products throughout their life cycle, and to the Medicines for Human Use (Clinical Trials) Regulations 2004/1031 ('Clinical Trials Regulations'), which govern the conduct of pre-authorization trials of medicines in the UK.

In this article, we focus on authorization of medicinal products, although similar amendments are made to both sets out regulations, and the precise requirements vary depending on whether the provisions relate to the authorized or clinical trial setting. Similarly, in most cases, the requirements for PoC medicinal products are described below, although similar requirements apply to MM medicinal products.

FIGURE 1

The PoC regulations provide a clear structure for the regulation of decentralized manufacture of a new range of categories of medicines as demonstrated in this MHRA infographic.



MHRA: Medicines and Healthcare products Regulatory Agency. MM: modular manufacture. PoC: Point of Care. Diagram based on [2].

WHEN DO THE PoC REGULATIONS APPLY TO ATMPs

The PoC Regulations bring PoC manufacturing sites under GMP, providing a flexible framework for the manufacture of ATMPs locally at the hospital. This is crucial for many ATMPs where there is a short shelf life and a need to minimize steps in the manufacturing chain. Importantly, the requirements of GMP are not relaxed, but the processes modified to enable flexibility in how they are applied to PoC manufacture.

As part of obtaining a manufacturing license, the applicant will need to set out how the relevant product is manufactured. Where there are reasons relating to the method of manufacture, shelf life, constituents, or method or route of administration, the product can only be manufactured at or near the place where the product is to be used or administered, the use of the PoC process can be applied. This is not necessarily a choice for the applicant, and the applicant will need to make an application for decentralized manufacture designation to the MHRA. The applicant will need to justify the need for a specific decentralized manufacturing approach against the relevant legal test, and provide supporting quality data, and where necessary, clinical data [3]. Therefore, if more standard manufacturing processes are possible, they should be used. Importantly, this process will not be available where the reason relates to convenience or costs alone; there must be other elements that mean PoC manufacture is required.

Therefore, while the PoC Regulations will be a welcome addition to the regulatory regime, it will not necessarily apply to ATMPs that are already authorized and therefore that already have a more standard manufacturing process in place. However, the hope is that the regime will mean more such products can be authorized and made available to patients.

STRUCTURE UNDER THE PoC REGULATIONS: HUB AND SPOKE

As set out above, a key difficulty with PoC manufacture is the sheer number of possible sites involved and that it is impractical under the current regime that each will be inspected and even named on the relevant licenses. To solve this process, the new UK framework is centered on a 'Control Site' concept: the Control Site is the location at which the holder of a manufacturer's license supervises and controls the manufacture or assembly of the medicinal product, whereas the PoC sites are the sites at which the manufacture or assembly of the PoC medicinal product physically takes place. MHRA guidance also sets out details of how this should operate and the systems that should be in place [4]. This process is similar to that of a 'hub and spoke' model used in the regulations of blood for transfusions and tissue and cell transplants, and establishes the decentralized PoC sites as the spokes, and the Control Site as the hub.

- **The Control Site:** the Control Site will be the only location named on the marketing authorization application of the PoC medicinal product and will provide the necessary controls on all aspects of the product manufacturing system
  - Key responsibilities of the Control Site include: the assessment and addition of new PoC sites; decommissioning PoC sites no longer needed; maintaining a strategy to ensure process performance and product quality; oversight of the quality system; training; provision and control of manufacturing equipment; maintenance of traceability information; audits of PoC sites; and implementing a system to capture incidents, breaches and adverse events
- **The PoC site:** physical manufacture will be devolved to the PoC sites, as named in the product's master file
  - The MHRA does not intend to inspect each PoC site but will consider the processes set out in the master file and likely conduct spot checks of sites to ensure the processes and oversight are operating as stated
  - Relationships with hospitals and treatment centers will be key to ensure they can meet the requirements for each product. However, it will be important to ensure that processes can be implemented on the ground, as if a hospital is a PoC site for many products, there will likely need to be some commonality between the various systems
- **The master file:** key to the operation of the PoC Regulations is the master file, which sets out a detailed description of the arrangements for the manufacture or assembly of the relevant PoC medicinal product. This concept is not new and has been adapted from existing regulations (for example, active substance master files)
  - The master file will need to be kept up to date as changes occur and supplied to the MHRA on a routine basis for review and assessment. This will require detailed processes and systems to document and evidence changes
  - Oversight of the Control Site will be performed by a qualified person. The master file must set out how the qualified person will have oversight of the PoC sites and ensure appropriate release of the product, how it is recorded and the records that will be put in place

KEY REQUIREMENTS UNDER THE PoC REGULATIONS

The PoC Regulations make various amendments to the Human Medicines Regulations and Clinical Trials Regulations to take into account the unique nature of such products. We set out some of note below:

- **Manufacturing license** [4]**:** it remains the case that the relevant medicinal product must be manufactured or assembled in accordance with a manufacturer's license and GMP. The PoC Regulations set out that this should also be undertaken in accordance with the relevant master file for the PoC medicinal product
  - Applications for a manufacturer's license must be accompanied by a dossier for each PoC medicinal product, which provides details such as location of operations, descriptions of processes and reporting requirements, and contact details of relevant personnel. This will take account of unique considerations relating to the products, such as the 'on demand' nature of PoC medicinal products
  - Once granted, the PoC medicinal product specified in the manufacturer's license must be handled, controlled, stored, or distributed on the Control Site or PoC site, and as specified in the master file
- **Marketing authorization applications** [5]**:** where made, marketing authorization applications for a PoC medicinal product (including for ATMPs) must be accompanied by the relevant master file for the product (along with all other accompanying material, as required under the Human Medicines Regulations)
  - As noted above, the marketing authorization will only name the Control Site, but the master file will set out the information on PoC sites and control and oversight of such sites
  - It must be ensured that the manufacturer's license and the master files are consistent with a marketing authorization relating to the product at all times
- **Pharmacovigilance requirements** [6]**:** the holder of the manufacturer's license should record and report all suspected adverse reactions linked to the product to the marketing authorization holder, and an appropriate pharmacovigilance system must be put in place
- **Packaging and labelling** [7]**:** packaging and labelling requirements apply only if the PoC medicinal product is not administered in its entirety immediately after manufacture. Otherwise, packaging and labelling requirements specific to PoC medicinal products must be complied with, which are similar to the requirements in place under the Human Medicines Regulations

POSITION IN THE EU

The position in the EU on PoC and modular manufacture is not clear-cut. Currently, only high-level considerations are set out in guidance (for example, in the European Commission's 2017 guidance on GMP specific to ATMPs [8] and the recently published Guideline on quality, non-clinical and clinical requirements for ATMPs in clinical trials [9]) and there is no specific regulatory framework governing decentralized manufacture. This means that in practice, decentralized manufacture does not take place.

However, there have been some discussions about decentralized manufacturing

within the EU institutions. The EU is currently considering a wholescale update to the regulation of medicinal products. The European Commission's proposal [10] highlighted the need for an EU regulatory framework that shifts away from existing structures designed to meet the expectations of large-scale manufacture. It set out that the proposed new framework should incorporate a "*risk-based and flexible approach that will enable the manufacture or testing of a wide range of medicinal products in close proximity to the patient*." A central site concept, similar to that of the Control Site concept adopted in the UK, was proposed to oversee decentralized sites. It is proposed that decentralized manufacture should be conducted under the responsibility of a qualified person of an authorized central site, with oversight of the decentralized sites, in a similar manner to that advanced in the PoC Regulations. Further, the decentralized sites should be registered by the competent authority of the Member State in which the decentralized site is established.

The European Parliament [11] made minimal changes to these proposals, although emphasized the need for coordination between the authorities. The European Council also made some proposed amendments to the draft framework [12,13], though the general concept as proposed by the Commission remains the same. Changes specify that a request for approval should be made within a marketing authorization application for use of decentralized manufacturing and the proposed amendments provide more prescriptive provisions on specific details that must be included in a manufacturing authorization application for a central site.

Crucially, however, it is currently unclear to what extent the new legislation will be approved and/or modified by the EU institutions as part of the trialogue discussions that are ongoing at the time of writing, and when the final legislation will come into force. This could take several years and therefore it may be some time before we see any significant and substantial legislative changes in the EU.

In addition, the International Coalition of Medicines Regulatory Authorities (ICMRA) has also considered these issues, and a workshop took place in December 2024 on decentralized or distributed manufacturing [14]. We understand that the ICMRA and relevant international regulatory organizations will develop regulatory guidance on this area, which will hopefully lead to harmonization of these requirements across jurisdictions, and could lead to changes to the UK legislation and guidance in the future.

CONCLUSION

The implementation of the PoC Regulations is a big step forward by the UK and recognizes the fact that as scientific and medical advances are made in the development of more complex and personalized treatments, such as cell and gene therapies, a one size fits all regulatory regime is no longer suitable or sustainable. The UK is at the forefront of making legal changes to allow more PoC products, including ATMPs, to be supplied to patients, while maintaining their quality and safety. The hub and spoke structure of the proposed regulatory regime has proven successful in other areas of regulation; however, nuances applicable to cell and gene therapies, such as short life span, use of autologous vs allogeneic human samples, and the specificity of treatment, must be considered and the master file must set out detailed provisions on how these factors will be controlled. This means that the MHRA will need to ensure that, and indeed has acknowledged that, the guidance accompanying the PoC Regulations will be adaptable, to allow the regime to work successfully and evolve over time to meet future needs.

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CELL & GENE THERAPY INSIGHTS

DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

REVIEW

Strategic IP landscapes for automated bioreactors in decentralized cell and gene therapy manufacturing: a concise overview

Will Rosellini, Oscar Chow, and Oscar Hernandez

The shift towards decentralized Cell and Gene Therapy (CGT) manufacturing necessitates advanced automated bioreactors. This manuscript analyzes the strategic intellectual property (IP) landscape driving these pivotal technologies. We observe a robust 7.52% CAGR in patent activity over five years, with significant innovation emerging from Asian hubs, notably China and South Korea, challenging traditional dominance. Key IP concentration areas include core bioreactor hardware, single-use technologies (SUTs), microfluidic systems, and the sophisticated integration of software, automation, and AI/ML for process control. The competitive landscape features established bioprocessing entities offering holistic solutions, while specialized providers focus on disruptive advancements. A predominant strategy involves creating 'closed ecosystems' through multi-layered IP, fostering platform lock-in. Significant 'white space' opportunities persist in edge-compatible software, advanced automated sterility assurance, and AI-driven real-time GMP compliance. Capitalizing on these requires a proactive, hybrid IP strategy aligned with global regulatory frameworks. Ultimately, astute navigation of this IP terrain is crucial for leadership in accessible, scalable, and compliant decentralized CGT manufacturing.

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INTRODUCTION

The intellectual property (IP) landscape for automated bioreactors in decentralized cell and gene therapy (CGT) manufacturing is characterized by intense innovation and strategic positioning by a range of players. This article details this landscape, mapping key technology areas of patent concentration, identifying dominant patent assignees, and delineating their respective strengths in specific niches. The analysis confirms that IP is a foundational asset, driving market differentiation, enabling

platform lock-in (making it difficult and costly to switch to a competitor's offering), and underpinning the significant investments required to develop and commercialize these sophisticated manufacturing solutions. Far from being merely a defensive shield for inventions, IP in this domain functions as a potent strategic weapon, crucial for establishing market dominance and justifying the substantial capital required in this high-cost, high-complexity field.

A pivotal shift towards decentralized CGT manufacturing models—including point-of-care (POC) and hub-and-spoke networks—is underway, driven by the need to improve patient access and cost–effectiveness. Automated bioreactors are critical enablers of this transition, and their associated IP is becoming a key determinant of competitive advantage. The push toward decentralization creates a strong demand for specific innovations, particularly for compact, user-friendly systems that can consistently meet Good Manufacturing Practice (GMP) standards. This demand drives the development of new intellectual property.

Global patent activity is robust, with a compound annual growth rate (CAGR) of approximately 7.52% over the last 5 years [1]. There is also a notable rise in innovation from Asian hubs like China and South Korea, challenging traditional US and European dominance [2,3]. Key technological trends include the ongoing refinement of traditional stirred-tank single-use reactors (SSTRs) by established giants (e.g., Danaher/Cytiva, Sartorius, Thermo Fisher Scientific) and the emergence of microfluidic systems driven by academic spin-offs and startups for niche applications. Single-use technologies (SUTs) remain a critical IP battleground, with companies leveraging proprietary designs that result in a market dynamic where customers are reliant on vendor-specific consumables.

Increasingly, the 'intelligence' of these systems—software, automation, process analytical technology (PAT), and artificial intelligence/machine learning (AI/ML)—is a major focus of IP [4]. This signals a shift in value creation and control towards the data and algorithms that manage these complex systems. Integrated end-to-end cell processing platforms, often termed 'GMP-in-a-box' systems (e.g., Lonza Cocoon®, Miltenyi Biotec CliniMACS Prodigy®, Cellares Cell Shuttle™, and Ori Biotech IRO® Platform), represent a dominant paradigm for decentralized applications, with companies using IP to create highly integrated, proprietary ecosystems.

Significant 'white space' (areas with untapped innovation potential) opportunities for innovation and IP generation persist, particularly in edge-compatible bioreactor software and analytics, advanced automated cleaning/sterilization for reusables or enhanced sterility assurance for SUTs, and AI-driven real-time GMP assurance. Capitalizing on these requires not only technological novelty but also alignment with evolving global regulatory frameworks.

Strategic recommendations for innovators include focusing on validated white spaces, adopting hybrid IP strategies for software/AI, and designing for modularity and regulatory adaptability. Investors should scrutinize IP portfolios for defensible control points and ecosystem control potential. Ultimately, the companies that successfully navigate and shape this IP terrain will define the future of accessible, scalable, and compliant decentralized CGT manufacturing.

To comprehensively explore this strategic domain, this paper is structured to guide the reader from the foundational market drivers to actionable strategic insights. First, it will establish the strategic imperative for decentralization in CGT and the role of automated bioreactors as critical enablers. Second, the analysis will map the global IP landscape, examining key growth trends, geographical innovation hubs, and the primary technology categories

attracting patent activity. Third, it will detail the competitive landscape by profiling the leading patent holders and their areas of niche dominance. Following this, the paper will deconstruct the specific IP strategies used to achieve market control, such as the creation of integrated ecosystems and protection of foundational technologies. Subsequently, it will identify and analyze key 'white space' opportunities for future innovation. Finally, the analysis culminates in a set of strategic recommendations for innovators and investors, translating these IP insights into tangible business opportunities.

THE EVOLVING LANDSCAPE OF AUTOMATED BIOREACTORS IN DECENTRALIZED CGT MANUFACTURING

The strategic imperative of decentralization in CGT

The manufacturing paradigm for CGTs) is undergoing a fundamental transformation, moving from traditional, large-scale centralized facilities towards more agile and patient-proximate decentralized models [5]. These emerging models encompass POC manufacturing, where therapies are produced at or near the site of patient treatment; hub-and-spoke networks, which combine centralized production capabilities with regional distribution and finishing sites; and CDMO-enabled distributed production, leveraging specialized third-party facilities closer to patient populations [6].

This strategic shift is propelled by compelling needs: to enhance patient access to these life-saving treatments, to mitigate the significant logistical complexities inherent in centralized production, and ultimately, to improve the overall cost–effectiveness of CGTs. Critically, this shift also confronts the primary commercial barrier of high cost per dose—often running into hundreds of thousands of dollars—which currently limits widespread adoption. Decentralization and automation are key strategies to drive down these costs by reducing reliance on manual labor and extensive, centralized cleanroom facilities. Furthermore, this model directly enhances the therapeutic value for patients by significantly reducing the 'vein-to-vein' time crucial for efficacy in aggressive diseases and by easing the immense travel and logistical burden placed on patients and their families. The logistical demands and critical 'vein-to-vein' time for autologous therapies, where a patient's own cells are harvested, modified, and re-infused, are particularly strong drivers. Centralized models can introduce considerable delays and complexities in shipping sensitive biological materials and scheduling challenges when scaling production for individual patient batches. Decentralization aims to overcome these hurdles by bringing the manufacturing process closer to the patient.

Consequently, the very nature of the manufacturing technologies required is being redefined. There is an expanding demand for systems that are not only automated but also compact, user-friendly, and capable of operating reliably in diverse less-controlled environments than traditional pharmaceutical plants [7,8].

The success of these decentralized CGT models will be significantly influenced by the ability to navigate and overcome substantial regulatory challenges. A primary concern for regulatory bodies worldwide is ensuring consistent product quality, safety, and GMP compliance across a network of multiple, potentially non-traditional, manufacturing sites. The inherent variability introduced by different locations, potentially varied staff skill levels, and diverse operating environments poses a risk to maintaining uniform GMP standards. Therefore, technologies and the intellectual property that protects them will be exceptionally valuable, supporting

or guaranteeing consistency, sterility, and compliance in these distributed settings. The ability of an automated bioreactor system to guarantee or simplify GMP compliance across diverse sites becomes a major competitive differentiator. Solutions offering robust closed-system operation, advanced remote monitoring and control capabilities, and automated compliance documentation are becoming critical for gaining regulatory acceptance and, by extension, for the commercial viability and widespread adoption of decentralized CGT manufacturing models [4]. Successfully embedding these technologies within clinical workflows requires a crucial partnership between industry innovators and healthcare providers. A proven paradigm for this is the UK's Advanced Therapy Treatment Centres (ATTC) network, which brings together clinical/academic expertise to work with industry on developing the systems and processes needed for delivering CGT at the point of care. This collaborative model allows for the co-development of platforms that are not only technologically robust but also practical for use in real-world hospital environments. Such partnerships are essential for de-risking the adoption of new technology, establishing standardized operating and training protocols for clinical staff, and creating a scalable pathway for rolling out decentralized manufacturing from centers of excellence to the broader healthcare network.

Automated bioreactors: critical enablers for distributed production

Automated bioreactors have emerged as critical infrastructure in the decentralization of CGT manufacturing. These bioreactors are essential for ensuring that manufacturing is consistent, scalable, and compliant with GMP standards across different locations. They also reduce the need for manual work and make processes more reliable. These systems are rapidly evolving from tools primarily used in research or large-scale industrial production into pivotal components of GMP-compliant treatment delivery at or near the point of care. Automation directly addresses the core challenges posed by decentralization, such as maintaining stringent quality standards with potentially less specialized personnel at each site and ensuring process reproducibility across geographically dispersed locations.

The intellectual property landscape for these automated bioreactors is, therefore, becoming a crucial indicator of competitive positioning within the broader decentralized CGT manufacturing market. Dominance in bioreactor IP can translate directly into control over how these innovative therapies are produced in distributed settings. Companies that develop and patent the most effective, reliable, and GMP-compliant automated bioreactor platforms will provide the essential tools for this new manufacturing paradigm. Consequently, therapy developers and healthcare providers seeking to implement decentralized models will likely gravitate towards these leading platforms, granting significant market influence and share to the IP holders of these critical enabling technologies. The IP for these enabling platforms effectively makes their owners gatekeepers for therapy developers pursuing decentralized models.

Commercial examples of 'all-in-one' closed bioreactor solutions vividly illustrate this trend, embodying the 'GMP-in-a-box' concept. These systems are a direct response to the core challenges of distributed manufacturing. Systems such as Miltenyi Biotec's CliniMACS Prodigy® [9] and Lonza's Cocoon® Platform [10] are designed to automate multiple critical steps of the cell therapy manufacturing workflow—including cell isolation, genetic modification (transduction), expansion, and final harvest—all within a single, functionally closed system. These platforms are

specifically engineered for patient-scale production and are crucial for maintaining sterility and consistency, particularly in point-of-care or hospital-based settings. Such systems demonstrate how sophisticated automation and integration are being realized in commercial products tailored for the unique demands of decentralized manufacturing.

The pivotal role of intellectual property in shaping the market

In the dynamic and high-stakes field of automated bioreactors for CGT, intellectual property is far more than a mere mechanism for protecting inventions. It functions as a potent strategic tool that underpins market differentiation, secures competitive advantage, attracts substantial investment, and establishes critical strategic control points, such as platform lock-in and the defense of pricing power. The inherently high costs and profound complexity associated with CGT manufacturing processes significantly amplify the importance of automation and, consequently, the IP that protects these automated solutions. The substantial research and development investments required to bring these sophisticated systems to market necessitate robust IP protection to ensure a viable return on investment and to prevent rapid commoditization by competitors.

The nature of IP in this domain is undergoing a significant evolution. Historically, bioreactor IP might have focused on isolated hardware components, such as novel stirring mechanisms or vessel designs. However, as these systems become increasingly automated and integrated to meet the specific demands of CGT, the locus of value is shifting. Value is no longer found in just the individual components, but in how the hardware, software, analytics, and single-use parts all work together smoothly and in compliance with GMP standards. This shift is compelling companies to build comprehensive IP portfolios that cover this entire integrated ecosystem.

The result is the creation of complex 'Closed ecosystem' environments, a deliberate IP-driven business model where users become locked into a specific vendor's complete platform. Switching any part of such a validated, integrated system often becomes prohibitively difficult and costly, thereby solidifying the vendor's market position. This strategic utilization of IP has profound implications for market structure and innovation dynamics. It could potentially lead to significant market consolidation, where companies possessing the most comprehensive and defensible IP portfolios acquire smaller innovators [11] or compel competitors to operate within narrower, niche markets. Such consolidation, while potentially streamlining some aspects of technology development, might also impact the diversity of innovation and pricing structures in the long term. If a few large players come to dominate the landscape through strong IP control, it could influence which types of innovative approaches receive funding and development focus, and may affect the overall cost of these critical manufacturing technologies. This concentration of IP could stifle innovation across the industry. It risks limiting the variety of new technologies and may slow down progress in areas that large companies do not prioritize.

MAPPING INNOVATION & IP TRAJECTORIES IN AUTOMATED BIOREACTOR TECHNOLOGY

Global IP trends and growth dynamics

The field of automated bioreactors for CGT manufacturing is characterized by intense and sustained innovation, as evidenced by global intellectual property trends. Patent activity in this sector has demonstrated a notable upward trajectory, with a compound annual growth rate (CAGR) of

approximately 7.52% over the last 5 years. This robust growth rate underscores the significant and ongoing R&D investment and the dynamic nature of this technological space. It reflects a strong industry-wide emphasis on creating more efficient, scalable, and GMP-compliant automated solutions designed to meet the escalating demands of the rapidly expanding CGT industry.

The broader CGT biomanufacturing market itself is experiencing rapid expansion, substantially driven by these advancements in automation and the increasing integration of artificial intelligence (AI). This implies that AI and automation are not merely features but are acting as multiplicative forces, enabling further innovation across the bioreactor stack, and leading to more IP generation. Furthermore, the criticality of single-use technology in this domain is highlighted by the fact that over 400 patents related to single-use bioreactors (SUBs) have been filed or granted in recent years [12].

This sustained CAGR in patent filings suggests that despite the existence of established IP in the bioprocessing field, innovators continue to identify and pursue new avenues for patentable improvements. This ongoing innovation likely focuses on several key areas: incremental enhancements to existing platform technologies, the development of solutions tailored for new applications (such as bioreactors optimized for specific cell types critical to CGTs or systems uniquely suited for decentralized deployment), and the integration of emerging technologies like AI and advanced sensor systems. The continued dynamism indicates that the field is far from mature, with ample opportunities remaining for inventive contributions that can address unmet needs in CGT manufacturing. The sustained patent growth points towards niche specialization and continuous improvement, where innovation targets refining existing technologies for specific CGT requirements and solving previously unaddressed challenges in automation and single-use systems.

Geographical hotbeds of innovation: USA, Europe, and the ascendance of Asia

The geographical distribution of patent filings reveals a significant global race to innovate and secure market positions in automated bioprocessing, with a notable shift in the global innovation landscape. China has emerged as a dominant jurisdiction in terms of the sheer volume of patent filings related to automated bioreactors, with the USA following closely. This trend is further illuminated by recent data indicating China's rapidly advancing capabilities in broader biotechnology innovation. China now leads in the number of impactful biotech publications and has witnessed a dramatic surge in biotech Patent Cooperation Treaty (PCT) patent filings, which rose from a mere 119 in 2010 to 1,918 in 2023. This output surpasses that of Europe in most biotechnology areas and even the USA in some specific fields [13]. Notably, in 2023, China accounted for a 29% global share of the most-cited research papers in the field of biological manufacturing. This surge in high-quality research and international patent filings from China suggests a strategic move beyond mere patent volume towards generating impactful innovations that could lead to globally competitive products, a more significant competitive threat than volume alone.

Concurrently, South Korea is rapidly ascending as a significant biotech hub, propelled by strategic government initiatives such as the National Bio Committee and the National Synthetic Biology Initiative. The South Korean government has set ambitious targets, including achieving a US$149 billion biotech output by 2035 and substantially increasing the number of biotech venture firms. This proactive governmental

stance, a key differentiator in emerging innovation hubs, is attracting considerable investments from global bioprocessing players like Merck KGaA and Cytiva, alongside fostering the growth of innovative domestic firms such as Orum Therapeutics and Alteogen [14,15]. Furthermore, South Korea's market for single-use bioprocessing systems is experiencing robust growth, with a CAGR of 16.84% [16].

While Asian innovation is clearly on the rise, North America maintains a strong position, particularly in leading POC) cell and gene therapy manufacturing efforts and in the broader cell therapy raw materials market, where it held a 47% share in 2023 [4]. This leadership is underpinned by a robust R&D infrastructure, supportive regulatory frameworks from agencies like the US FDA, and significant ongoing investment. However, the Asia Pacific region, as a whole, is identified as the fastest-growing market, indicating a broadening and diversification of the global innovation landscape.

The UK has cultivated a leading global position in cell and gene therapy through a deliberate national strategy that integrates government, academia, and industry. A key strategic advantage is its agile regulatory environment; the Medicines and Healthcare products Regulatory Agency (MHRA) established the world's first comprehensive framework for decentralized and POC manufacturing, positioning the nation to lead this manufacturing paradigm shift. This forward-thinking approach, which includes the world-first approval of a CRISPR-based therapy, is underpinned by unique national assets like the CGT Catapult, an organization that bridges the gap between research and commercialization by providing critical manufacturing infrastructure and expertise.

This globalization of innovation, with emerging regional specializations, suggests that a purely US/EU-centric view of the IP landscape is no longer sufficient. The rise of these Asian innovation hubs is poised to introduce new competitive dynamics into the global automated bioreactor market, potentially leading to increased price pressures on established Western suppliers, and creating significant opportunities for cross-border collaborations, licensing agreements, and strategic partnerships. Furthermore, this trend may lead to a diversification of the global supply chain for critical bioprocessing technologies. Consequently, all stakeholders in the CGT manufacturing ecosystem must adopt global IP monitoring and filing strategies, as significant competition, valuable collaboration opportunities, and even new technological paradigms may increasingly arise from these rapidly advancing Asian regions. This globalization demands proactive global IP management from all players.

Key technological focus areas and patent categories

The innovation in automated bioreactors for CGT is multifaceted, with patent activity concentrated in several key technological domains. These categories reflect the critical needs of CGT manufacturing, from basic cell culture to complex, integrated processing and data management.

Core bioreactor hardware and novel designs (including 3D systems, perfusion)

Patents related to the core bioreactor hardware form a foundational layer of the IP landscape. This includes innovations in the bioreactor vessel itself, agitation mechanisms (e.g., stirred-tank, rocking motion), perfusion systems for continuous culture and high-density cell growth, and overall system configurations designed to optimize critical process parameters such as nutrient supply, gas exchange, pH, and temperature control.

Beyond conventional designs, there is a significant trend towards specialized

bioreactor architectures tailored for the unique requirements of different cell types and therapeutic applications. The specific needs of CGT, such as handling sensitive cells, developing 3D tissue structures, or achieving high-density immune cell cultures, are driving this diversification beyond traditional bioreactor designs and creating new IP niches. For instance, 3D bioreactor technologies, which aim to mimic the *in vivo* cellular microenvironment, are a focus for companies like Pluri Inc. (formerly Pluristem Therapeutics). Pluri has developed and patented systems for the 3D expansion of various cell types, including placental cells and immune cells like MAIT cells, often emphasizing the creation of lymph node-like conditions. United Therapeutics Corporation, with its focus on organ manufacturing, also holds IP likely covering specialized bioreactor systems for complex tissue and cell culture.

Perfusion systems are critical for achieving high cell densities and extended culture durations. Cytiva's Xcellerex™ Automated Perfusion System (APS) [17], Thermo Fisher Scientific's HyPerforma™ Single-Use Bioreactor (S.U.B.) with its patented crossflow sparger [18], and Sartorius's Ambr® and BIOSTAT® STR families all feature advanced perfusion capabilities [19]. Emerging companies are also contributing novel hardware designs. PBS Biotech is known for its Vertical-Wheel™ bioreactors for sensitive cells, and BioThrust is developing a 'bionic bioreactor' with a unique membrane architecture for bubble-free gas exchange, aimed at sensitive stem cell cultures.

A notable bifurcation in bioreactor technology development and associated IP strategies is evident. Traditional SSTRs remain the established standard for many applications, dominated by giants like Danaher (Cytiva, Pall), Sartorius Stedim Biotech, and Thermo Fisher Scientific. Innovation here centers on scalability, advanced single-use components, and PAT integration, often through incremental innovations building on extensive existing IP. In contrast, newer or more specialized companies such as Pluri Inc., PBS Biotech, and BioThrust are developing fundamentally novel bioreactor concepts, frequently tailored to specific CGT demands. This bifurcation creates a dynamic IP ecosystem where large players refine established platforms, while smaller innovators introduce disruptive specialized hardware, leading to potential M&A or licensing activities. The distinct IP landscapes—dense comprehensive web of patents for SSTRs versus newer IP for novel designs—will shape these interactions.

Single-use technologies: consumables and interfaces

Single-use technologies (SUTs) have revolutionized bioprocessing by eliminating cleaning and sterilization validation between batches, reducing turnaround times, and minimizing cross-contamination risks. Consequently, a significant volume of IP, with over 400 patents filed by various players [12], is dedicated to single-use bioreactor bags, tubing assemblies, impellers, sensors, aseptic connectors, and the overall integration of these disposable components. This is particularly critical for CGT, where closed and automated systems heavily rely on robust SUTs for sterility and reproducibility, especially for therapies like CAR-T cells.

The 'disposable kit interface' represents a major IP battleground. Companies that control the IP for critical single-use components can establish a business model based on recurring revenue and foster platform dependency. Leading bioprocessing companies like Danaher (Cytiva Xcellerex flow kits, Pall filtration), Sartorius Stedim Biotech (Flexsafe® bags, Biowelder® TC, Opta® SFT connectors), and Thermo Fisher Scientific (HyPerforma S.U.B. bags with BioTitan™ retention) have substantial IP in this area.

The IP strategy for SUTs is holistic, extending beyond the basic material of the disposable bag to encompass the entire integrated consumable assembly, including proprietary connector designs, specific impeller mechanisms, sensor integration methods, and defined fluid management pathways. This makes it exceptionally challenging for third-party manufacturers to offer compatible disposables, thereby reinforcing the user's reliance on the original vendor's platform. The defensibility of this model lies not just in the plastic material, but in the complex, patented design of the entire integrated assembly and its hardware interface.

Despite the maturity of the single-use paradigm, persistent challenges related to leachables and extractables, pre-use integrity of bags, and lack of standardization are fueling a 'second wave' [20] of innovation. This innovation focuses on enhanced robustness, improved material science, advanced sterility assurance mechanisms (like novel pre-sterilized connectors and reliable in-situ integrity testing methods), and broader applicability for CGT. These unresolved SUT challenges are active drivers for new IP opportunities. The lack of standardization, while a hurdle for users, is often a deliberate IP strategy by vendors. However, increasing regulatory or user pressure for interoperability could eventually lead to some standardization, potentially reshaping the current IP-driven competitive landscape.

Microfluidic systems and lab-on-a-chip bioreactors

Microfluidic bioreactors, or 'lab-on-a-chip' systems, represent an emerging and highly innovative frontier, enabling precise manipulation of extremely small fluid volumes for applications in research, process development, and potentially small-scale autologous therapies or POC manufacturing. Key principles include laminar flow, high surface-to-volume ratios enhancing mass transfer, and the ability to mimic *in vivo* microenvironments.

Intellectual property in this domain often originates from academic institutions and their spin-off companies, a distinct innovation pathway compared to incumbent-led SSTR development. Examples include Redbud Labs (microfluidic devices for cell processing) [21], Kytopen (an MIT spin-off with Flowfect® technology for non-viral gene delivery) [22], and others like Stilla Technologies and Fluid-Screen. Advantages include reduced reagent consumption, high-throughput screening, and enhanced microenvironment control, translating to potential scalability via parallelization and cost reduction for CGT.

However, scaling production volumes for therapies requiring very large cell numbers remains a key challenge, often involving massive parallelization of individual micro-reactors with their own complexities. This limitation shapes IP strategy, making it most impactful when focused on enabling technologies (like Kytopen's gene delivery platform) or niche applications (diagnostics, small-dose therapies) rather than direct competition with SSTRs for all large-scale cell expansion, unless significant IP breakthroughs overcome current scaling hurdles.

Software, automation, monitoring, and control (including AI/ML)

The 'intelligence' embedded within automated bioreactor systems—their software, automation capabilities, and sophisticated monitoring and control methods—is an increasingly critical area of IP concentration. This domain encompasses advanced sensor integration, real-time data analytics, PAT, automated feedback control, process orchestration, secure data management, cloud connectivity, remote GMP compliance, and the transformative applications of AI/ML for predictive control, anomaly detection, and real-time GMP assurance. The 'brains' of the bioreactor are becoming the primary value and IP driver.

Software control systems manage critical process parameters (CPPs), while data analytics convert raw data into actionable insights. PAT ensures final product quality through real-time monitoring and control. Established players and newer entrants are heavily investing in IP around these 'smart' system aspects:

- **Sartorius Stedim Biotech:** BioPAT® toolbox (sensors like Viamass, Xgas, Trace; software like SIMCA®, MODDE®, MFCS) [23]
- **Danaher (Cytiva):** integration of Rockwell's PlantPAx™ or Emerson's DeltaV™; Xcellerex APS with Wonderware™ [17]; Figurate™ automation platform
- **Thermo Fisher Scientific:** TruBio™ software with G3 Bioprocess Controllers; digital integration for CAR-T workflows [24]
- **Miltenyi Biotec:** CliniMACS Prodigy proprietary software for integrated workflows [9]
- **Ori Biotech:** IRO Platform with flexible, user-programmable software, remote HMI, and OriConnect™ for automated sterile fluid transfer [25,26]

AI/ML and digital twin technologies are rapidly advancing, with applications in optimizing perfusion rates, predicting batch success, detecting anomalies, and ensuring real-time GMP compliance [27]. However, AI/ML in bioprocessing faces a dual challenge: the complexity of IP protection for algorithms (often requiring demonstration of a concrete technical application rather than abstract concepts) and the need for rigorous regulatory validation of AI systems, especially those making autonomous GMP decisions. This necessitates strategies combining patents for specific technical implementations with trade secrets for core algorithms or datasets and drives innovation in explainable AI (XAI) to meet regulatory demands for transparency.

Integrated end-to-end cell processing platforms ('GMP-in-a-box')

A dominant trend, particularly for autologous therapies (e.g., CAR-T cells) and decentralized production, is the development of 'GMP-in-a-box' systems. These highly integrated platforms automate multiple, if not all, critical steps of the cell therapy manufacturing workflow within a single, functionally closed instrument. Intellectual property in this area is comprehensive, covering individual unit operations, their seamless integration, the overall system architecture, single-use fluidic pathways, and the orchestrating software. The IP value of these platforms lies critically in this patented integration, creating a powerful 'closed ecosystem'.

Several companies have established strong IP positions:

- **Lonza's Cocoon Platform:** automated, closed, flexible system for patient-scale manufacturing, integrating T-cell enrichment, activation, transduction, and expansion in a single-use cassette [10]
- **Miltenyi Biotec's CliniMACS Prodigy:** integrated solution for cell separation, cultivation, transduction, and formulation within a closed, single-use tubing set [28]
- **Cellares Corp's Cell Shuttle:** aims for true walk-away, end-to-end automation, integrating robotics and forming a core of their IDMO concept
- **Ori Biotech's IRO Platform:** designed to close, automate, and standardize CGT manufacturing, featuring the patented OriConnect system for automated sterile fluid transfer [25,26]

- **Terumo Blood and Cell Technologies:** offers the Quantum® Cell Expansion System and Finia® Fill and Finish System [10]

These platforms simplify CGT manufacturing complexities, reduce cleanroom footprints, minimize operator variability, and enable broader therapy adoption, especially in decentralized settings. The complex, multi-layered IP portfolios (a strategic collection of various intellectual property rights designed to protect an entire technology ecosystem rather than just a single invention) protecting these systems create strong vendor lock-in, significantly amplified by the substantial time and resources required for GMP process validation on a specific platform, making switching vendors prohibitively difficult. A strategic tension exists between developing highly optimized, locked-down systems for specific processes and the market demand for more flexible, adaptable platforms suitable for diverse cell types and protocols. IP that enables user-configurability and adaptability could become a key competitive differentiator.

COMPETITIVE LANDSCAPE: KEY PLAYERS, IP PORTFOLIOS, & NICHE DOMINANCE

The IP landscape for automated bioreactors in CGT is populated by a diverse mix of established bioprocessing giants, diversified life science companies, specialized CGT technology providers, emerging innovators, and academic institutions.

Leading patent assignees: profiles and strategic focus

Established bioprocessing giants and diversified life science companies

These companies typically leverage their extensive experience and broad IP portfolios in general bioprocessing to offer comprehensive solutions for CGT manufacturing. Their strengths often lie in robust, scalable platforms, well-characterized consumables, and strong regulatory support.

Key examples include:

- **Danaher Corporation (Cytiva, Pall Corporation):** a major force with wide-ranging patents in bioreactor design (Xuri™, ÄKTA™, Xcellerex), SUTs, automation, and Pall's critical filtration technologies

- **Sartorius Stedim Biotech:** a leading provider of bioreactors (BIOSTAT family, Ambr micro bioreactors), SUTs (Flexsafe bags), and PAT solutions (BioPAT toolbox)

- **Thermo Fisher Scientific:** significant IP in SUTs (HyPerforma S.U.B. series with patented sparger technology, BioTitan retention device), automation software (TruBio), and closed systems

- Lonza has established a formidable IP position with its Cocoon Platform, which exemplifies a 'multi-layered' IP strategy for controlling the integrated, patient-scale manufacturing workflow. This goes beyond protecting just the hardware. For example, patent WO2019046766A2 does not merely claim a device, but rather an entire automated method for producing genetically modified immune cells within a fully enclosed system. This broad process claim creates a significant 'Strategic control point' for competitors seeking to develop similar end-to-end automated CAR-T solutions. The 'layers' of Lonza's IP are further fortified by patents on the design of the proprietary single-use cassette and the software that controls the automated process, creating a deeply integrated and defensible 'closed ecosystem'

- **Miltenyi Biotec:** known for its CliniMACS Prodigy, holding substantial IP in closed-system cell separation, integrated bioreactor design, single-use tubing sets, and automation software. Other relevant players include Boehringer Ingelheim, Merck KGaA, WuXi AppTec, and Becton, Dickinson, and Company

These established players often pursue a strategy of providing validated, end-to-end solutions, frequently creating 'a comprehensive web of patents' (dense webs of overlapping patents covering foundational technologies and incremental improvements). This defensive IP strategy aims to protect substantial market shares and makes it challenging for new entrants to compete without infringement. Incumbents leverage these webs of patents as a primary defensive shield. Their primary challenge lies in maintaining agility against disruptive technologies from smaller firms, often leading them to rely on mergers and acquisitions (M&A) to acquire innovative startups and integrate next-generation technologies into their portfolios. M&A thus becomes a key strategy to counter agility deficits and access external IP.

Specialized CGT technology providers and emerging innovators

This category includes companies more narrowly focused on specific CGT challenges, often developing disruptive technologies or highly specialized solutions. Their IP portfolios typically center on novel bioreactor concepts, advanced automation, or unique cell processing approaches. Examples include:

- **Pluri Inc.:** known for 3D bioreactor technologies for placental and immune cell expansion
- **Athersys Inc.:** focuses on its MultiStem® allogeneic stem cell therapy platform with IP on scalable manufacturing
- **United Therapeutics Corporation:** involved in organ manufacturing, with IP in specialized bioreactors for complex tissue culture
- **Cellares Corp:** emerging leader with the Cell Shuttle platform, IP centered on robotics, end-to-end automation, and the IDMO model
- **Ori Biotech:** developing the IRO Platform, with IP including the OriConnect system and a flexible bioreactor design for decentralized manufacturing. Other companies like ImmunityBio, Inc., Chr. Hansen Holding A/S (microbial fermentation focus), and Weyerhaeuser Company (plant cell culture IP) also appear in patent landscapes, though their direct impact on human CGT bioreactor hardware may vary

These specialized innovators use IP as a 'spearhead' for market entry and differentiation. Their survival and growth depend heavily on the strength and enforceability of their foundational IP, which allows them to carve out unique, defensible market positions. The IP portfolio is a primary determinant of an emerging innovator's exit strategy (often M&A) or its potential growth trajectory; they are prime M&A targets for larger companies seeking cutting-edge technologies, with IP quality being key to their valuation.

Academic institutions and their spin-offs

Universities and their spin-offs are crucial incubators of novel technologies and foundational IP, particularly in cutting-edge areas like microfluidics, novel sensor development, and specialized bioreactor designs. Key academic institutions active in patenting include the University of New South Wales (UNSW), the University System of Maryland, and the Karlsruhe

Institute of Technology (KIT); Oxford University also has numerous spin-outs in related fields [29]. Academic IP often represents high-risk, high-reward foundational technology.

Spin-offs translate these innovations into marketable products:

- **Redbud Labs, Inc.:** focuses on microfluidic components and systems for cell manipulation
- **Kytopen (MIT spin-off):** developed the patented Flowfect technology, a microfluidics-based platform for non-viral cell engineering [22]
- **MaxCyte:** with its Flow Electroporation® technology, it has academic roots and is a key enabler in cell engineering. This academic-to-spin-off pipeline is a vital source of disruptive innovation. The terms of licensing agreements for this foundational IP between universities and spin-offs (and subsequently to larger companies) have long-term strategic consequences for the entire value chain, heavily influenced by the initial academic IP strength

Competitive clusters: dominance in specific technology niches

To clearly delineate organizational dominance in specific niches within the automated bioreactor landscape for CGT, Table 1 maps key patent assignees against critical technology categories [30,31]. The assessment of strength is based on company focus, product offerings, and explicitly mentioned IP strengths or patented features.

Established bioprocessing companies like Danaher, Sartorius, and Thermo Fisher demonstrate broad strengths across general hardware, SUTs, and PAT. Specialized platform providers such as Lonza and Miltenyi Biotec excel in integrated end-to-end systems. Newer entrants like Cellares and Ori Biotech are pushing boundaries in automation, robotics (notably Cellares), and flexible, closed systems. Academic spin-offs like Redbud Labs and Kytopen are key innovators in microfluidics, while Pluri Inc. shows strength in 3D bioreactor systems.

Competitive dominance in one technological niche often creates significant leverage in adjacent ones. For instance, a company holding strong IP in SUTs can strategically design its integrated bioreactor platform to be exclusively compatible with those SUTs, reinforcing its market position in both segments and enhancing platform lock-in. This interconnected IP strategy across multiple categories creates synergistic market control.

The emergence of 'Next-Generation Automation: Robotics and Highly Integrated, Flexible Platforms' as a distinct competitive cluster signifies a potential paradigm shift. IP in true robotics for cell handling (e.g., Cellares' 'IDMO Smart Factory' model or Cellular Origins' Constellation™ platform) [30], AI-driven operational flexibility, and industrial-scale automation concepts could prove disruptive if these platforms deliver markedly superior scalability, cost–effectiveness, or adaptability. This focus on robotics and industrial-scale automation represents a potential 'leapfrog' disruption over current integrated systems.

STRATEGIC IP CONTROL POINTS: ARCHITECTING MARKET LEADERSHIP AND PLATFORM INTEGRATION

Core bioreactor IP and the creation of 'closed ecosystem'

In the context of automated bioprocessing, a 'closed ecosystem' is a deliberate, IP-driven business strategy where a vendor creates a closed ecosystem consisting of a central instrument, proprietary software,

TABLE 1

Top patent holders by automated bioreactor technology category for CGT.

Technology category	Danaher (Cytiva, Pall)	Sartorius Stedim Biotech	Thermo Fisher Scientific	Lonza	Miltenyi Biotec	Pluri Inc.	Cellares Corp	Ori Biotech	Other key players (examples)
Novel bioreactor hardware (general)	High (Xcellerex™, Wave™)	High (BIOSTAT®, Ambr®)	High (HyPerforma™ S.U.B.)	Medium (Hardware for Cocoon®)	Medium (Hardware for CliniMACS Prodigy®)	Medium (specialized designs)	Medium (hardware for Cell Shuttle™)	Medium (IRO® hardware)	Athersys (scalable for MultiStem®), United Therapeutics (Organ mfg.), PBS Biotech (Vertical-Wheel™), BioThrust (Bionic)
3D Bioreactor systems	Medium (research focus)	Medium (research focus)	Medium (research focus)	Low/niche	Low/niche	High (patented 3D expansion)	Low/niche	Low/niche	
Perfusion systems	High (Xcellerex APS)	High (Integrated in BIOSTAT)	High (Capabilities in HyPerforma)	Medium (Cocoon capabilities)	Medium (Prodigy capabilities)	N/A	Medium (Cell Shuttle capabilities)	Medium (IRO capabilities)	
Single-use bioreactor bags and consumables (SUTs)	High (extensive portfolio, proprietary interfaces)	High (Flexsafe® bags, integrated consumables)	High (HyPerforma bags with BioTitan™, Aegis™/CX films)	High (Cocoon single-use cassettes)	High (Prodigy single-use tubing sets)	Medium (For 3D systems)	High (Consumables for Cell Shuttle)	High (Single consumable for IRO)	
Aseptic connectors and sterile fluid transfer	High (Pall Colder products, Cytiva components)	High (Opta® SFT, Biowelder® TC)	Medium (standard and custom solutions)	High (integrated in Cocoon cassettes)	High (integrated in Prodigy tubing sets)	Medium	High (integrated in Cell Shuttle)	High (OriConnect™ patented system)	
Microfluidic bioreactors/ lab-on-a-Chip	Low/niche (likely via partnerships/acquisitions)	Medium (Ambr leverages microscale, research tools)	Low/niche	Low/niche	Low/niche	Low/niche	Low/niche	Medium (conceptually, for precise control)	Redbud Labs (high), Kytopen (high—Flowfect®), academic spin-offs (emerging)
Sensors and monitoring (PAT)	High (integrated sensors, Cytiva Figurate™ automation)	High (BioPAT® toolbox: Viamass, Xgas, Trace, Fundalux)	High (integrated sensors, TruBio™ software compatibility)	Medium (sensors in Cocoon)	Medium (sensors in Prodigy)	Medium	Medium (sensors in Cell Shuttle)	Medium (integrated sensors in IRO)	Applikon (Getinge), Mettler Toledo
Automation software and control systems	High (Figurate, PlantPAx™, DeltaV™ integration)	High (BioPAT: SIMCA®, MODDE®, MFCS, Biobrain®)	High (TruBio™ software, G3 controllers)	High (Cocoon proprietary software)	High (CliniMACS Prodigy®software)	Medium	High (Cell Shuttle automation software)	High (IRO flexible software, HMI)	
AI/ML and predictive analytics in bioprocessing	Emerging (developing capabilities)	Medium (SIMCA® for MVDA, exploring AI)	Emerging (developing capabilities)	Emerging	Emerging	Low	Emerging (implied in 'Smart Factory')	Emerging (data analytics focus)	Specialized AI/software firms
Integrated end-to-end cell processing platforms	Medium (modular solutions, Cytiva Chronicle™)	Medium (modular approach, e.g., Ambr to BIOSTAT)	Medium (modular, e.g., CTS™ Rotea system and other modules)	High (Cocoon Platform)	High (CliniMACS Prodigy)	N/A (focus on expansion)	High (Cell Shuttle 'GMP-in-a-box')	High (IRO Platform 'end-to-end')	Terumo BCT (Quantum®, Finia®)
Robotics in cell manufacturing	Low/niche (automation, not full robotics focus)	Low/niche	Low/niche	Low/niche (automation within Cocoon)	Low/niche (automation within Prodigy)	N/A	High (core to Cell Shuttle platform)	Medium (automation)	Cellular Origins (Constellation™, academic research

Data from [30,31,32].

and essential, patented single-use consumables. The 'walls' of this ecosystem are built with intellectual property that makes the components functionally interdependent and incompatible with third-party products. This strategy creates 'platform lock-in', making it too expensive and difficult for users to switch away from a vendor's system once it has been validated. In the competitive field of automated bioreactors, companies use intellectual property as a key tool to control the market and make customers dependent on their platforms. Companies strategically concentrate IP filings around key aspects of the bioreactor 'stack'—hardware, software, sensors, and consumables—to create critical 'control points'. These control points are instrumental in developing 'closed ecosystem', where users become reliant on a specific vendor's proprietary and integrated platform, thereby defending the pricing power of these systems. This 'closed ecosystem' effect is a deliberate outcome of a multi-layered IP strategy.

Core areas for IP control include:

- **Closed system architecture:** IP covering novel single-use bag designs, aseptic connectors, sterile fluid transfer

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mechanisms, and integrated cell separation technologies are paramount for preventing contamination and ensuring GMP compliance

- **Sensor integration and automated feedback control:** patents on novel sensors for real-time CPP monitoring and the algorithms enabling automated feedback control allow companies to offer 'intelligent' bioreactors that optimize processes and reduce manual intervention

- **Single-use components and disposables:** a significant volume of IP is dedicated to proprietary single-use items, covering material compositions, design features, and integration methods

While beneficial for the IP holder, these 'closed ecosystem' can stifle broader innovation, limit interoperability, and potentially lead to higher costs for users. A powerful, non-IP factor that reinforces these IP-based lock-ins is the high cost and risk associated with GMP re-validation; once a process is validated on a specific platform, switching becomes a massive economic and regulatory deterrent.

Illustrations of strategic IP for foundational technologies

The establishment of 'strategic control point', meaning a type of intellectual property that gives a company control over an indispensable component, system module, or operational workflow within a broader technological process, through IP is a cornerstone of competitive strategy. By securing broad patents on entire operational workflows or indispensable system modules, companies can significantly influence the market, compelling competitors to license their technology or invest heavily in non-infringing alternatives, often confining them to narrower innovation corridors. These strategic control points are strategically chosen to control irreplaceable process steps or components.

Dominating workflows: end-to-end automated systems

Patents claiming entire automated manufacturing processes grant substantial market leverage. For example, WO2019046766A2, describes an automated method for producing genetically modified immune cells (e.g., CAR-T cells) in a fully enclosed system [33]. If upheld, such broad claims create a significant barrier for competitors aiming to develop similar comprehensive approaches. Similarly, US20130210130A1, detailing an automated cell culture arrangement with a closed cell culture module, covers a fundamental element in automated CGT, granting considerable control [34].

The 'Proprietary consumable model': IP in single-use connectors and components

This strategy, mirroring the 'printer and ink' model, involves designing hardware for exclusive compatibility with patented single-use components. The combination of IP on the consumable and the burden of GMP re-validation creates powerful user lock-in. Examples include:

- **CPC (Colder Products Company):** extensive portfolio of aseptic connectors (MPC™, MPX™, SaniQuik™) with patented design features ensuring sterility and ease of use [35–38]

- **Pall Corporation (Danaher/Cytiva) Kleenpak™ Connectors (e.g., US 8,454,059; US 7,959,192):** patented sterile connectors/disconnectors with features like a gendered design and peel-away strip, compelling reliance on Pall [39,40]

- **Sartorius Stedim Biotech Opta SFT Connectors:** patented ergonomic and

reliability-enhancing features for aseptic connections [41]

- **Cytiva ReadyMate™ Connectors (EP3803181A1):** a reusable connector member with proprietary disposable sterile cover portions, creating multi-layered lock-in [42]

Integrated hardware, software, and consumables ('closed ecosystem')

Companies construct comprehensive 'closed ecosystem' by securing IP over the entire integrated platform. as a prime example, integrating multiple cell processing steps with proprietary single-use tubing sets and control software [43–47].

Proprietary sensor integration: controlling data and process optimization

IP related to novel sensors and their seamless integration for real-time monitoring and automated feedback is a key strategic domain. Patents such as US10227555B2 (and related family) for 'composite sensor assemblies for single use bioreactors' and US11886176 for the 'bioreactor control system and method of use' [48–50]. These patents cover physical integration and signal processing, leading to physical, data/software, and process optimization dependency. Control over sensor technology and its data output is evolving into control over data ecosystems and future AI-driven optimization, creating a new layer of dependency.

Company IP strategies: defensive thickets, offensive maneuvers, and collaborations

Companies in the automated bioreactor space employ a range of IP strategies. A common approach, particularly among established players, is defensive patenting, creating 'web of patents'—dense webs of overlapping patents covering hardware, software, sensors, and SUTs to deter competitors and solidify market control. This mirrors the 'blockbuster drug' IP playbook, where companies like Genzyme (for agalsidase beta) and Roche (for Tocilizumab) built extensive patent estates around successful biologics and their associated production technologies [51–54], indicating that manufacturing platforms themselves are now viewed as high-value, defensible assets.

In response, competitors, especially new entrants, may utilize offensive IP strategies, such as 'IP leapfrogging' or designing around existing web of patents. Innovations in areas like continuous bioprocessing, novel SUT designs, or AI-optimized cell lines requiring unique bioreactor conditions can provide pathways to circumvent originator patents and establish new, defensible IP positions. This is a vital offensive strategy for challengers.

While core platform IP is often siloed, licensing, collaboration, and patent pools can occur for complementary technologies or to enable broader market access, similar to practices in other tech sectors and the broader life sciences [11,55,56]. Finally, there is an emerging trend of open-source hardware and software initiatives for bioreactors (e.g., minimalist bubble column bioreactors, the 'JANUS' 3D printable perfusion bioreactor), often from academic or DIY bio communities [57,58]. While not yet a significant commercial threat in GMP CGT, these initiatives could, in the long term, influence market expectations for cost and flexibility, potentially pressuring proprietary vendors to adapt.

The competitive dynamics described within this analysis, characterized by established incumbents refining complex systems versus agile entrants introducing novel platforms, closely mirror the classic theory of disruptive innovation articulated by Clayton Christensen. The large, established bioprocessing companies are engaged in sustaining innovation, incrementally improving their sophisticated

bioreactor platforms (like SSTRs) to serve the high-end demands of their existing customers. Their creation of 'closed ecosystem' ecosystems is a strategy to protect this profitable, high-margin market.

Conversely, disruptive innovations are emerging from newer, often smaller, companies focused on the specific needs of decentralization. Platforms like integrated 'GMP-in-a-box' systems or specialized microfluidic bioreactors may initially address niche or lower-margin applications, such as point-of-care manufacturing, that incumbents may overlook. However, as Christensen's model predicts, these disruptive technologies have the potential to 'move upmarket'. By simplifying complexity, reducing cost, and enabling manufacturing in entirely new settings, they could fundamentally restructure the industry. Over time, as these decentralized platforms mature and prove their scalability and reliability, they may challenge the dominance of the traditional, centralized manufacturing model, potentially displacing the very incumbents who once led the market. This dynamic suggests that the future industry structure will be shaped not just by incremental improvements but by the successful deployment of these disruptive, decentralized manufacturing technologies.

Strategic implications of IP control for market participants

The existence of potent IP control points carries significant strategic implications for all participants in the automated CGT manufacturing ecosystem.

For new entrants and smaller players, the dense IP landscape necessitates meticulous 'freedom to operate' (FTO) analysis before market entry. Strategies include designing around existing patents, innovating in narrower technological corridors, or seeking licenses.

For established players and incumbents, the focus is on reinforcing their 'closed ecosystem' through continuous IP filings, strategic acquisitions, and leveraging their IP portfolios to deter new entrants.

For all stakeholders, including therapy developers, CDMOs, and investors, a thorough understanding of the IP landscape is crucial when selecting an automation platform. Considerations must extend beyond technical specifications to include long-term consumable costs (the 'Proprietary consumable model'), vendor dependency, flexibility and switching costs (often prohibitively high post-validation), supply chain resilience, and interoperability (rare due to IP strategies). This means IP due diligence is no longer just for vendors but a critical strategic imperative for users and investors too, as platform choices have profound long-term lock-in and cost implications.

The competitive environment shows a clear trend: companies are strategically building IP portfolios around entire integrated systems and proprietary consumables. This creates an 'IP arms race' where the objective is to control the most comprehensive, user-friendly, and GMP-compliant ecosystem, shifting focus towards ecosystem control rather than just individual product protection. Success is increasingly intertwined with the strength, breadth, and strategic deployment of a company's IP portfolio covering these integrated solutions.

ENABLING DECENTRALIZATION: BIOREACTOR DESIGN & IP FOR DISTRIBUTED CGT MANUFACTURING

The strategic shift towards decentralized CGT manufacturing imposes unique demands on bioreactor systems, requiring them to be highly automated and meticulously designed for deployment in diverse, often space-constrained environments. IP in this domain increasingly focuses on features enhancing portability, ease of use,

interoperability, remote management, and overall system integration.

IP for compact, mobile, and integrated 'GMP-in-a-box' systems

A key IP thrust for decentralized applications centers on creating compact, mobile, and highly integrated 'GMP-in-a-box' solutions. Patents in this area cover:

- **Miniaturization and footprint reduction:** innovations consolidating multiple functionalities (cell separation, expansion, washing, harvesting) into smaller units, often involving novel layouts, microfluidics, and lightweight materials
- **Portability and robustness:** features facilitating easy transport, rapid setup, and maintenance of system integrity and sterility during movement (e.g., integrated carts, shock absorption)
- **Ease of use and reduced infrastructure demands:** systems minimizing specialized infrastructure needs (standard power, less cleanroom space via closed designs) and possessing intuitive user interfaces for less specialized personnel. IP that enables operation by personnel with less bioprocessing expertise, gains significant value as manufacturing moves to POC settings

Leading companies like Lonza (Cocoon Platform), Miltenyi Biotec (CliniMACS Prodigy), Cellares (Cell Shuttle), and Ori Biotech (IRO Platform) are developing platforms embodying these principles, often protecting these aspects through IP. The 'GMP-in-a-Box' concept extends beyond mere hardware miniaturization; it involves creating a self-contained, validated manufacturing environment. The IP protecting the *integration* of all necessary GMP functionalities (sterility assurance, monitoring, control, documentation) within that compact footprint is paramount. For decentralization, IP on system integration and ease of deployment is as critical as core process IP.

IP for plug-and-play interfaces, modularity, and system integration

For seamless decentralized workflows, bioreactors must integrate smoothly with other essential manufacturing modules (fill-finish, QC, cryopreservation). Consequently, IP is being generated around standardized connectors and interfaces, modular system integration, and automated data transfer.

- **Standardized connectors/interfaces:** development of universal aseptic connectors and data interfaces to allow bioreactors to 'plug into' downstream operations easily, enhancing sterility and efficiency
- **Modular system integration:** patents on architectural designs of modular platforms where unit operations can be flexibly combined and controlled as a cohesive system
- **Automated data transfer/process orchestration:** software IP for automated data handoff and overall process orchestration across integrated units

A fundamental tension exists, however, between the user-benefiting desire for 'plug-and-play' interoperability and the dominant 'Closed ecosystem' IP strategy of many vendors, which actively hinders true vendor-agnostic interoperability. IP for 'controlled interoperability', such as proprietary semi-open systems or specialized adaptors, may emerge as a pragmatic compromise, allowing vendors to maintain core control while offering some flexibility.

Software interoperability, cloud/edge monitoring, and remote compliance: IP considerations

Software and data management are pivotal for effectively managing distributed manufacturing networks and ensuring consistent quality and compliance. IP in this critical area includes:

- **Software interoperability and data standards:** developing software architectures and communication protocols (e.g., based on OPC UA) for secure data exchange and cohesive operation in distributed networks
- **Cloud-enabled remote batch monitoring and analytics:** systems for secure transmission of real-time batch data to a central cloud platform for remote monitoring, centralized data aggregation, and predictive analytics
- **Edge computing for localized intelligence and autonomy:** this is a crucial and rapidly emerging white space for IP. It involves performing advanced analytics and critical decision-making 'at the edge'—directly on or near the bioreactor system. This is vital for sites with limited connectivity or needing immediate autonomous adjustments without cloud latency. Local AI/ML algorithms can enable real-time decisions and adaptive control. IP protecting efficient edge AI algorithms, localized intelligent control, and robust offline operational capabilities are key to unlocking truly autonomous and robust decentralized operations
- **Remote GMP compliance and data integrity:** software platforms facilitating remote GMP enforcement (secure electronic batch records [EBRs], automated compliance documentation, remote audits). Robust cybersecurity measures and potentially blockchain for immutable audit trails are also areas for IP. Ensuring data integrity (e.g., FDA 21 CFR Part 11, EU Annex 11) is paramount. Cybersecurity and data integrity IP for distributed networks is non-negotiable for regulatory acceptance and commercial trust

WHITE SPACE ANALYSIS: UNTAPPED INNOVATION POTENTIAL IN AUTOMATED BIOREACTORS

While the IP landscape for automated bioreactors is increasingly populated, several domains present 'white space' opportunities for significant innovation (Table 2). To capitalize on these opportunities, innovators must not only create new technology but also ensure from the beginning that their designs align with regulatory standards, which is especially important for decentralized manufacturing.

Scrutinizing key white spaces

The following areas represent plausible white spaces or areas ripe for continued innovation:

Edge-compatible bioreactor software and analytics:

- **Opportunity:** sophisticated on-device software for advanced analytics, predictive maintenance, real-time anomaly detection, and adaptive control, enabling autonomous operation, especially with limited connectivity. This is vital for robust offline operation, reduced latency, and data security in distributed models
- **IP and feasibility:** identified as an under-patented 'white space [59,60]. While general AI patenting is up, specific bioreactor edge applications

TABLE 2

Detailed analysis of key white spaces in automated bioreactors for CGT.

White space area	Description and opportunity	Current IP density (rationale/evidence)	Key innovators/ potential players	Feasibility and challenges	Strategic importance for decentralized CGT
Edge-compatible bioreactor software and analytics	On-device advanced analytics, predictive maintenance, real-time anomaly detection, adaptive control for autonomous operation, limited connectivity	Low to medium; general AI patents rising, specific bioreactor edge applications less crowded; focus on technical application for patentability	Tech companies (IoT/edge AI), bioreactor manufacturers, startups	High feasibility; AI for real-time monitoring advancing; challenges: data standardization, integration, security, regulatory validation of AI	Critical; enables robust offline operation, reduced latency, data security, autonomous control in distributed/POC settings
Advanced automated CIP/SIP and SUT sterility assurance	Compact, automated CIP/SIP for reusables; advanced in situ integrity testing, novel materials/designs for superior SUT sterility assurance	Medium; general CIP/SIP and SUT sterility patents exist; novelty in full integration/automation for CGT or advanced verifiable SUT sterility	Bioreactor manufacturers., specialized cleaning tech companies, SUT suppliers, research institutions	Medium to high feasibility; automation key; challenges: CIP/SIP complexity for flexibles, cost of advanced SUT features, validation of novel sterility methods	High; ensures GMP compliance, economic viability for some reusables, patient safety, critical for less controlled decentralized environments
Real-time GMP assurance via AI (anomaly detection)	AI analyzing sensor/batch data to proactively ID deviations (contamination, malfunction, CQA drifts), predict compliance issues, suggest actions	Low to medium; general AI in QC/GMP emerging; specific, validated AI for predictive GMP in CGT bioprocessing is newer; patenting AI needs effect	AI/software companies, bioreactor manufacturers, Pharma companies (PAT), academia	High feasibility; AI tools exist; Challenges: data quality, model validation, explainability (XAI) for regulators, QMS integration	Very high; aligns with PAT/QbD; enhances product quality/consistency, reduces batch failures, streamlines compliance, enables release-by-exception
Microfluidic production systems for CGT	Precise, miniaturized, automated systems for small-scale autologous therapy mfg., PD, research	Medium (general microfluidics); low (full CGT production systems); dominated by academia/ startups in R&D	Startups, university spinouts, specialized microfluidics companies	Medium feasibility (niche production); challenges: scaling (larger doses), cell handling (shear, clogging), integration, chip CoGs	High for POC/personalized medicine; potential for cost reduction, faster turnaround (autologous), new research models
Modular 'factory-in-a-box' platforms	Integrated, automated, closed systems combining multiple CGT mfg. steps into a compact, deployable unit	Medium to high; several companies have platforms (Lonza, Miltenyi, Cellares, Ori) with IP on integration and automation	Established cell therapy platform providers, new entrants (full automation)	High feasibility (prototypes exist/ commercializing); challenges: true 'plug-and-play' interoperability, cost, validation of complex integrated systems	Critical for decentralization; simplifies deployment, standardizes processes across sites, reduces facility needs

Source data from [32]

are less crowded. Patentability hinges on demonstrating concrete technical application improving system efficiency or enabling new functionalities. Feasibility is high due to advancing AI and real-time monitoring

- **Players:** tech companies (IoT/Edge AI), bioreactor manufacturers, startups. The patentability challenge underscores the need for IP strategies focusing on the technical application of AI to solve specific bioreactor problems

Advanced automated CIP/SIP and SUT sterility assurance:

- **Opportunity:** for reusables, compact, efficient, fully automated cleaning-in-place (CIP)/sterilization-in-place (SIP) modules [61]. For SUTs, advanced pre-sterilized, pre-assembled, easily verifiable closed systems with enhanced, rapid, reliable *in situ* integrity testing methods
- **IP and feasibility:** medium IP density for automated CIP/SIP in POC/allogeneic applications; high for hub-spoke scalability. General CIP/SIP and SUT sterility patents exist, but novelty lies in full integration/automation for CGT or next-gen verifiable SUT sterility. Automation is a strong trend
- **Players:** bioreactor manufacturers, specialized cleaning tech companies, SUT component suppliers, research institutions. The key SUT white space is verifiable and automated *in situ* integrity testing

Real-time GMP assurance via AI-based anomaly detection and predictive compliance:

- **Opportunity:** AI analyzing complex, multi-parametric data in real-time to proactively identify subtle deviations and predict potential GMP compliance issues (contamination, equipment malfunction, CQA drifts) before they escalate. This aligns with PAT and QbD frameworks
- **IP and feasibility:** low to medium IP density. Specific AI applications for predictive GMP in CGT biomanufacturing is an emerging field. Feasibility is high, with AI explored for predictive QA. Explainability (XAI) is critical for regulatory acceptance
- **Players:** AI/software companies, bioreactor manufacturers, pharma companies developing PAT, academia. 'Predictive compliance' offers transformative potential, moving beyond reactive control to intelligent manufacturing. IP for XAI methods applied to GMP bioprocessing is also a valuable sub-white space

Microfluidic production systems for CGT:

- **Opportunity:** precise, miniaturized, automated systems for small-scale autologous therapy manufacturing, process development, or research. Potential for cost reduction and enabling POC deployment
- **IP and feasibility:** medium IP density in general microfluidics (often academia/startups); lower for full CGT *production* systems. Feasibility for niche production is medium; scaling for larger doses and GMP compliance at microscale are challenges
- **Players:** startups, university spinouts, specialized microfluidics companies. The primary white space lies in the integration and automation of multiple CGT processing steps onto a single, robust, GMP-compliant microfluidic production platform

Modular 'factory-in-a-box' platforms

- **Opportunity:** integrated, automated, closed systems combining multiple CGT manufacturing steps into a compact, deployable unit, simplifying deployment and standardizing processes for decentralization
- **IP and feasibility:** medium to high IP density, with companies like Lonza, Miltenyi, Cellares, and Ori having

platforms with IP around integration and automation. Feasibility is high (systems exist/commercializing)

- **Players:** established cell therapy platform providers, new entrants focusing on full automation. The white space may lie in achieving true flexibility and adaptability within a standardized platform architecture, enabling one platform to handle diverse therapies

Next-generation single-use sensors and analytics

- **Opportunity:** improved single-use, robust, reliable, multi-parameter sensors seamlessly integrated into SUTs, providing real-time data on a wider range of CPPs and CQAs. Integration with AI/ML for enhanced real-time monitoring and predictive control

- **IP and feasibility:** ongoing drive for improvement despite existing sensor IP. Better real-time data is fundamental for PAT, QbD, and AI-driven insights

- **Players:** sensor technology companies, bioreactor manufacturers, SUT suppliers, research institutions. The white space includes sensor fusion and data analytics at the sensor level

The analysis of these white spaces reveals a significant overarching trend: the increasing importance of 'software-defined biomanufacturing'. Many identified opportunities point towards a future where software, data management, and AI are as critical to a bioreactor system's value and performance as its physical hardware. Consequently, IP in these digital domains will likely become a key differentiator. Another key area of evolution lies in the definition and assurance of 'sterility', with innovation moving towards advanced, verifiable methods of ensuring system integrity and closure, especially for SUTs, and truly automated, verifiable CIP/SIP for reusables.

Aligning innovation with evolving regulatory frameworks

Innovations in automated bioreactors, particularly those targeting white spaces, must be developed with keen awareness of and alignment with evolving global regulatory standards (e.g., from FDA, EMA, MHRA). This is crucial for successful market translation, especially for decentralized CGT.

Regulatory considerations are paramount for:

- **Edge AI and analytics:** systems must ensure data integrity (e.g., FDA 21 CFR Part 11), security (HIPAA, GDPR), and traceability, even in distributed models

- **Automated CIP/SIP and SUT sterility:** reusables must meet stringent sterility and cleaning validation. SUTs require superior sterility assurance (e.g., aligning with EU Annex 1)

- **AI for GMP assurance:** AI systems need thorough validation, explainability for regulators, and data integrity, aligning with PAT and QbD frameworks

There is an opportunity for 'regulatory IP'—innovations and patents specifically addressing or simplifying compliance. Proactive engagement with regulatory agencies during development (e.g., FDA INTERACT meetings, EMA innovation task force consultations) can de-risk innovation and provide a first-mover advantage.

TRANSLATING IP INSIGHTS INTO BUSINESS OPPORTUNITIES & STRATEGIC IMPERATIVES

Successfully navigating the complex IP landscape demands connecting innovations to tangible business opportunities by

solving critical industry problems, improving manufacturing efficiency and compliance, and enhancing patient outcomes.

IP strategies for capitalizing on white space opportunities

Tailored IP strategies are essential for each white space:

- **Edge-compatible software/analytics:** hybrid IP (patents for technical solutions, trade secrets for algorithms/datasets) to establish indispensable edge capabilities
- **Automated CIP/SIP and SUT sterility:** patent novel integrated module designs, cleaning methods, verification sensors for CIP/SIP. For SUTs, patent advanced *in situ* integrity tests, novel materials, verifiable closed system designs, and aseptic connectors
- **AI for real-time GMP assurance:** patent AI algorithms for detecting GMP deviations and systems for automated alerts/actions or batch record review. Demonstrating technical effect is key
- **Microfluidic production systems:** patent novel chip architectures, microfabrication techniques, precise cell manipulation/culture methods, and integrated sensing/actuation for CGT
- **Modular 'factory-in-a-box' platforms:** secure broad IP on overall system architecture, integration methods, fluidic pathways, and orchestrating software
- **Improved single-use sensors/analytics:** patent novel sensor materials, modalities, multi-parameter sensing, and sterile/robust SUT integration. A 'one-size-fits-all' patenting strategy is insufficient; hybrid approaches combining patents with trade secrets are increasingly important, especially for software and AI

Articulating commercial potential: market sizing and impact

The commercial value of IP-protected innovations stems from addressing critical CGT manufacturing challenges, such as automating QC to reduce labor and variability, or advanced SUT integrity testing to reduce contamination risk [62–64].

The market context is compelling:

- Global CGT market: US$18.13 billion in 2023, projected to US$97.33 billion by 2033 (CAGR 18.3%) [65]
- CGT tools and reagents market: US$10.0 billion in 2024 to US$16.7 billion by 2029 (CAGR 10.8%) [65]
- Cell therapy manufacturing market: US$4.90 billion (current year) to US$13.83 billion by 2035 (CAGR 9.90%) [66]
- Single-use bioreactors market: projected to US$10.42 billion by 2034 (CAGR 9.0%) [67], with some estimates suggesting ~17% CAGR through 2035. Capturing even a modest share [1] of this booming multi-billion dollar market offers significant returns. For example, an IP-protected AI solution for predictive compliance in decentralized CAR-T manufacturing (T-cell therapies projected >45% of clinical demand by 2035) [68] could capture substantial revenue

Broader benefits amplify value:

- **Faster turnaround times:** automation reduces vein-to-vein time, critical for aggressive diseases [69]

- **Lower cost per therapy:** efficiency gains can reduce high CGT costs, improving accessibility [70]
- **Improved therapy success rates and safety:** enhanced process control and sterility lead to higher quality, safer, more efficacious therapies [71]
- **Enhanced patient access through decentralization:** 'factory-in-a-box' systems simplify logistics and improve access [72]. Articulating this human impact alongside financial projections strengthens the business case for IP-protected innovation

Strategic recommendations for innovators and investors

To thrive, proactive and informed strategies are needed.

For innovators (technology developers, bioreactor manufacturers):

- **Focus on validated white spaces:** prioritize R&D and IP in areas like edge AI, advanced automation in sterility assurance, and AI for real-time GMP compliance
- **Adopt hybrid IP for software/AI:** combine patents for technical applications with trade secrets for core algorithms and datasets [73]
- **Design for modularity/interoperability (with IP considerations):** develop IP supporting modular designs and standardized interfaces where feasible for decentralization, while strategically protecting proprietary interfaces for critical consumables/software to create lock-in
- **Invest heavily in data systems/software IP:** protect innovations in software, AI, cloud/edge computing enabling robust remote control, monitoring, analytics, and secure data management [74,75]
- **Prioritize regulatory adaptability:** design systems and file patents with global regulatory trends (PAT, QbD, real-time release, electronic records) in mind
- **Consider full lifecycle IP:** extend protection beyond the bioreactor to integrated QC, fill-finish, logistics, and data management [62,76]
- **Monitor global IP landscape:** track activity from emerging hubs (e.g., China, South Korea) [2,3,13–16]

For investors (venture capital, private equity, corporate venture):

- **Scrutinize IP portfolios:** conduct thorough due diligence on patent strength, breadth, defensibility, FTO, and blocking IP
- **Target companies in validated white spaces:** focus on innovations with significant market potential and strong IP strategy
- **Evaluate ecosystem control potential:** assess if IP strategy can lead to significant control (proprietary consumables, software platforms, integrated systems), indicating market power and M&A attractiveness [11]
- **Assess regulatory astuteness:** favor companies whose innovations facilitate compliance
- **Look for global IP awareness:** invest in companies with global IP strategies

CONCLUSION: ALIGNING IP STRATEGY WITH PLATFORM DEPLOYMENT & MARKET REALITIES

The journey towards effective, widespread decentralized cell and gene therapy manufacturing is inextricably linked to continued advancements in automated bioreactor technology and the strategic deployment of intellectual property. These sophisticated systems are fundamental to achieving the consistency, scalability, GMP compliance, and cost–effectiveness demanded by distributed production models.

The IP landscape surrounding these automated bioreactors is dynamic, fiercely competitive, and increasingly global. Key players are establishing strategic control points around closed-system architectures, advanced sensor integration, proprietary single-use consumables, and critically, sophisticated software, data management, and AI solutions. This strategic patenting aims to create 'closed ecosystems', ensuring platform lock-in and defending pricing power.

Key findings from this analysis indicate a shifting geography of innovation, with Asia (particularly China and South Korea) emerging as a significant force. Distinct technological clusters are solidifying, with established giants refining SSTRs while startups and academia drive microfluidic and novel reactor designs for niche applications. While SUT principles are mature, innovation persists in advanced sterility assurance and integrity verification. Crucially, significant 'white space' opportunities persist, especially at the intersection of bioprocessing and digital technologies: edge-compatible software and analytics, AI-driven real-time GMP assurance, and advanced data management for decentralized networks.

To capitalize on these opportunities, a proactive, forward-thinking IP strategy is essential, intrinsically linked to a company's platform deployment model and the tangible market needs it aims to address. The value of IP is magnified when it solves critical problems related to CGT cost, scale, quality, and accessibility. For innovators, this means aggressively patenting in white spaces, employing hybrid IP approaches for software/AI, focusing on modularity while strategically protecting proprietary interfaces, and designing for regulatory adaptability. For investors, it requires diligent scrutiny of IP portfolios for defensible control points, FTO, and a clear link between innovation and significant business opportunity within the multi-billion dollar CGT market [1,65–68].

Looking ahead, while proprietary systems currently dominate, the potential for increased collaboration or open standards for foundational technologies could emerge. However, the prevailing trend suggests that companies successfully navigating and shaping the IP landscape for automated bioreactors—those securing and leveraging IP to control scalability, quality, compliance, and data at the manufacturing edge—will be best positioned to lead. A well-crafted IP strategy, aligned with technological innovation, market realities, and regulatory foresight, is paramount in realizing the full potential of decentralized CGTs for patients worldwide.

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CELL & GENE THERAPY INSIGHTS

DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

Manufacturing and clinical development strategies to expand access to CAR-T cell therapy for patients in India

INTERVIEW

"...maintaining consistent quality standards across multiple sites would be a challenge without central oversight, especially given India's size and diverse patient pool."

Abigail Pinchbeck, Commissioning Editor, *Cell & Gene Therapy Insights*, talks to **Amit Mookim**, CEO, Immuneel Therapeutics, about ongoing efforts to expand access to affordable autologous CAR-T cell therapies across India and beyond.

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Q What are you working on right now?

AM We are working on developing CAR-T cell therapies for leukemia and lymphoma. We have plans to expand into solid tumors and potentially allogeneic platforms, too. We have an ongoing clinical study—a CD19 CAR-T cell therapy trial in leukemia, which is an extension of the IMAGINE study.

Q What is the current situation in India in terms of the availability of CAR-T cell therapies to patients? What specific obstacles do you encounter when trying to make cell and gene therapies accessible and affordable in India?

AM CAR-T cell therapy is still relatively new in our country but the burden of diseases that could be addressed with this modality is massive—specifically, there are thousands of eligible patients with hematological malignancies in India. However, a significant amount of work is required on each of the key aspects that factor into adoption: awareness, availability, and accessibility.

Awareness of CAR-T cell therapy in India is still limited to large institutions and the major urban centers. While oncologists do have an appreciation of the clinical outcomes of CAR-T therapies now, the patients themselves need to be educated and helped to understand what this therapy means. With respect to accessibility, the insurance-based reimbursement model is still limited in India and for the vast majority of the population, current insurance policies are not sufficient to cover the relatively high cost of CAR-T therapies. Immuneel is in conversation with the insurance companies to share with them real-world data demonstrating how effective these therapies are. We are hopeful that over time, insurers and other payers in India will understand the need to include CAR-Ts in their coverage plans.

Regarding infrastructure, India is obviously a very large country. While there are hundreds of eligible hospitals, only a small percentage of them have adopted CAR-T therapies to date. Again, Immuneel is working extensively to accredit hospitals and provide the requisite training to clinicians and other staff, so that they too can offer these therapies to patients.

The good news is that CAR-T cell therapy is available in India at an 80–90% cost reduction compared to developed markets. That's a huge plus point. We are hopeful that with this kind of effort to bring prices down, we will slowly but steadily see adoption rates rise.

Q Can you share some of the key innovations and approaches that Immuneel Therapeutics is adopting to help achieve these twin goals of reduced cost and increased access?

AM High therapy costs are a function of a number of things. One is imported raw materials, which in the case of CAR-T therapy involves viral vectors as well as expensive licensing and logistics. Another is the difficulty in accessing economies of scale when working with autologous cell therapies. At Immuneel, we are working on both. Our focus is on continuing to innovate the manufacturing process and integrating insights gained into the earlier stages of development in order to bring down the costs of production.

We are exploring various ways to reduce the cost of raw materials, looking at both different sourcing strategies and local manufacturing options. We are also investigating how to build scale in the most efficient fashion. Immuneel was one of the first companies in

"We need to wait and see whether a completely decentralized model would work in India. I believe the technology is becoming available, but everything else has to fall into place, too."

India to establish a GMP manufacturing facility for CAR-T cell therapy. That gives us significant know-how in terms of commercializing production of these therapies. We are now applying that knowledge in assessing manufacturing processes with enhanced scalability, which in turn will lead to improved utilization of our capacity. Currently, we manufacture CAR-Ts in closed systems such as the Miltenyi Biotec's CLINIMACS Prodigy platform. We are working extensively with Miltenyi and others to see how we could increase capacity on these platforms.

Q How do you view decentralized advanced therapy manufacturing in India? And can you explain Immuneel's hub-and-spoke strategy to improve access to CAR-T cell therapy across the country?

AM Starting with the hub-and-spoke strategy, our current model is to partner with dozens of hospitals across India on both the initial apheresis and final product infusion, but to keep the manufacturing in a single centralized facility.

There are several benefits to this model, especially in a large country like India. For one thing, there is a relatively small pool of sufficiently trained staff available. Additionally, CAR-T therapies must be manufactured in a highly sterile environment, so the need to establish GMP-grade facilities is of paramount importance.

The jury is still out on decentralized manufacturing models with respect to cost, quality systems, and clinical outcomes. However, we do recognize the fact that these therapies require very close coordination with hospitals compared to a typical biological product, which is generally available off-the-shelf. The individualized nature of autologous cell therapy means that the hospital plays a huge role in working with both manufacturer and patient to achieve a successful outcome.

The question of whether or not cell therapy manufacturing will eventually move towards a decentralized model will depend on many factors. Availability of enabling technology will play a role; another key factor will be the scale required to justify establishing and maintaining decentralized GMP-compliant facilities with all of the specialized staffing and equipment that entails. India is a highly fragmented market with hundreds of hospitals across the country. It would be necessary to evaluate which of these hospitals should house facilities, and also decide whether or not they will cater just for their own patients or for other hospitals in the wider region. It is a different model to the USA, for example, where you have established Centers of Excellence.

We need to wait and see whether a completely decentralized model would work in India. I believe the technology is becoming available, but everything else has to fall into place, too.

Q Can you expand on the practical challenges of implementing decentralized manufacturing in India, and how Immuneel is going about addressing them to ensure quality and scalability?

AM As I mentioned earlier, the greatest challenge is finding a sufficiently large and skilled workforce to manage both production of advanced therapies and also the clinical side. While India remains a hub for talent, I think that's a practical challenge that we will continue to face for a long time. There are also major infrastructure gaps, as we have discussed, with many hospitals still lacking the setup and capabilities required to manage delivery of cell and gene therapies. And with a decentralized model especially, the most important aspect in CAR-T cell therapy delivery becomes quality control.

In my view, maintaining consistent quality standards across multiple sites would be a challenge without central oversight, especially given India's size and diverse patient pool. At Immuneel, working with a hub-and-spoke model, we run very stringent, comprehensive training programs for doctors, nurses, lab technicians, and transplant teams to ensure safe and effective delivery to patients. We are collaborating now with the top 30 bone marrow transplant centers in India that already have requisite infrastructure and expertise, and we have a methodology for accreditation of such centers.

Q How do you navigate the regulatory landscape in India, and what changes do you believe are necessary to foster further growth in this space?

AM The regulatory landscape in India for these novel products is evolving, as it is in other countries around the world—regulators and industry are working together and we are all learning as we go along. We have to keep safety and clinical efficacy at the center of everything, of course. We are bringing in global best practices, including insights from our international partners such as those in Europe from whom we licensed the CAR-T technology.

Having said that, establishing patient safety, infrastructure readiness, and standards are all aspects that still need to be fully worked through. As we've discussed, the single largest piece of the puzzle in India is building scale and accessibility in order to create an ecosystem where the cost of CAR-T therapy can be reduced. I think both the regulators and the wider Indian government are keen to explore the role that companies like Immuneel can play in helping to establish this ecosystem.

When it comes to cell and gene therapy, the entire model for how clinical trials are conducted—the number of patients involved, the data generated, etc.—differs somewhat from most other small and large molecule drugs. The approach to clinical development in

"...the single largest piece of the puzzle in India is building scale and accessibility in order to create an ecosystem where the cost of CAR-T therapy can be reduced."

this space is still evolving in India, and clearly there is a lot of learning that needs to come from the more established markets. There are numerous hospitals and institutions around the world that have already done a lot of work in CAR-T cell therapy development. It is important that the regulators understand what the starting point could be and take on board some of the work and the data that has gone before. That's one area where we are working closely with the Indian regulators.

Q What are your key goals and priorities, both for yourself in your own role and for Immuneel as a whole, over the next 2–3 years?

AM We have several goals moving forward, the most important being the expansion of patient access to our CAR-Ts across India. I think it's important that we remain close to our original purpose, which is to bring affordable cell and gene therapies to markets like India and to the patients who need them the most. That's something we'll continue to do, building greater awareness and establishing partnerships that allow us to reach more patients. Another key priority is building clinical readiness. We want to play an important role in training healthcare professionals to ensure safe and effective CAR-T delivery.

We are currently headquartered in Bengaluru, which is the location of our Integrated Cell Therapy Development and Manufacturing Facility. As we grow and seek to treat more and more patients, we will need to expand our own operations—that's going to be another important focus area. Linked to that, we will need to continue investing in R&D pipeline therapies targeting cancers, rare diseases, and autoimmune diseases, as well as technology platforms. Additionally, we are in constant dialogue with the regulators and the government, and we are collaborating with other industry bodies and policymakers to drive regulatory clarity and support building the ecosystem for cell and gene therapy in India, which is still very nascent.

Last but not least, a long-term dream for us is to build a company that is both from India and for India, as well as the rest of the world. We want to standardize Immuneel as a global platform and organization to take affordable, scalable therapeutic technologies across the world.

BIOGRAPHY

As CEO of Immuneel Therapeutics Private Ltd, **Amit Mookim** is a seasoned business leader with a strong focus on innovation, collaboration, and policy, driven by a purpose to improve healthcare access and outcomes. With a blend of consulting and operating experience in a career spanning 24 years with extensive work across healthcare, technology and analytics, and private equity advisory, he previously worked as Managing Director at IQVIA, overseeing operations across over 20,000 professionals and significantly expanding the commercial business. Prior to IQVIA, Amit headed healthcare at KPMG India, where he built the practice from the ground up, working with hospitals, PE funds, and global healthcare companies to establish their presence in India. His contributions as an advisor to national bodies and industry organizations have made him a respected thought leader in healthcare strategy and market access. In the field of life sciences, he chipped in to guide the National

Health Authority on creating market access for start-ups in PMJAY and has advised industry organizations such as the Indian Pharmaceutical Alliance, APACMED, OPPI, FICCI, and NATHEALTH on universal healthcare, market access, pricing, and innovation. Additionally, he has been involved in leadership committees and task forces to drive collaborative programs between industry and regulators. He possesses deep knowledge of commercializing new business models and expanding organizations and has worked across South Asia, APAC, the Middle East, sub-Saharan Africa, and Europe.

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CELL & GENE THERAPY INSIGHTS

DECENTRALIZED/DISTRIBUTED ADVANCED THERAPY MANUFACTURING

SPOTLIGHT

COMMENTARY

Decentralized patient access: how do we get there?

Becky Butler Cap

Medicine today has moved from harnessing the power of nature around us to unlocking the strength of cells within us. With multiple licensed CAR-T and cell therapy products on the market, patients benefit, but, even today, too few and too slowly 8 years after initial approval. Commercial success and ongoing investment in the space for therapies and technologies to support them are critically dependent on increasing the treated patient population. Meanwhile, eligible patients are struggling to get to care. The total treated population is in the tens of thousands of patients, with only 20% of the eligible patients ultimately receiving treatment. In a 2022 abstract published at ASCO, statistics across multiple institutions highlighted a 6-month waiting period and 25% treatment rate for patients with refractory multiple myeloma. It is expensive, time-consuming, far from home, requires a caregiver to be with you at all times for weeks near the point of care—in other words, the commitment to receiving care is a commitment to turning your world upside down. The solution is not the same for every community, but in the name of speed, we need to consider solutions that leverage existing infrastructure, talent, and process to make as big a difference as fast as possible. It will be easier to justify investment in tomorrow's innovations if we focus on solving today's problems and systematically learn from our collective experience.

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THE SYSTEM

In the 8 years since the first CAR-T product was approved, confidence in the clinical performance of these products has steadily increased. Because of that, the US FDA is focused on meaningful data and increasing patients' access through faster review times and more inclusive data reviews to move therapies to earlier lines of use in hematologic malignancies. In late June, the FDA announced its category-wide policy shift to eliminate the requirement for a Risk Evaluation and Mitigation Strategies (REMS) program for CAR-T cell immunotherapies and reduced the proximity requirement from 28 to 14 days. The decision maintained the requirement for 15-year follow-up, sustaining commitment to long-term monitoring. Even with the remaining

weeks of disruption required in patients' lives, this move by the FDA signals comfort with the knowledge gained thus far about patient management and eliminates a significant burden on treatment programs and patients. The FDA's decision is encouraging and emboldening as we think about how to disrupt current systems and thinking to make room for healthcare delivery infrastructure that can scale out autologous CAR-T cell therapy and lay the groundwork for other CGT products.

Thus far, CAR-T has been concentrated in academic health centers (AHCs). Clinical trials for novel therapies begin in these prestigious centers accustomed to dealing with the unknown and the operationally and clinically unusual. As therapies are licensed, they are introduced first in these centers where staff have been trained to deliver them. These centers also have the resources and the will to develop and maintain robust treatment and product management infrastructure required to support both product and care delivery. Patients keep coming because of the reputation of the center and the lack of treatment alternatives where they live.

Therapeutic developers align with AHC's through centralized manufacturing and tailored logistics support. Geographic concentration of centers in major metropolitan areas near logistics hubs facilitates this solution. Maximizing the connectedness between the developer/manufacturer and the AHC has been critical as we generated proof of concept that the promising science delivers clinical benefit. Tightly controlled access provided immediate feedback on models of care and the nuances of clinical management. With initial models established, getting therapy to patients who live outside those centralized hubs is critical. The locations and practical treatment volume limits of the AHCs mean that there is neither scale nor convenience to provide sufficient support for these therapies.

Why now? Why the urgency? Recalling Gartner's Hype Cycle, the cell and gene therapy industry has been in the Trough of Disillusionment for some time now, wrestling with the thorny issues that stand in the way of widespread adoption. We are emerging and creating pragmatic solutions to patient access, manufacturing success, and payment models. With the tailwinds of FDA's decisions, we have an opportunity to rethink solutions. We need to move from blockbuster *potential* to a blockbuster *reality* and make these therapies commonly available to ensure that investors have confidence to continue enabling scientific development.

The priorities must be increasing product use and increasing patient access. Getting to scale that rivals traditional pharmaceuticals or even biopharmaceuticals is one big hairy audacious goal (BHAG) [1]. Like any BHAG, this one is better accomplished by breaking it down to manageable and achievable tasks and goals.

The challenge before us is as big as the entire healthcare system and infrastructure–treatment, production, and reimbursement. The Darkhorse Consulting group modeled the centralized production capacity required to support billion-dollar, blockbuster-level patient treatment volumes. A single blockbuster-level product would require more than 8 million^2 feet of production space at a facility cost of $9 billion [2]. This analysis does not address the time required to build. Even using modular design and open warehouse space, construction time ranges from 18–60 months depending on the scale and scope of the facility build, available finances and people. This is time that the industry—and the patients—do not have. We need to rethink solutions and creatively deploy resources we already have in a new way.

DECENTRALIZING CARE

Decentralized manufacturing has been the focal point of debate and subject

of regulatory discussions and consultant analyses for several years. Recently, Sanjay Srivastava led a team in crafting a framework for how, when and where decentralization may be a meaningful solution [3]. The organizing question today, however, is 'How do we decentralize care while decreasing the waiting period and increasing the patient treatment rate?' [4,5]. In other words, get the right therapy to the right patients at the right time in the right geography, the biotherapy version of the rights of medication administration. The answer varies. Some patients and some therapies should remain centrally controlled. But to meet the demands of current and growing populations, we need broader access. Even among this very sick population of current patients, we see 55% of Americans battling cancer being treated in community oncology settings [6]. According to Johnson & Johnson Oncology and The Harris Poll [7], 91% of healthcare professionals (HCPs) agree that a patient's proximity to care significantly influences their treatment decisions, whether through clinical trials or licensed therapeutic options. Getting treatment options available closer to patients and their homes increases patient access, reduces stress burdens on families, and lowers cost and other access barriers in the system [3]. Even when patients and their families are motivated by the severity and acuity of their disease, few have the financial resources and support network to disrupt everything about their lives to relocate for the duration of therapy and monitoring. The reduced proximity requirement from 28 to 14 days will help but may not be enough. We need to simplify complex processes, reduce the expense of manufacturing, improve the speed of delivery, and move everything closer to the patient to extend access and improve outcomes for all.

These challenges grow further as we contemplate even larger target population indications of high-functioning patients in earlier lines of heme malignancies and in populations like autoimmune disease, neurological conditions, and cardiac conditions. The Alliance for Regenerative Medicine's Q4 2024 clinical trial data indicated that 289 cell therapy trials were ongoing for non-malignant conditions, 589 gene therapies [8]. 73% of surveyed HCPs say there is a gap between the availability of new/cutting-edge treatments and their successful implementation in clinical practice. Three out of four oncologists find the pace of new treatment development overwhelming, and seven out of ten struggle to navigate the complexities of cancer treatment guidelines [7]. Faced with larger patient populations and infrastructure gaps, the challenges in the system to expand treatment have an even greater impact. If physicians must think about the operational constraints of care delivery along with keeping up with medical innovation, progress will remain stalled.

BREAKING DOWN THE PROBLEM

In the current centralized model, the AHC handles all elements of patient care AND all first and last mile operations. As we push to move treatment into the community, we need to think about not only how decentralized manufacturing can help, but how decoupling the first and last mile activities from patient care and from manufacturing might create a different set of solution options. We need to think about how to leverage existing infrastructure to knock down time and expense hurdles and get treatment to communities where patients live.

Table 1 provides a schematic of options to develop and evolve product manufacturing and clinical delivery. Moving stepwise through these solutions increases speed, reduces cost, and creates a stable path forward for supporting therapeutic development through multiple scientific cycles.

TABLE 1

Evolution of product manufacturing and care delivery

Care and product delivery models	Rationale/role	System requirements	Patients served
Centralized care and manufacturing	Tight control on manufacturing processes; develop logistics and care model	Centralized manufacturing for each therapeutic developer; complete first and last mile support within each hospital	Restricted to most acute patients who have resources
Decentralized care with first and last mile support	Centralized manufacturing maintains control; leverages existing infrastructure to accelerate timeline; reduces budget impact both for hospitals and developers; creates baseline comfort level within hospitals; allows hospitals to focus on patient care; limits impact on patient resources	Centralized manufacturing; decentralized first and last-mile support; decentralized care in community hospitals; increased development of data systems	Allows acutely ill patients to be treated in communities where they live; allows for inclusion of earlier line patients
Regional hub manufacturing	Reduced logistics cost; reduced product transit risk	Current equipment exists; modular systems; facility locations	Stable patients; larger patient populations
Point of care manufacturing	Time-sensitive, large volume, fresh product	Automation; closed systems; integrated data networks; small footprint equipment; care facility space allocation	Wide range of patient populations
Regional manufacturing in a controlled non-classified (CNC) space	Eliminates cost of clean room production for CGT products; expands the available workforce pool; leverages the model used to provide the world's blood supply; allowed by closed system and automation; reduces facility costs; allows for more focused production teams delivering for a region	Automation; closed systems; integrated data networks; scaled production of small footprint equipment; CNC space in a regional hub	Increases access for all patients elligible for the most technically stable products to be readily treated in their community

These models illuminate options that had not been clearly visible before and offer solutions that can be tailored to a region or a therapy type.

PRODUCT PREPARATION & DELIVERY

Required community infrastructure includes facilities, equipment, people, and process.

- **Trained physicians:** disease management and cell and gene therapy delivery;
- **Clinical staffing:** mix of physician specialties to be on staff and available to support delivery per FACT accreditation standards [9];
- **Starting material collection**: apheresis collections **infrastructure** and **capacity** to collect cellular starting materials—SOPs, equipment, nursing staff, space;
- **Starting material testing:** laboratory support for processing and evaluating leukapheresis collections–cell count, viability, and cell marker ratios;
- **Cryopreservation**: technology and storage infrastructure and space;
- **Storage:** Intermediate and final product storage across a range of appropriate conditions—refrigerated at 2–8 °C, in a standard freezer at -80 °C, or in liquid nitrogen storage—until the next step in the process;
- **Thaw and prep:** at the time of delivery to the patient, therapeutic product needs to be thawed, prepped for infusion, and delivered to the bedside;
- **Infusion**: the simplest task, but the one without which none of the rest of it matters—delivery and infusion of the product to the patient;

- **Monitoring**: short-term following treatment and 15-year patient monitoring and data collection;
- **Logistics management:** packing; product preparation; shipping; receiving; COI/COC documentation and storage of shipping materials and containers;
- **Process documentation**: at each step, manufacturing process and quality control documentation for batch record completion, traceability, and trackability;
- **Data management**: a unified or connected system to contain both the manufacturing and patient follow up data.

Extending into community care settings without an identified infrastructure to support puts unsustainable strains on those clinical sites and on the developers' systems. The cost and the operational burden are intense.

LEVERAGING EXISTING INFRASTRUCTURE FOR TIME & MONEY: THE BLOOD CENTER SOLUTION

As we engage in this strategic planning debate, several models are being considered under this decentralized umbrella.

- Each clinical site could replicate required facilities and infrastructure within their walls;
- Therapeutic developers could build regional hubs, each specific to its therapy's process;
- Combine fit-for-purpose clinical care and outsourcing models to leverage clinical support infrastructure already in the community.

When considering the solution, we must return to the key drivers of time and money. What can we implement quickly and cost-effectively? The most efficient first step leverages existing infrastructure and focus to deliver a new solution. Clinical care systems in the community provide patient care. Centralized manufacturing maintains control and consistency while we evolve other parts of the system.

Blood centers currently manage critical biologics infrastructure across the nation. In some communities, the first- and last-mile steps between the patient and the therapeutic developer in cell and gene therapy are being delivered by these same community blood centers. Many of them can deliver core support services:

- Apheresis collections infrastructure and capacity
- Laboratory support to process and evaluate apheresis collection products

A growing number of centers in a growing number of locations can do more to close the gaps in the product delivery system:

- Cryopreservation technology and storage infrastructure
- Product shipment under controlled conditions
- Manufactured product receipt and storage until clinical delivery
- Product thaw and prep for infusion
- Product infusion
- Longer-term (15-year) patient monitoring
- IT infrastructure to support use of a mix of industry portals for data capture

In managing their internal operations and providing the blood supply across the country, blood centers have already tackled:

- Hiring, training, and motivating staff
- Training at multiple locations on consistent SOPs for licensed products
- Decentralized manufacturing of the nation's blood supply
- Manufacturing using closed, automated systems in CNC space

NETWORK OF NETWORKS

Speed is of the essence in solving this infrastructure problem. Blood centers form a network of networks purpose-built to support hospitals—historically with blood products—and now bringing cell and gene therapy products to patients. Some consolidation in the blood center space has led to the creation of large, multi-community blood centers; themselves a network of networks and part of a larger ecosystem of community blood centers that deliver blood products and services across the nation. Facilities in major cities serve their immediate and surrounding communities, remote centers serve less densely populated areas, and a network of nurses and technicians are in place to travel into additional communities to perform procedures.

SUPPLY CHAIN & LOGISTICS

The supply chain, similarly, is well developed. Communication, coordination, product transport, clinical licenses and privileges for nurses and clinical staff all work well to support the clinical side of the logistics equation. On the blood processing and manufacturing side, blood centers have developed robust relationships and network bargaining positions with suppliers of disposables, reagents, and hard equipment. During COVID, those skills became finely honed. The internal quality procedures to manage disposables inventory are already developed as a framework. Those functions and relationships are readily expanded to address cell and gene therapy.

Availability is key. With consolidation and centralization of centers, depots have been established closer to the patients–a robust hub and spoke model that get the products that are needed, when and where they are needed. This is critical logistics and supply chain infrastructure since blood products have a short shelf-life of days to weeks, not months to years. Margins are tight on products that are the unsung heroes of healthcare, taken for granted until you or a loved one needs them. As such, centers work hard to maximize efficiencies to ensure that these products can reach the patients who need them in the communities where they live. This efficiency mindset translates well to the CGT space.

STABLE WORKFORCE

That enterprise-wide culture devoted to mission and to saving lives is what helps blood banking organizations attract and retain talent for decades. Introducing new demands and new opportunities for growth injects enthusiasm into the environment and gives younger staff looking for a new skillset the opportunity to think more broadly about how they can contribute. The DNA of these blood center organizations is leveraging their scientific and technical skills to provide life-saving community services. This new chapter of scientific and clinical breakthrough using the cells they have been working with in a different way has infused these organizations with an energy and enthusiasm that is palpable. The combination of meticulous attention to detail and process, and excitement for 'the new' amongst staff

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puts blood centers in a position to leverage underlying infrastructure and grow team members through some of the robust training and development programs that exist today.

BLOOD CENTER CREDIBILITY: LONG-STANDING CLINICAL ENGAGEMENT

Across the lifespan of blood centers, active partnerships have developed between those centers, clinical care partners and their broader communities. Hospitals experienced with those services have asked blood center colleagues for support. They recognize the connection between current clinical services and the needs for supporting immediate growth in cell and gene therapy. Over that time, blood centers have gained credibility through:

- Millions of clinical products managed each year
- Maintenance of regulatory filings
- High compliance—regulatory and accreditation audits (FDA, FACT, AABB, ASHI, CAP, CLIA, etc.)
- Providing outsourced clinical services:
  - BMT/HSC laboratory functions
  - Transfusion services
  - Coagulation, diagnostics and monitoring HLA Typing, and Immunohematology Reference lab

REGULATORY INFRASTRUCTURE

Within each blood center operation, there is a standardized Quality Management System that governs all sites. A set of consistent Standard Operating Procedures that drives both operational alignment and product quality across the organization is critical for regulatory compliance. Blood centers' quality control and SOPs navigate the range of requirements of 21 CFR 606.20 and 606.100, 21 CFR 640 and 21CFR 1270/1271, along with compliance across accreditation bodies. Some centers have navigated to compliance with 21 CFR 211.22(a), making their operations and procedures more specific in task and language. Staff training and equipment maintenance are monitored centrally with consistent standards, with experienced teams traveling from the hub to introduce new capabilities to 'spoke' sites, and internal auditors supplementing compliance overseen by FACT, AABB, and FDA. Centralized contracting that covers all activities and sites is a further operational boon for clients working within these networks. Engaging with centers to develop a smooth operating relationship requires a partnership mindset and a clarity of communication that ensures a full and consistent understanding of expectations.

Blood centers have achieved a balance between clinician and patient needs and product use requirements and regulatory standards over the past eight decades of operation. Many centers manufacture products that cross state lines and so have experience filing and maintaining Biologics License Application (BLAs). Again here, as with many of the regulations surrounding blood and CGT products, there is additional work to be done to navigate the differences between operational intent behind regulations and guidances that sound similar, but sometimes with different intent. The BLAs filed by blood centers today are, on a practical level, most comparable to completing Process Performance Qualification (PPQ) batches demonstrating consistency in manufacturing across settings. In this setting, manufacturing is done in a controlled, not classified space. While the differences are real, we can borrow and adapt this framework from the blood world to speed

up our progress in the CGT space. These same types of systems and practices can be leveraged to support decentralized manufacture of cell and gene therapies. This experience and underlying systems set the stage for how blood centers could play a role as the patient population expands and manufacturing decentralizes.

CLOSING GAPS

Building the manufacturing capabilities that the DHC group referred to is difficult, expensive, and time-consuming. Blood centers have 60–80% of the infrastructure needed across the country to support the first-mile to last-mile delivery of therapy. Some systems are fully operational in the space. They have the physical infrastructure and laboratory environment, the direct connection to, and sometimes presence in, the clinical treatment setting, and the quality systems and employee mindset critical to supporting clinical operations. Moving that infrastructure from 60–80% ready to 100% will require time and money, but at a far lower price point than having either individual hospital systems or therapeutic developers build their own. Many centers have already made these investments and more to meet local needs, including hundreds of Optias for apheresis collection, solitary clean rooms in five cities and at least three ISO 7 background cGMP manufacturing facilities. Infrastructure aside, fully closing the gap requires development of trust and familiarity in relationships between therapeutic developers, blood centers and hospitals. The regulatory language is clear in its expectation that the manufacturing complex is an extension of the developer: 21 CFR 200.10(b) 'The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer's own facility'. Adjusting to partnership with and language of therapeutic developers is a substantial shift. Working the stepwise path of first- and last-mile partnership opens the door for progress and relationship to build a strong foundation for further growth.

DECOUPLING THE VALUE CHAIN

The blood center solution for first- and last-mile moves the product closer to the community, increasing treatment volumes. Moving manufacturing in that direction will be an important next step. It brings the product closer to the patient, reduces timing and operational barriers, risk of product loss, and supports unclogging the hub and spoke model.

Decentralized manufacturing is not the definitive solution for increasing access to care for all types of therapies, but it is a critical component to scaling [5]. One day, not too far away, assuming regulatory standards support it, we will be able to produce therapies at point of care, some in a modular clean room nearby, others using portable closed systems. These systems are being developed and programmed with appropriate automation to respond to the cellular makeup of the patient receiving treatment that day and with release testing capabilities built into the system. That is a next step that reduces even more barriers. Getting treatment closer to patients where they live and doing it more efficiently and cost-effectively, leveraging existing infrastructure, systems, and talent—is our best next step toward that goal. As they have many times before, blood services professionals are stepping into the gap to help navigate the clinical, technical, regulatory and accreditation requirements for the production and delivery of cell therapies. This step into care delivery in the community leverages expertise and focus at every level: patient care in the clinical setting, manufacturing centralized with therapeutic

developers and first- and last-mile with community care experts.

MANUFACTURING: WHAT'S OLD IS NEW

The biggest challenge today comes in the form of production equipment and environmental requirements imposed by the FDA. The FDA has established a standard for manufacture that is closer to pharmaceutical/chemical products produced in large volumes rather than the bespoke batches produced in closed systems today. Maintaining manufacturing in an ISO 7 classified clean room environment is a significant leap for any decentralized processing function. There are mobile and modular systems being developed and trialed in geographies around the world—notably in Brazil and India—launched and are testing out the model. The UK and Spain are experimenting with decentralized models. Modular and mobile systems with built in automation and manufacturing support are being developed. So, potential solutions exist—GermFree, Hitachi, G-CON—if we need to go that direction, that will allow for distributed manufacturing in this environment. The Hitachi–Children's National Hospital collaborative effort, CellBuilder, is an innovative example of packaged facility, equipment, training, and IP that could support broad distribution of production capacity.

These innovations are encouraging if we are to move toward decentralized manufacturing under current regulatory standards. It affords us an opportunity, however, to re-examine the underlying assumptions behind the need for clean room manufacture *for **all** CGT products*. While this serves as an effective barrier to entry for teams that are not adequately trained and fully qualified to deliver safe products, we have enough experience as an industry and enough innovation in closed production equipment, that it is time to broaden our view.

We now have 8 years' experience since Kymriah was approved, and roughly 20 since Dendreon was approved, to look at the contamination rates for products manufactured in ballroom-style clean rooms using process controls to manufacture in closed systems. We also have decades of blood and stem cell processing experience in closed systems in controlled non-classified (CNC) space. The manufacturing team in blood centers walk around large, open rooms in lab coats and gloves carrying bags of blood and blood product in their hands and on carts. The bags get connected to or placed in equipment that then works to process blood into its component parts and package them for use in a clinical transfusion; getting them ready to save the life of a bleeding patient just rescued from the scene of a horrible automobile crash or to rescue a mother and baby suffering complications bringing a new life into the world or to bring color, life, and energy back into a cancer patient who desperately wants to have a 'normal day' interacting with family after a round of chemotherapy. Blood products make a difference in people's lives every day. They are critical for the patients with inherited bleeding disorders, with sickle cell disease, with complications from medical procedures. All these products are manufactured in closed systems in CNC spaces with no clean rooms, no controlled air exchanges, and no operators in full personal protection equipment (PPE). Walking the production floor, one meets operators and leaders who were manufacturing at a time when there was no automation, no sterile docking mechanism. Notably, this *step up* to closed systems and a CNC environment has occurred in the lifespan of our production staff. Thirty years ago, blood products were processed in open systems with even fewer controls.

We need to get therapy to more patients. Closer to the communities they live in. Before we spend extravagant amounts replicating smaller, lighter footprint

TABLE 2

Benefits of centralized vs decentralized manufacturing, and blood center contributions.

	Centralized manufacturing	Decentralized manufacturing	Blood center contributions
Benefits	High control; proof of concept; nuanced care model development; streamlined connections with developer	Product closer to patients; eliminates/reduces transport costs	Community relationships—hospitals, physicians, and patients; facility, process, and people infrastructure well developed; clinical mindset

manufacturing operations in every community and hospital, we should take the time to think critically about the frameworks that Srivastava *et al.* laid out and push them further. The production environment should align with sensitive product characteristics and one of those options should be to use closed system equipment in a CNC environment. Even with the innovations of Cell Builder and GermFree, implementing a CNC production option for closed systems could allow current CNC sites to accelerate the introduction of local production for current CAR-T products with a cost avoidance of $1–5 million per site. With this change, the time and money required to close gaps in available infrastructure shrink, just what the industry needs.

REMAINING HOSPITAL & SYSTEM CHALLENGES

There is no shortage of challenges that neither blood centers nor decentralized manufacturing address currently:

- The number of physicians, throughout the industry, trained to deliver cell and gene therapy
- The number of physicians throughout the industry, who make up the mix required by FACT to support delivery
- Automation and closure of this equipment (coming)
- Data management tools (coming)
- Segmented reimbursement and billing infrastructure
- Accreditation standards for community clinical settings (in revision)
- Collaboration and cooperation (will it come? will it come soon enough?)

Fortunately, technical and engineering teams, regulatory, accreditation, and health economics experts are all working toward the common goal of enabling patient treatment (Table 2). When we get to a system that supports the use of CGT to its full potential, we will have fundamentally created new paths in healthcare. The more efficiently we do this, the more resources we can spend on developing new science and creating new options for care.

Note: About the Johnson & Johnson & The Harris Poll: This survey was conducted online within the United States by The Harris Poll on behalf of Johnson & Johnson, from November 21–December 13, 2024 among 500 adults age 18+ who are duly licensed and either hematologists/oncologists, urologists, APPs in hematology/oncology, or APPs in urology (MDs in Oncology [n=221], MDs in Urology [n=160], Advanced Practice Providers (APPs) in Oncology [n=102], and APPs in Urology [n=17]). Oncologists and APP oncologists treat at least one patient with blood and

one patient with solid-state tumor cancer, while urologists and APP urologists treat at least one patient with solid state tumor cancer.

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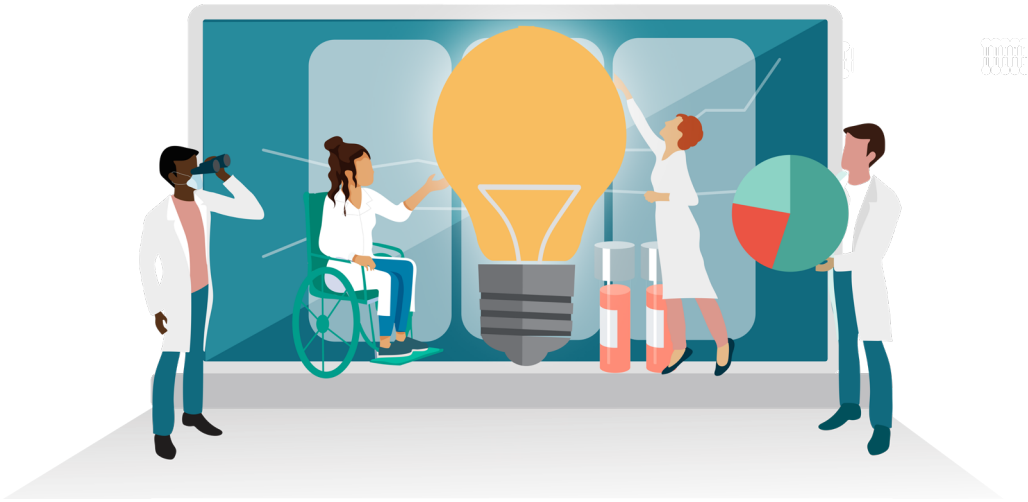
CELL & GENE THERAPY INSIGHTS

COMMUNITY INSIGHTS

SPOTLIGHT

Mapping the cell and gene therapy landscape: community insights

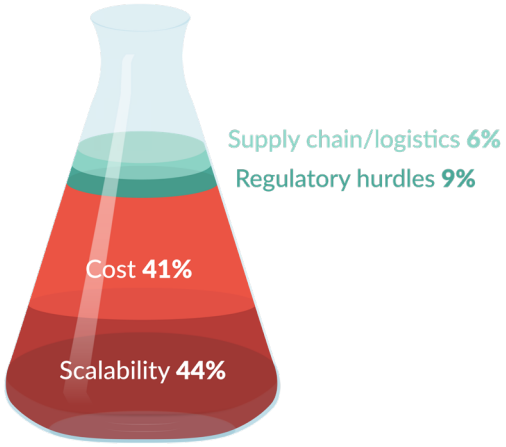


Over a six-week period in May 2025, we surveyed the *Cell and Gene Therapy Insights* community on LinkedIn to evaluate the current state of the cell and gene therapy (CGT) field—exploring current challenges, emerging technologies, and expectations for the future. With 950 total responses, the results revealed key pain points, major barriers to progress, and the most promising innovations expected to drive the field forward.

Cell & Gene Therapy Insights 2025; 11(6), 797–801 · DOI: 10.18609/cgti.2025.089

THE KEY CHALLENGES IN THE CGT FIELD

As the number of CGT products approved by regulatory agencies such as the US FDA and the EMA continues to rise each year, demand for these therapies has grown substantially. This surge emphasizes the urgent need for manufacturers to innovate and streamline their production processes to keep up with the rapid evolution of the CGT landscape. However, several challenges must be addressed to alleviate the clinical translation of CGTs and increase patient access.

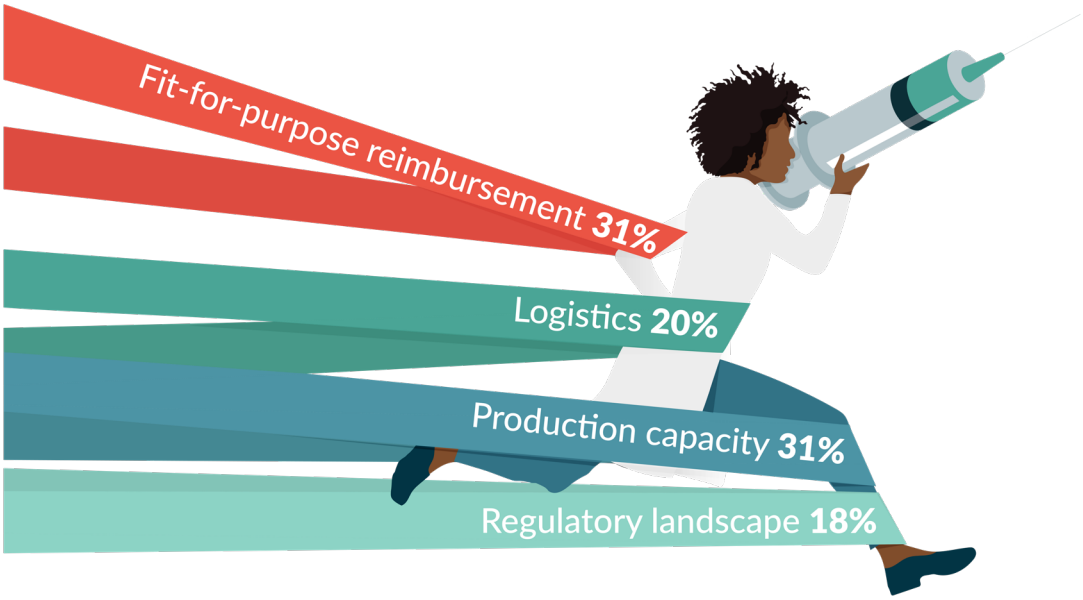


WHAT IS THE BIGGEST BOTTLENECK IN CELL AND GENE THERAPY MANUFACTURING TODAY?

According to our polls, 44% of respondents see scalability as the biggest bottleneck in CGT manufacturing, closely followed by cost at 41%. While supply chain (6%) and regulatory challenges (9%) are still concerns, they are viewed as less significant in comparison.

Regarding patient access, the high cost of CGTs is still a major barrier, which raises discussions around affordability, reimbursement, and long-term value.

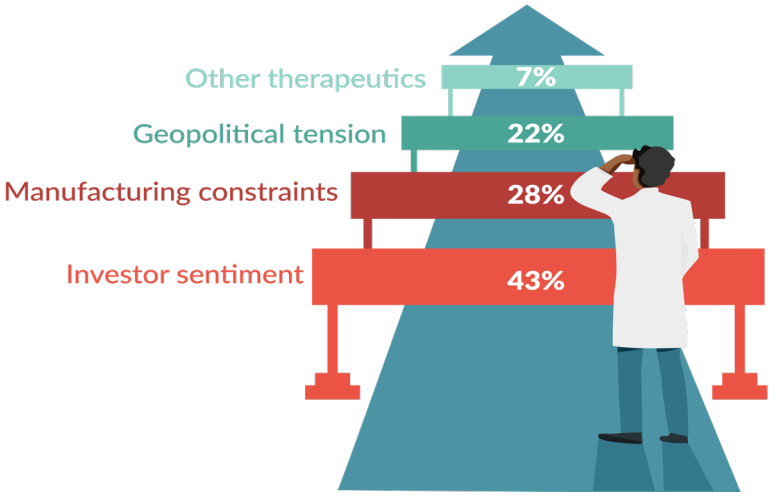
EXCLUDING COST, WHAT IS THE MOST SIGNIFICANT BARRIER TO ENSURING GLOBAL PATIENT ACCESS TO CELL AND GENE THERAPIES?



Cell & Gene Therapy Insights 2025; 11(6), 797–801 · DOI: 10.18609/cgti.2025.089

Apart from cost, our community identified fit-for-purpose reimbursement models and limited production capacity as equally pressing challenges (both at 31%). Logistics (20%) and regulatory hurdles (18%) also continue to pose hurdles to global access.

WHAT REPRESENTS THE GREATEST THREAT TO THE CELL AND GENE THERAPY SECTOR IN THE COMING 5 YEARS?

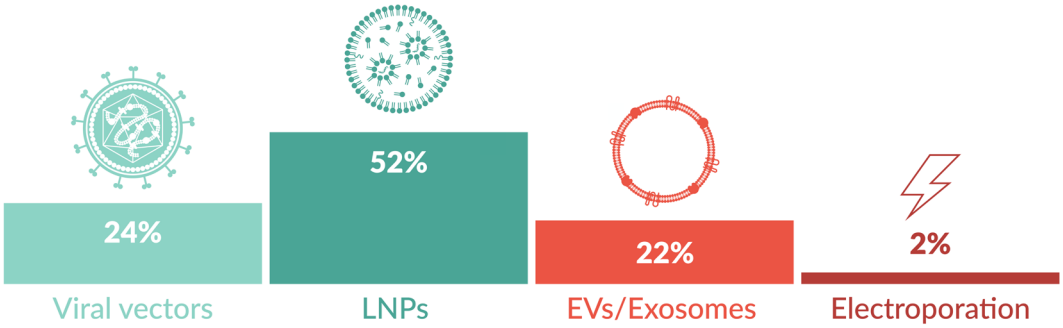


Furthermore, our polls highlight investor sentiment as the most significant perceived threat to the CGT sector over the next five years, cited by 43% of respondents. Manufacturing constraints also pose a major concern, accounting for 28% of responses, while geopolitical tensions were noted by 22%. Comparatively, competition from other therapeutic modalities was viewed as a lesser risk, identified by only 7%. These findings suggest that financial confidence and scalable production capabilities are seen as critical challenges for the future growth of CGT.

EXPLORING NOVEL TECHNOLOGIES

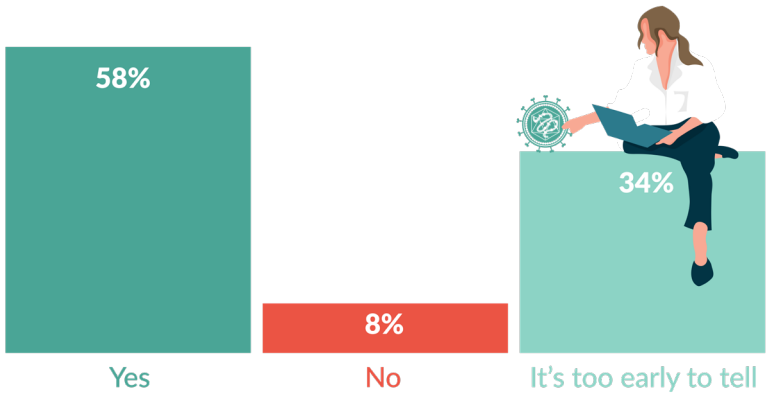
The emergence and maturation of novel technologies are transforming both the development and delivery of CGTs, including non-viral genetic material delivery tools such as lipid nanoparticles (LNPs), as well as the rise of AI. Together, these technologies are helping to overcome longstanding challenges in CGT, creating space for more effective, scalable, and personalized therapies.

WHICH GENE DELIVERY TECHNOLOGY AREA WILL WITNESS THE GREATEST INNOVATION OVER THE NEXT 5 YEARS?



Our survey results indicate that LNPs are expected to drive the most innovation in gene delivery over the next five years, with 52% of respondents selecting them as the leading area of advancement. Viral vectors and extracellular vesicles/exosomes followed at 24% and 22% respectively, reflecting continued interest in these platforms. Electroporation, by contrast, was seen as having limited innovation potential—only 2% of respondents highlighted it.

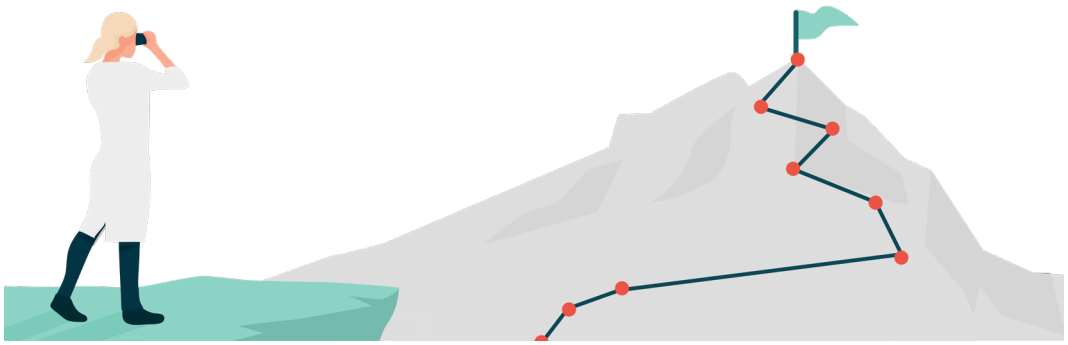
CAN AI/MACHINE LEARNING TECHNOLOGIES REVOLUTIONIZE CELL AND GENE THERAPY MANUFACTURING?



When it comes to AI and ML, most respondents (58%) believe that these technologies have the potential to revolutionize CGT manufacturing. While some remain uncertain or skeptical, the prevailing sentiment suggests strong optimism around the role of advanced data analytics and automation in streamlining production, improving quality control, and accelerating process development in the CGT sector.

Cell & Gene Therapy Insights 2025; 11(6), 797–801 · DOI: 10.18609/cgti.2025.089

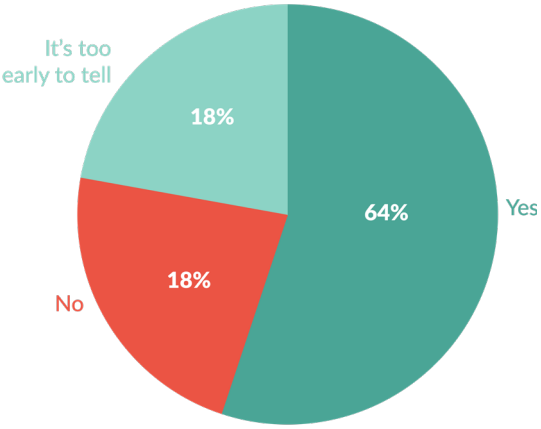
EXPLORING THE FUTURE DIRECTION OF THE CGT SECTOR



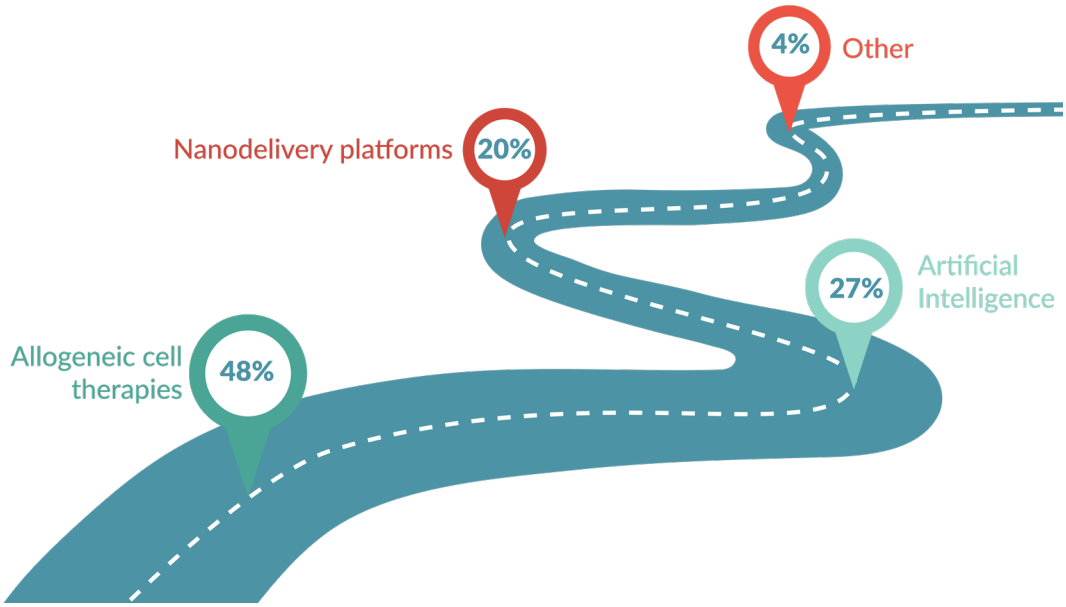
While many challenges are yet to be addressed, the CGT sector is rapidly advancing and showing tremendous promise for the future of medicine. With 43 CGT products now approved by the FDA, the field is transitioning from experimental treatments to commercially viable therapies.

DO YOU SEE GENE THERAPIES BECOMING PART OF ROUTINE TREATMENT FOR CONDITIONS LIKE HEMOPHILIA AND MUSCULAR DYSTROPHY IN THE NEXT FEW YEARS?

For example, nearly two-thirds (64%) of our respondents believe gene therapies will become part of routine treatment for conditions like hemophilia and muscular dystrophy in the coming years.



WHICH 'FUTURE OF CELL AND GENE THERAPY' TOPIC ARE YOU MOST CURIOUS ABOUT?



Continued innovation in areas such as gene delivery, manufacturing, and data-driven development is paving the way for broader access, improved efficacy, and expanded indications across a range of diseases.

When asked which future topic in CGT they're most curious about, 48% of respondents chose allogeneic cell therapies, followed by artificial intelligence (27%) and nanodelivery platforms (20%)—highlighting strong interest in scalable, next generation treatment approaches.

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CELL & GENE THERAPY INSIGHTS

ANALYTICS

Reference standards for autologous products: material is not immaterial

Alison Caldwell

VIEWPOINT

"...the [cell and gene therapy] field is rapidly advancing, and guidance documents are often trying to keep pace with innovation."

Reference standards are highly characterized materials that are used to ensure the quality and consistency of drug products. They play a critical role in calibrating assays, validating analytical methods, qualifying critical reagents, and ensuring batch-to-batch comparability. Despite their importance, there is no specific regulatory guidance for the development of reference standards within the cell and gene therapy sector. This inevitably leads to a lack of consistency in identifying and qualifying suitable reference standards which can delay or hinder clinical development. This article highlights some of the challenges that cell and gene therapy developers face when selecting and characterizing suitable reference standards.

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MATERIAL AVAILABILITY/ SUITABILITY

A small selection of reference materials that are applicable for the cell and gene therapy sector are available from international standards organizations such as the National Institute for Standards and Technology (NIST, USA) and the National Institute for Biological Standards and Control (NIBSC, UK). These include assay standards for cell enumeration and viral vector characterization and flow cytometry standards such as pre-labelled CD4+ cells. However, these materials are not specific to individual products and are limited in the critical quality attributes (CQA) they measure. Consequently, most manufacturers have to develop their own product-specific internal reference standards. In many cases, this would be a well-characterized batch of Drug Product (DP).

Depending upon batch size, allogeneic therapy developers can follow similar processes to the biopharmaceutical sector and follow a defined reference standard life cycle throughout the drug development process. In this context, several batches of reference standards are generated: interim, primary and working. An interim reference standard is generated from a development or toxicological testing batch and is typically used in initial Phase I/II clinical trials. During pivotal clinical trials, a primary reference standard is then generated, which serves as a basis for establishing all future reference standards including working standards, which are used to release manufactured batches. The primary reference standards must be sufficient for qualifying working reference standards throughout the commercial life of the product, with risk assessments in place to ensure sufficient inventory and an established strategy in place in the unlikely event that material needs to be replaced.

For autologous therapy developers, defining the life cycle of reference standards is more challenging due to the availability of DP and variability of patient specific starting material. In some cases, it may be possible to use DP batches derived from healthy donors. However, it is critical to ensure that the healthy donor derived material is suitably representative of the clinical DP and has comparable CQAs. For some autologous products it may be possible to combine DP from multiple production runs to generate a larger stock of reference material. In this approach, each batch is individually characterized and then the material pooled. Pooling material increases supply of the batch and decreases the requirement for multiple batch stability studies. Furthermore, pooling material from multiple manufacturing runs could ensure a more representative reference standard as it incorporates the inherent variability of the autologous product. However, pooling of material is not always possible for autologous products depending on cellular composition. In contrast to allogeneic therapy, it may be difficult to have sufficient stock of a primary reference standard to qualify all lots of working reference standards. In this respect, for autologous therapy a pre-defined lower limit quantity of reference standards must be identified and a robust qualification strategy for all lots of material must be in place.

REFERENCE MATERIAL CHARACTERIZATION

To determine the suitability of a DP batch as reference material, each lot must be qualified using both release assays and additional in-depth characterization assays. In many cases, it is not required to perform all the release assays performed during clinical DP release but only those relevant to the CQAs the reference material is being used to calibrate or control for.

During the life cycle of reference standards in autologous therapy, where new lots

of DP reference standards are introduced, a bridging assessment must be performed as a minimum to demonstrate comparability of old and new lots of material. This bridging assessment should include multiple independent assays where the new lot is compared to the old lot to determine comparability of the lots in the tests they are required for. Further, where the reference material is used in potency assays, pre-defined statistical analysis should be used to assign a potency value to the new lot of reference standard.

REFERENCE MATERIAL STABILITY

Finally, the stability of the reference standard must also be monitored. This should be monitored over the life cycle of the reference standard using the relevant release assays and characterization assays as identified in the batch qualification. Developers should ensure that stability is accounted for when defining the reference standard life cycle and introducing new lots of DP to ensure stability does not impact the comparability of old and new lots of material.

CONCLUSION

Cell and gene therapies present many challenges for the development and implementation of reference standards and often limit the application of traditional approaches used by established sectors such as the biopharmaceutical industry. However, these challenges do not diminish the critical need for robust systems to ensure product quality, consistency, safety, and efficacy.

Regulatory bodies are actively working to establish guidelines for the cell and gene therapy sector. The recent US FDA draft guidance on *Potency Assurance for Cellular and Gene Therapy Products* highlights the importance of reference standards and the need for bioassays calibrated to reference material that have arbitrary potency. However, the field is rapidly advancing, and guidance documents are often trying to keep pace with innovation.

The question of what constitutes an acceptable reference standard or an alternative approach to ensure consistency, particularly for autologous therapies, is a subject of ongoing discussion and debate. However, no material is immaterial.

BIOGRAPHY

Alison Caldwell obtained her BSc (Hons) in Microbiology at the University of Glasow, Glasgow, UK and her PhD in Immunology and Cancer at the University of Southampton, Southampton, UK between the years of 2010 and 2018. After her postdoctoral research training, she worked for a number of years as a Study Director at Charles River Laboratories in Edinburgh within the immunology department. In February 2023, she joined Resolution Therapeutics as Analytical Development Group Lead, where she is leading the development of analytical assays for regenerative macrophage therapies, with a keen interest in CMC regulatory affairs. Alison is a member of the BioIndustry Association Manufacturing Advisory Committee Leadership Programme (BIA MAC LeaP) and a mentor on Phacilitate's Woman in Advanced Therapies (WIAT) mentorship programme.

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CELL & GENE THERAPY INSIGHTS

TRANSLATIONAL R&D

Bringing cell therapies closer to patients: the role of automation, analytics, and decentralized manufacturing

INTERVIEW

"For certain indications and types of therapies, I believe autologous cell therapy and decentralized manufacturing can truly increase patient access."

Jokūbas Leikauskas (Editor, BioInsights) speaks to Therese Choquette (Head of Analytical and Translational Sciences, Tigen Pharma) about autologous cell therapy manufacturing challenges, analytics strategies, decentralized production models, the importance of collaboration, and the role of automation and digitization in improving scalability and patient access.

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Q What are you working on right now, and what are the key focus areas at Tigen?

TC Tigen is a Swiss clinical-stage biotech company that aims to fight cancer using autologous cell therapies such as CAR-Ts and tumor-infiltrating lymphocytes (TILs). We want to bring those breakthrough innovations to patients, accelerate

the development, and enable the adoption. We have an armored CAR-T cell therapy targeting relapsed/refractory Acute Myeloid Leukemia (AML) in Phase 1, in collaboration with Memorial Sloan Kettering Cancer Center (MSK) in New York. Eventually, we want to bring manufacturing closer to patients through a decentralized model. Alongside the clinical development plan for our armored CAR-T cells, we are working on optimizing the manufacturing process and supply chain, keeping commercialization in mind, while the analytical team is focusing on the strategy for the next phase of the clinical trial. Another important part of the industrialization is our work on a highly versatile platform for characterizing both the starting material and the final product.

Q With your background in immunology and experience as a licensed practical nurse, why do you think autologous cell therapies hold particular promise for patients, especially from a clinical care perspective?

TC Early in my career, I started as a nurse, which gave me unforgettable memories of working with patients. To this day, patients are the reason I work hard to move these therapies forward and bring them closer to the patients, as well as provide access to more people beyond the wealthiest nations.

Immunology is a very exciting space, and it is evolving quickly with all the advanced technology we have now. With increased knowledge, more data, and smarter technologies, we are able to harness the inherent power of immune cells and develop autologous cell therapies, allogeneic, and *in vivo* therapies. Autologous cell therapies are especially suitable for manufacturing close to the patient, allowing developers to use fresh material, which improves cell robustness, since cryopreservation has an impact on both the process and the product.

Autologous cell therapies are also beneficial because they reduce the risk of non-self-reactions, making them safer. With decentralized manufacturing, there is a shorter turnaround time, reduced logistics complexity, and simpler scheduling. It should also be easier to secure manufacturing slots, as production is spread across multiple sites.

Ultimately, patients can stay closer to home when getting the treatment, and they may not need to be in the hospital for an extended time in the decentralized setting. For certain indications and types of therapies, I believe autologous cell therapy and decentralized manufacturing can truly increase patient access.

Q What are the critical challenges in patient-to-product-to-patient cell therapy development?

TC Firstly, the starting material comes from the patient or donor, hence there is always a heterogeneity to initiate the process. Manufacturing the best therapy for the patient is an art, based on various scientific disciplines. No matter how great the process control is, there will remain patient-specific tailoring in the final product. This will show up as different nuances in cell phenotypes or varying levels of functionality —some cells with stronger cytotoxicity, others with higher cytokine release.

"...the continuous advancement in digitalization, process and analytical technology (PAT) sensors, and connectivity will further boost the decentralized and highly personalized approach"

Secondly, cell therapies are not metabolized and taken up like traditional drugs. They are living products that, once administered, interact *in vivo* with the patient's tissues and cells and continue to differentiate. As a result, the outcome is not only dependent on the product but also on the *in vivo* environment and the interaction between the two. As we do not yet scientifically fully understand the mechanism of action *in vivo*, this adds to the complexity.

Again, the heterogeneity complicates the translational analysis. We have many parameters to consider—not just CMC manufacturing parameters but also patient parameters. We have to integrate both the clinical and the manufacturing data to get clearer insights into what attributes are important. With that many parameters, you need a lot of data points in your analysis. The limited number of patients or batches often limits meaningful analysis or reduces the statistical power of the data. Being still a rather young discipline, every additional patient and data point generated will add to the viability of the products.

Due to the heterogeneous starting material, the process must be flexible enough to handle all starting materials from different donors while still generating a reasonably consistent product batch-to-batch. The same applies to analytics—the heterogeneity makes it hard to develop methods that work for both high performers and low performers without using too many cells.

Challenges aside, I do think there are many positives—and the continuous advancement in digitalization, process and analytical technology (PAT) sensors, and connectivity will further boost the decentralized and highly personalized approach. We are seeing next-generation bioreactors decrease the risk of contamination and increase the number of cells at harvest. Also, on the analytical side, we see an increase in automation. All of this enables us to work with fresh material closer to the patient. We have great momentum, but there are still hurdles to overcome.

Q How can these hurdles be addressed? What strategies or innovations could help accelerate clinical development?

TC Firstly, I believe we need to further embrace digitalization, which includes collecting data and making data more readily accessible for larger-scale analysis using artificial intelligence (AI) and machine learning (ML). We must also accelerate the analytical testing, and with improved data availability, the batch can be reviewed and released faster.

AI and ML have the potential to see or detect patterns faster and better than our human brains. They are powerful complements, especially when dealing with the ever-growing datasets. We can use the insights to inform both product development and clinical strategies.

Additionally, thorough characterization of both the starting material and the final product is crucial during product development. Release testing alone is not enough to truly

understand your product. You must know your product inside and out from the very beginning. If you do not, you might face unexpected hurdles later, which may even stop product development.

For example, leveraging powerful omics technologies allows developers to fully characterize the product. Furthermore, organoids are a promising tool to gain more insights into interactions with other cell types or the tumor microenvironment.

Cross-departmental collaboration is also incredibly important. We work with living products that are deeply influenced by the patient, so close collaboration between the clinical and the manufacturing teams is necessary. Clinical and patient data might be highly relevant for CMC development and data evaluation, and vice versa.

Early collaboration with regulatory bodies is also essential to ensure your strategies are aligned from the beginning. Additionally, QC and QA teams must be factored in early so that you, for example, do not develop overly complex analytical methods that cannot be used in QC environments.

Many exciting tools are emerging, and we need to learn how to use them effectively across departments. In essence, the only real way to push this field forward is to stop working in silos. We need a more open collaboration across R&D, biotech, hospitals, pharma, and regulators to truly advance this promising therapeutic space.

Q In decentralized manufacturing models such as point-of-care, what unique challenges arise for analytics and quality control? How can they be addressed?

TC The first step is to collaborate and work closely with regulatory and health agencies, because decentralized manufacturing brings specific challenges, especially around the quality space. On the analytical side, it is crucial to move toward automation of the release tests in QC. We also need automated data transfer from the instrument and its software directly into the laboratory information management system and the data cloud. Today, there are many advanced technologies emerging, such as microfluidics and cartridge-based platforms. This is an advantage when working with a sensitive living product since it is important to handle and manipulate it as little as possible, for example, avoiding centrifugation and staining. The automated analytical instruments minimize the input from the analyst, both in the execution of the tests as well as the generation and analysis of results.

The minimal handling reduces the risk of laboratory errors and simplifies the documentation workflow. In QC, every step in the testing procedure needs to be documented. With a fully automated system, there are minimal manual steps to log since the instrument is performing most of them. It decreases the hands-on time by the analysts, and it also increases the data integrity.

Furthermore, to implement this in a decentralized setup with multiple sites, the cost of instrumentation becomes a challenge. For example, you cannot place costly flow cytometers at every location. The smaller automated benchtop instruments also facilitate decentralized manufacturing due to a more manageable price range.

Another challenge is maintaining control and oversight to ensure your analytical methods do not drift over time and that they perform consistently across sites. A robust control system needs to be developed for this. Ideally, all sites should use the same system

suitability controls, which are provided by the central site, so the methods are directly comparable. Training of the analysts is key here. The fully automated instruments facilitate this—for example, you do not need a highly specialized analyst for this type of system, but you do need a highly competent analyst who knows how to handle cells properly and understands the workflow.

In essence, learning and training are paramount. For more complex functional assays, such as more elaborate potency tests, it's beneficial to set strict qualification criteria. For example, the analyst in training could be required to run a standardized test sample and stay within a certain coefficient of variation over a defined number of runs before becoming certified. The more complex the assay, the more runs are needed. Retraining should also be part of the plan, and most importantly, the analyst should feel fully confident performing the test.

All things considered, there are many hurdles, but having more automated systems also makes training and method transfer easier. It reduces the required time and resources, which is critical when you are operating across multiple manufacturing sites.

Q How do you design an analytical strategy that spans from starting material to final product?

TC To begin with, it is important to have deep knowledge about the product based on the development work that has already been done. The target product profile (TPP) and the quality target product profile (QTPP) need to be known. It's an advantage to understand what was observed during the discovery and early development—what was identified as important, what should be avoided, and what the conclusions were. From there, knowing the developers' thinking around the mechanism of action is an advantage, because that influences both your release tests and your characterization panel. The analytical strategy should be planned with the end (large-scale adoption) in mind.

However, analytics is challenging because it is a phase-appropriate development, especially regarding potency assays and selecting the right one for commercial use. Additionally, cross-departmental collaboration is key; discuss the analytical strategy with the regulatory department and liaise with the QC and QA teams to ensure all critical items are included in the strategy.

It is essential to engage with the process development team because it's important to understand the process to ensure all needed in-process samples are included in the sampling plan and how they can be funnelled down over time to the minimum number of samples.

Q Finally, what are your goals and priorities over the next 1–2 years, both for yourself and for Tigen as a whole?

TC Tigen's strategy is centered around collaboration—working closely with innovators, academic centers, product developers, and treating hospitals to accelerate development. They bring the development skills, and we know what is needed to get to a commercial product.

"I would love to start a podcast—not focused on science or technology, but on people and personal stories. Ultimately, my driving force is the patients. I want to bring awareness for cell and gene therapies in a way that is accessible to everyone"

We are continuously advancing our armored CAR-T cell product for AML to get it ready for a Phase 2 pivotal trial. We are building a manufacturing process and analytics strategy that enables the Biologics License Application and commercial requirements. We implement automation in both the process and analytical workflows, digitalized procedures and data management, and always with a focus on high product quality, safety, efficacy, and, ultimately, patient access.

Furthermore, we are constantly scouting, evaluating, and implementing innovative technologies, whether for process, analytics, data handling, or digitalization. We are heavily investing in translational tools such as AI and ML, always with automated and potentially decentralized manufacturing in mind.

On a personal level, I have a lot I want to accomplish. I am enrolled in a certificate program in Clinical Trial Design and Management, which has proven incredibly valuable to align analytical and translational strategies with clinical needs.

I am also committed to deepening my knowledge in immunology, cell therapy, and the ever-evolving regulatory landscape, especially with the latest exciting advancements of the US FDA, UK MHRA, and EMA. Beyond the 'established' CGT nations, we are also increasingly collaborating in China and upcoming geographies, like, for example, India. After all, this is a truly global endeavour. Attending conferences is also essential for me—not just to stay on the cutting edge know-how and tech, but mainly to network and learn from peers.

One of my biggest passions is to advocate for the importance of analytics, automation, and characterization. I truly believe that a product is only as good as the analytical methods are (specificity, precision, etc.). Fortunately, analytics has gotten more spotlight lately, and I want to contribute where I can. The analytics in cell and gene therapy have the potential to leapfrog the development, and we can support that by starting the analytical development work much earlier in the process. If we take the time to get it right from the start, we can accelerate everything downstream.

Lastly, I would love to start a podcast—not focused on science or technology, but on people and personal stories. Ultimately, my driving force is the patients. I want to bring awareness for cell and gene therapies in a way that is accessible to everyone—family, friends, or anyone curious about cancer and these transformative treatments.

BIOGRAPHY

Therese Choquette has a long-standing experience in cell and gene therapy and analytical development; from early development into the commercial space. She started at Novartis in 2014 to lead the potency assay development group for the newly transferred CAR-T product (now named Kymriah) from University of Pennsylvania and later entered the role of analytical project leader. After 6 years at Novartis, Therese moved on to Janssen Pharmaceuticals as Analytical Scientific Integrator for vaccines and cell therapy products, and thereafter to

Iovance Biotherapeutics as Director for the Global QC working with TIL cells. She is now at Tigen Pharma as the Head of Analytical and Translational Sciences, focusing on early development of T cell therapy products. As a former Licensed Practical Nurse (in Sweden), her passion is to provide high quality cell therapies to patients and is having a deep interest in elucidating what constitutes a high-quality cell therapy product and to provide the best analytical methods for this. Therese earned a PhD in Rheumatology at the Karolinska Institute in Sweden, and during her PhD project she studied the immune system and cells from humans (patients with rheumatic diseases) and for her post doc (in Professor Kornfeld's group at UMass Medical School in Worcester, now UMass Chan Medical School) she studied the impact of hyperglycemia on host defense against mycobacterium tuberculosis.

Therese Choquette PhD, Head of Analytical and Translational Sciences, Tigen Pharma, Lausanne, Vaud, Switzerland

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: The named author takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

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CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

Industrialization of AAV manufacturing by Xcite® transient and stable production platforms

Suparna Sanyal and Peng Wang

Current challenges in AAV manufacturing include limited production efficiency, difficulties in scaling up processes, expensive materials, complex supply chains, and variability in results between batches. The key to overcoming these challenges is to industrialize AAV manufacturing by improving scalability and efficiency. Novel AAV transient transfection and stable producer cell line platforms have been designed to optimize AAV yields and packaging efficiency. The packaging efficiency for AAV is a crucial quality attribute for the manufacturing and industrialization of AAV production. By increasing the full/total capsid ratio of AAVs, it is possible to reduce dosage and subsequently cost of goods. In order to meet productivity and scalability goals, it is important to choose the appropriate manufacturing approach.

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INDUSTRIALIZATION OF AAV MANUFACTURING USING Xcite® TRANSIENT TRANSFECTION AND STABLE PRODUCER CELL LINE PLATFORMS

Xcite AAV suspension transient transfection platform

The Xcite AAV suspension transient transfection platform uses the Xcite proprietary suspension clonal cell lines as part of its process. These cells are grown in single-use bioreactors, at a chosen scale, until they are ready for transfection. Three plasmids are used for AAV production:the Helper and RepCap promoter plasmids as well as a transfer plasmid containing the sequence of the gene of interest (GOI). Once the plasmids are introduced through transfection, the cells are further grown to the stage where they are ready for harvest. This is followed by clarification and a tangential flow filtration (TFF) concentration step to generate the column load material, which is then purified using two-column chromatography. The first column is for capture using affinity chromatography, and the second column is a polishing step to enhance the percentage of full AAV capsids using ion exchange chromatography. After purification, the material undergoes a second TFF step to achieve its final formulation. It is then filter sterilized twice to generate the bulk drug substance

at the required concentration for fill–finish. This material is subjected to release testing to generate the final AAV drug product (Figure 1). This process can be optimized at individual steps to be utilized for multiple serotypes and AAV capsids.

GENE TO GMP IN 12 MONTHS

The first part of the process involves conducting a comprehensive feasibility assessment. This is crucial for understanding the baseline production, which helps decide next steps. To determine the optimal production parameters needed to grow AAV, different sets of parameters are used at shake flask scale. Once the optimum condition has been selected, the AAV is produced at a 3 L scale. All upstream and downstream operations are performed, including analytical characterization. This helps form the baseline production, which indicates whether it meets target criteria. If the target criteria are met, then the process is scaled up to approximately 50 L. If further optimization is needed at the 3 L scale, then this can be performed using DoE. Following the confirmation run, any of the remaining GMP readiness activities are completed, as well as assay verification and qualification. This is followed with production of the bulk drug substance in GMP and a fill–finish step. The final step is the GMP release testing. The full platform process takes approximately 12 months.

SCALABILITY OF THE AAV TRANSIENT TRANSFECTION PLATFORM

Platform scalability was evaluated by measuring relative AAV titer with a GFP transgene and a non-GFP GOI. An increase in relative titer was observed in conjunction with scaling up from the shake flask level to 3 L and 50 L (Figure 2). Importantly, once the 3 L baseline is established to meet the target criteria, subsequent scale-up to 50 L and 250 L is reliable and consistent. Assessing feasibility and performing a relatively comprehensive run at the 3 L scale helps save time in determining the subsequent path to GMP.

AAV PRODUCTIVITY IN 3 L BIOREACTORS USING THE AAV TRANSIENT TRANSFECTION PLATFORM

An analysis of the typical productivity of the AAV transient transfection platform with cells and plasmids across multiple AAVs was conducted. AAV2, 5, 6, and 8 were tested with GFP whereas AAV9 was tested with the non-GFP GOI. ddPCR analysis was used to determine titer. At harvest, the AAV titer ranged from approximately mid-10^{11} to 10^{12} vg/mL (Figure 3). A 3 L bioreactor generates a typical yield of 3–6×10^{14} vg/mL. Whereas a 50 L bioreactor generates approximately 1×10^{16} vg/mL of AAV.

ENHANCED AAV PRODUCTIVITY USING THE Xcite CELL LINE AND PLASMIDS COMPARED TO AN ALTERNATIVE SYSTEM FOR MULTIPLE SEROTYPES

A comparison on the overall AAV titer was conducted between the Xcite cell line and plasmids with an alternative cell line and standard AAV plasmids, using the transient transfection platform process. The relative titer observed using the Xcite AAV platform process and production components increased the overall AAV titer between two- to nine-fold (dark blue bars), depending on the serotype tested (Figure 4).

AAV SUSPENSION TRANSIENT TRANSFECTION PLATFORM COMPONENTS SIGNIFICANTLY IMPROVE FULL TO EMPTY CAPSID RATIOS AT HARVEST

A comparison of AAV packaging efficiency between the Xcite cell line and plasmids

FIGURE 1

The Xcite® AAV suspension transient transfection platform.

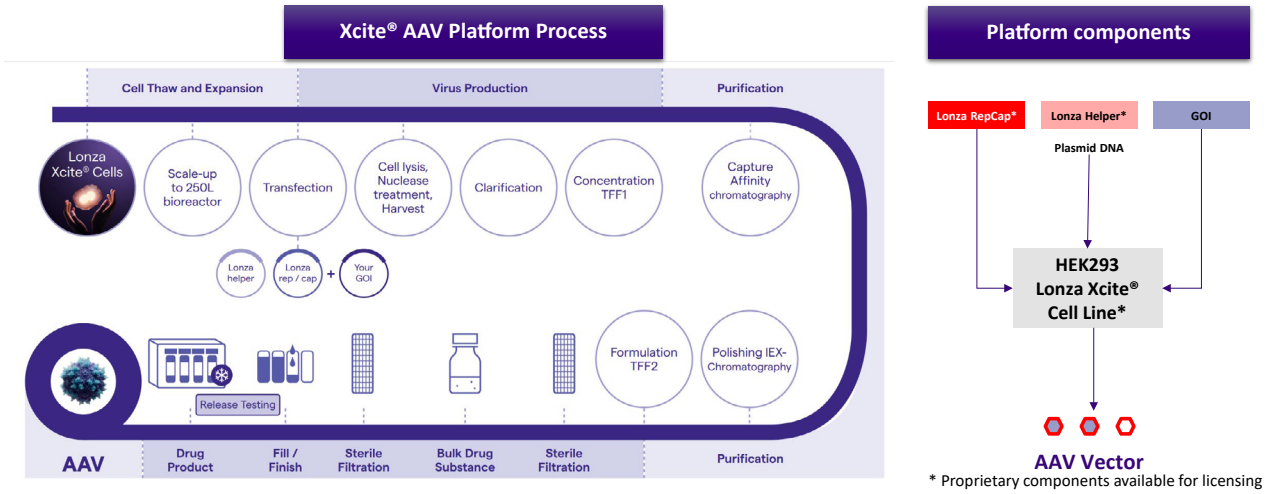
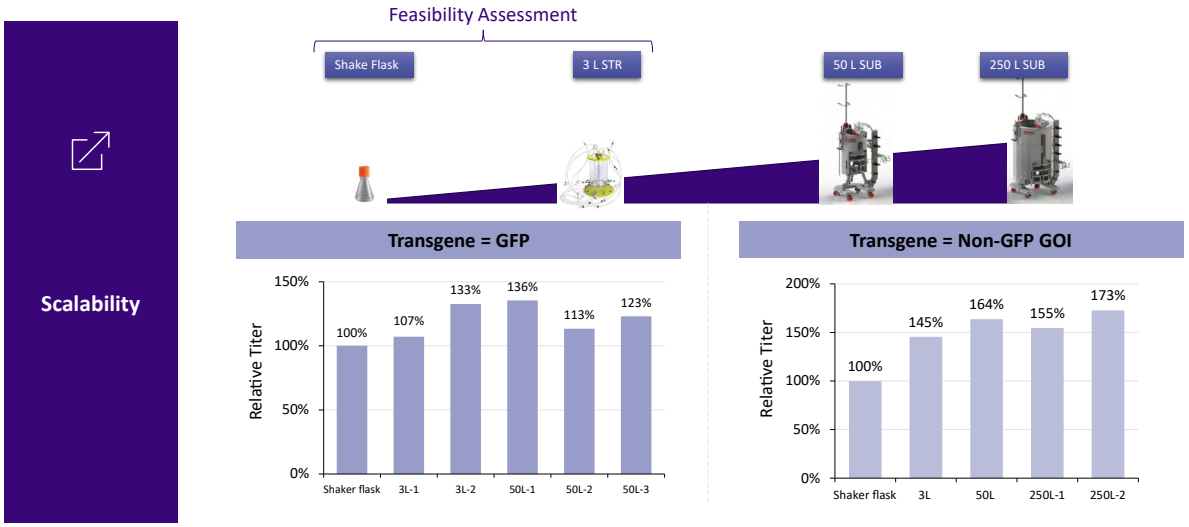


FIGURE 2

Relative titer increases when the process is scaled up from shake flask to 3–250 L.

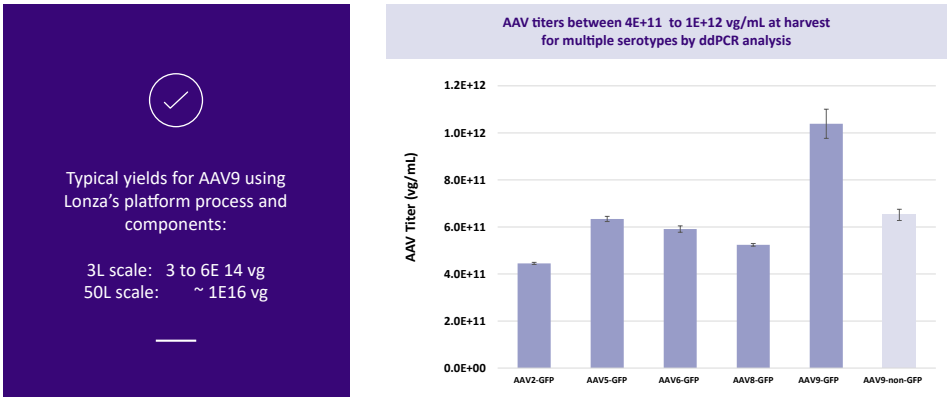


with an alternative cell line and standard plasmids was conducted using three AAV serotypes (AAV2, 8, and 9). Mass photometry was used to evaluate the percentage-full AAV after crude harvest. The results showed that the competitor cell line and plasmids had an AAV %-full of 8–13% (top panel; Figure 5) in comparison to 33–51% for the Xcite cell line and plasmids (bottom panel; Figure 5), thus showing a two- to nine-fold increase in titer in AAV serotypes.

Importantly, the high ratio of full capsids reduces the burden on downstream processing and leads to improved final product purity. This also leads to lower capsid load, which is important for high doses that are required for certain indications.

FIGURE 3

High titers are consistently observed for multiple AAV serotypes.



Furthermore, a high AAV percentage-full at the harvest stage can lead to an improved safety profile of the product.

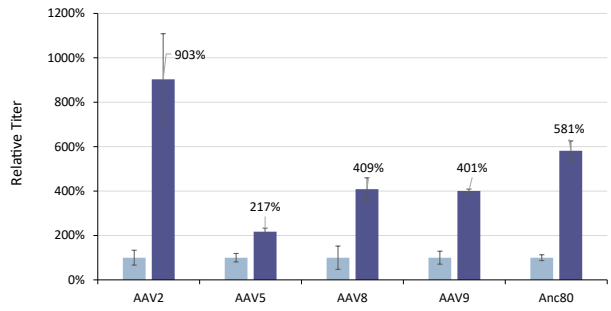
DOWNSTREAM PROCESS OPTIMIZATION LEADS TO HIGH PERCENTAGE OF FULL AAV CAPSIDS FOR MULTIPLE SEROTYPES

Isolation of full AAVs can be further improved by introducing a polishing step using ion exchange chromatography. In Figure 6, the dark blue and light blue bars represent the material before and after polishing, respectively. Following polishing, the percentage of full AAV particles is between 78% and 94%.

Importantly, the above experiments were performed with mass photometry as opposed to AUC, which is the gold standard. To determine whether there were any differences in result between the two methods, a comparison was undertaken, using the serotype AAV9 before and after polishing. Mass photometry showed comparable results to AUC, before and after polishing, both with GFP as a transgene and with a non-GFP transgene (Figure 7). This demonstrates that there is alignment between the two methods when used to identify the parameters and conditions required for obtaining the best titer and percentage-full ratios.

FIGURE 4

There is a two- to nine-fold increase in titer in AAV serotypes when using the Xcite cell line and plasmids compared with an alternative cell line and standard plasmids.



Transgene = GFP
Control: Competitor cell line + standard plasmids
Lonza: Xcite® cells + Lonza plasmids (LHI pHelper + LHI pRep/Cap)

APPROACH FOR AAV PRODUCTION OPTIMIZATION

In some cases, DoE optimization is needed for certain GOIs. There are two main ways to achieve this; either by using a shake flask method, which is a faster approach, or by performing a high-throughput analysis of the DoE parameters using a high-throughput bioreactor. Various

parameters are considered depending on what aspect of the process needs to be adjusted, such as cell density, plasma DNA ratio, transfection, transfection reagents, media conditions, pH, temperature, and dissolved oxygen agitation.

CASE STUDY: SMALL SCALE DoE OPTIMIZATION

A DoE optimization experiment was conducted to boost the titer of both single stranded AAV and self-complementary AAV. The baseline titer for the single-stranded AAV was less than 5×10^{10} vg/mL, whereas the titer required was five-fold or higher for the initial productivity. Using DoE optimization, the titer was increased to over 4×10^{11} vg/mL for the single-stranded AAV (Figure 8). Similar results were observed for the self-complementary AAV, where an eightfold increase in titer was achieved, to over 1.5×10^{11} vg/mL.

Figure 9 shows different DoE conditions that were used to optimize both productivity and percentage-full. Productivity increase was highest with the F7 condition, although percentage-full was not much higher than baseline levels. This condition may suit requirements of high productivity but only 30% full AAV capsid. To meet requirements of higher productivity and a higher %-full, conditions such as F3, F4, or F13 may be more suitable, where the %-full at harvest was close to 70%.

Xcite AAV STABLE PCL PLATFORM

The AAV producer cell line (PCL) represents a novel platform capable of reducing CoGs and enabling industrialization of AAV manufacturing. In this cell line, all three components, RepCap, Helper, and GOI, are stably integrated into the genome of suspension HEK-293 cells. AAV production can be initiated by a small inducer, such

FIGURE 5

Lonza's cell line and plasmid system drives high percentage-full AAV capsids compared to alternative systems.

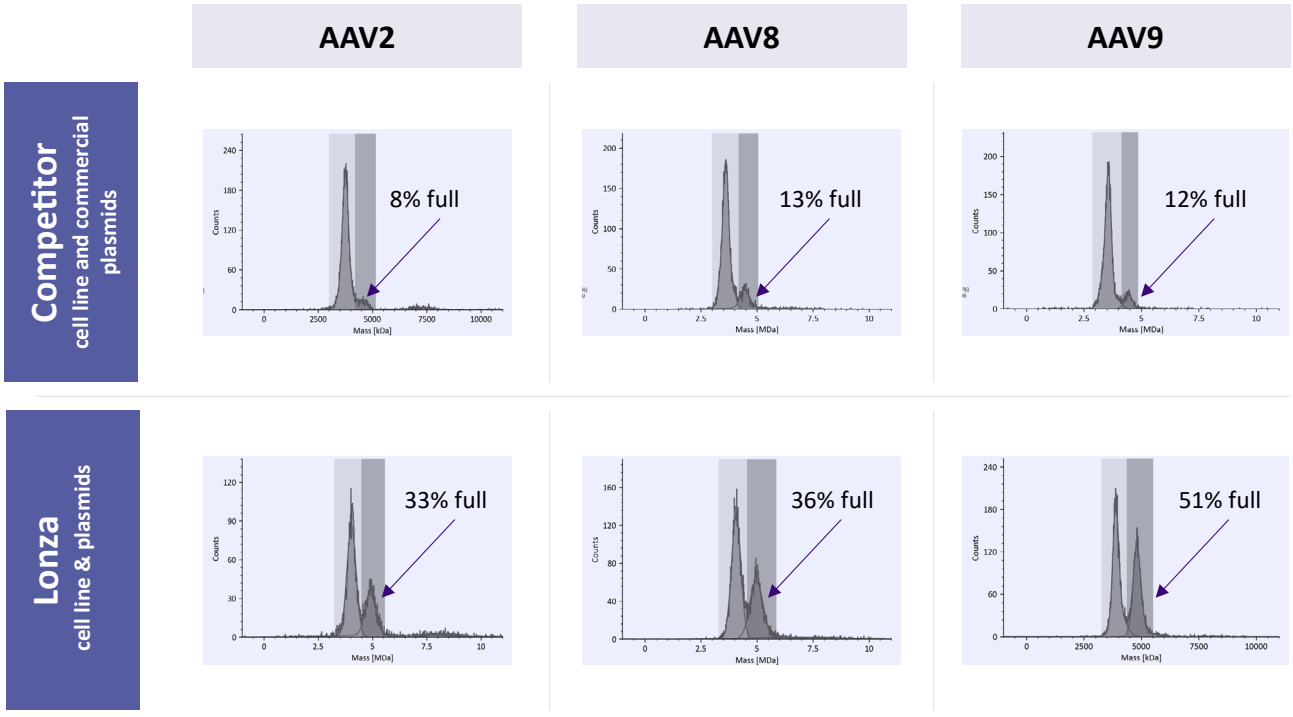


FIGURE 6

AAV capsid enrichment before and after polishing.

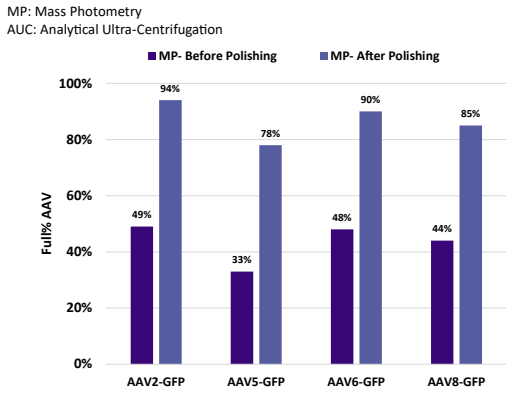
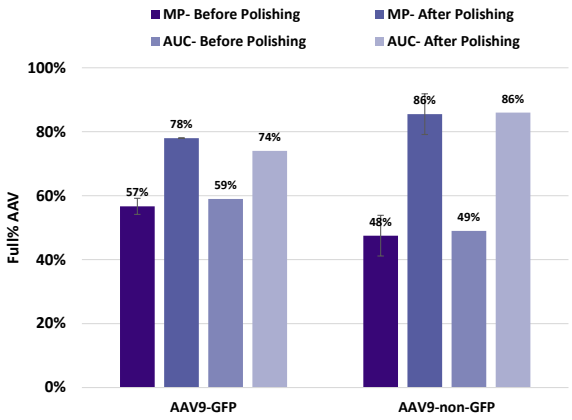


FIGURE 7

Comparison between mass photometry and AUC in determining precentage-full AAV.



as doxycycline, in the cell media. The key advantages of this system are:

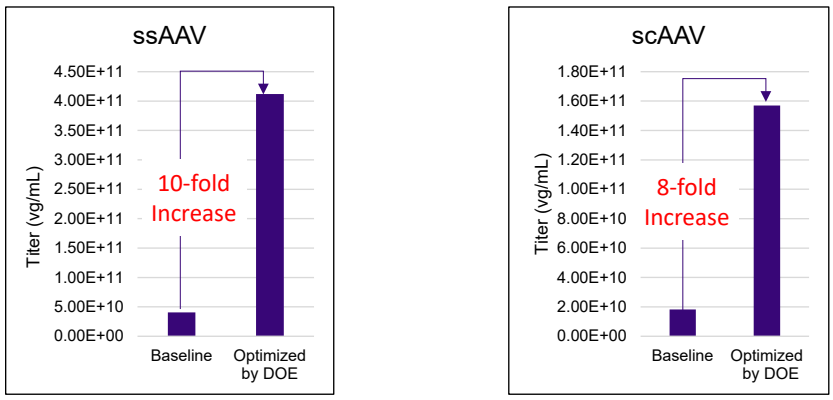
- Safety: it is helper-virus free unlike other PCLs, which still require wildtype adenovirus;
- Cost efficiency: it eliminates the need for expensive plasmids;
- Scalablity: it is feasible to intensify the PCL process and increase scalability to over 2000 L;
- Process robustness: it increases batch success with improved process robustness, consistency, and simplicity.

THE AAV PRODUCER CELL LINE PLATFORM ENABLES INDUSTRIALIZATION

The main feature which differentiates this new PCL technology is its proprietary vector design, which addresses complex molecular regulation and enables high levels of AAV production. A key factor is the tighter control in gene expression of both Helper and Rep genes, which are toxic to cells. Additionally, the piggyBac™ transposon system is utilized for stable DNA

FIGURE 8

Increase in titer following DoE optimization for single stranded AAV and self-complementary AAV.



integration. Moreover, three transposon vectors can be multiplexed for integration in a single step, which can significantly improve cell line construction efficiency.

Lonza's PCL cell line also achieves a titer of approximately 2 x 10^{12} vg/mL at harvest, which is higher than other AAV stable cell lines. Furthermore, the AAV packaging efficiency is approximately 35% for full capsids.

AAV PCL DEVELOPMENT WORKFLOW

In general, the time taken to develop PCL clones from a DNA sequence is about 8 months, followed by 3 months of cell line stability testing. The process begins with cloning the capsid and GOI into a single transposon vector, followed by co-transfection of triple transposons

FIGURE 9

The different DoE conditions used to optimize productivity and percentage-full of single-stranded AAV and self-complementary AAV.

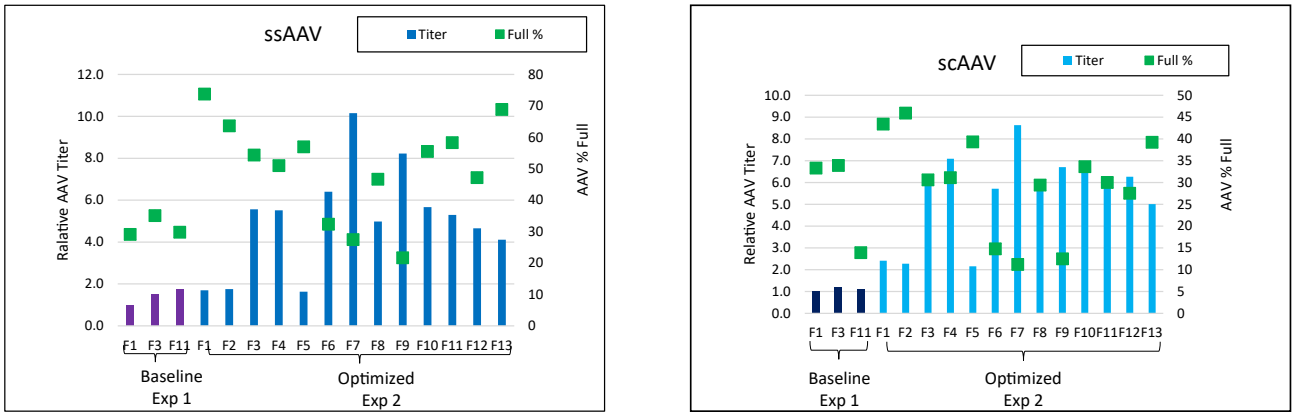
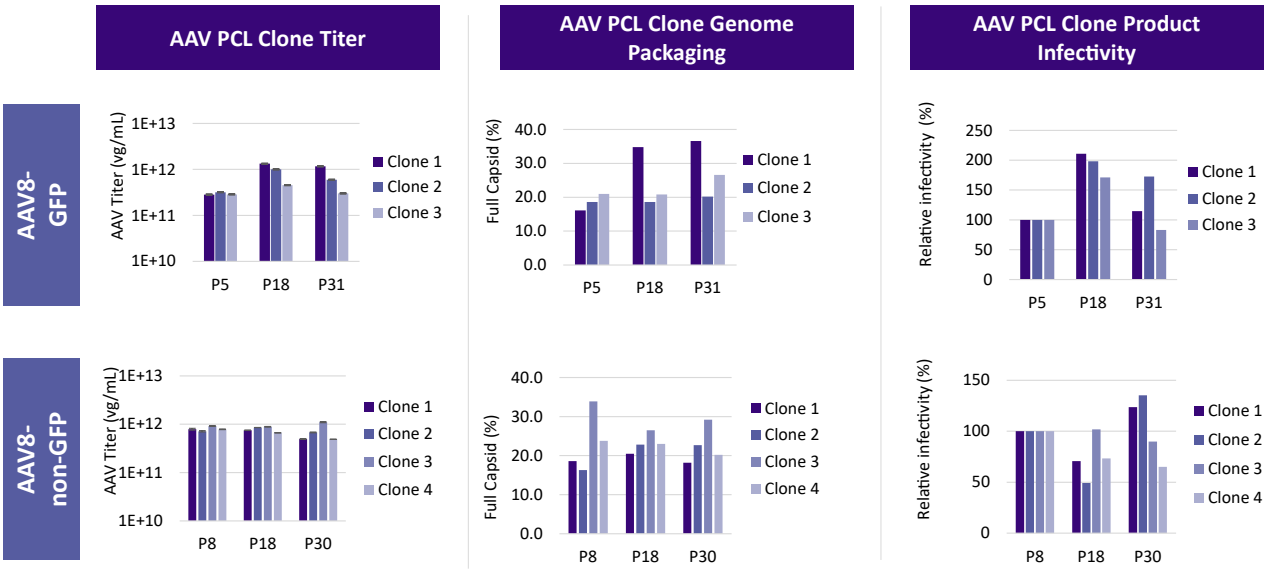


FIGURE 10

AAV titer and packaging efficiency for selected clones.



with transposase mRNA. Stable pools are screened and selected pools are used for single-cell cloning with a single-cell printer and imager, ensuring high assurance of clonality. The expanded clones are banked and screened based on three key parameters:

- Genomic titers, measured by ddPCR;
- Packaging efficiency, assessed by mass photometry;
- Functional infectivities, evaluated through transgene expression assays.

HIGH AAV PRODUCTIVITY OF SELECTED AAV PCL CLONES IN HIGH-THROUGHPUT BIOREACTORS USING ddPCR TITER ANALYSIS

Among >100 isolated single-cell clones, the productivity of the top dozen clones were further evaluated in Ambr® 15 bioreactors. Compared to the parental stable pools, the clonal cells showed a broad distribution of productivity. Notably, the top clones produced 1 x 10^{12} vg/mL at harvest for both GFP and non-GFP GOIs, which is two- to three-fold higher than what is achieved with a transient transfection process.

The next step was to measure AAV genome packaging in these top clones using mass photometry. Both GFP and non-GFP cell clones showed >30% full capsid at harvest. This packaging efficiency is comparable to the high packaging efficiency achieved with the transient transfection platform.

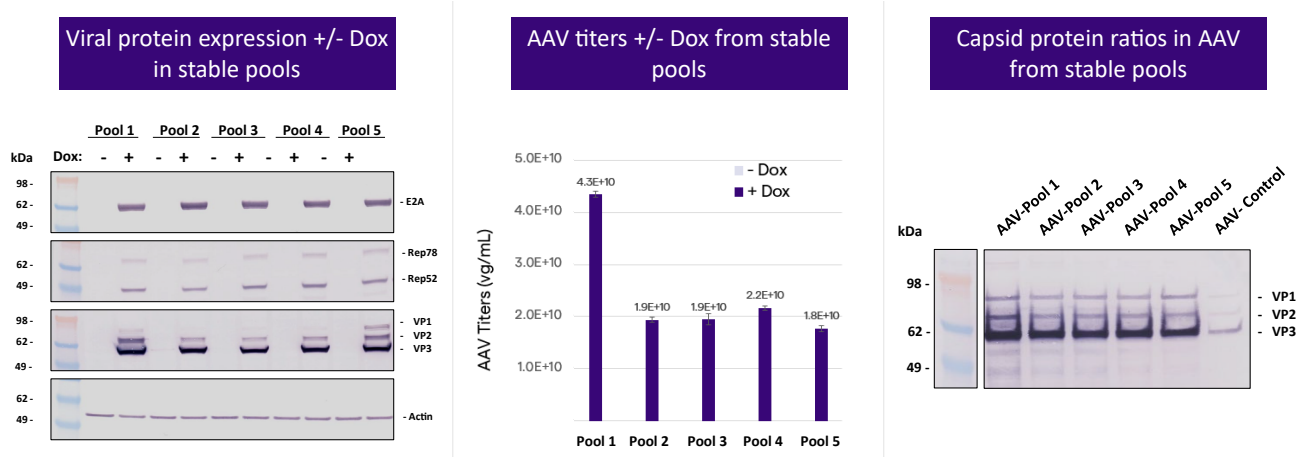
One of the main attributes of a stable cell line is the stability of the product yield and quality. To test this, the top three clonal GFP-produced cell lines were selected. These clonal cells were for 5, 18, and 31 passages, and were tested for AAV production in high-throughput bioreactors. Stable AAV productivity was observed for these clones across 30 cell passages, corresponding to a scale above 2000 L (Figure 10). The AAV genome packaging efficiency also remained stable, between 20% and 35%. Importantly, this stability was not only observed for the GFP–GOI but was also reproduced for non-GFP-GOIs using four top clones.

CASE STUDY: STABLE AAV PCL POOL GENERATION

An experiment was conducted to evaluate the viral protein expression in five stable

FIGURE 11

Evaluating viral protein expression and capsid protein ratios in five stable PCL pools, with and without doxycycline.



PCL pools, with and without doxycycline. AAV titer was measured using ddPCR. In the absence of doxycycline, no viral vector was detected, demonstrating that viral protein expression is tightly controlled. Pool 1 showed the highest productivity (Figure 11). Notably, productivity at the pool level matched the level of productivity of the transient transfection system. Purified AAV from the pool showed similar ratios of VP1, VP2, and VP3 compared to AAV controls. This demonstrates that at the stable pool level, it is possible to achieve the same productivity as the transient transfection system in a tightly controlled manner.

CASE STUDY: SCREENING OF PCL CLONES USING ddPCR TITER ASSAY

The next step was to isolate single clones. A dozen clones that showed higher productivity compared to the transient transfection system were identified. The top clones exhibited a three- to four-fold increase in titer, which was achieved without any further process optimization (Figure 12). However, it is possible to achieve even higher productivity levels with these top clones.

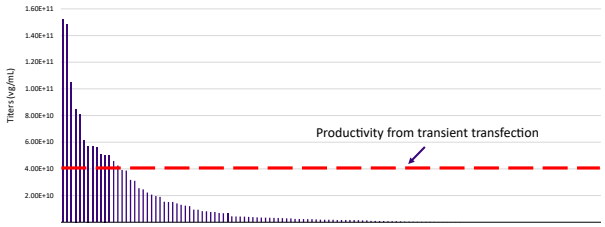
3D LINKAGE ANALYSIS WITH DIGITAL PCR FOR GENOME INTEGRITY AND IDENTITY OF AAV

Digital PCR assay for rAAV genome titer characterization

qPCR has been the standard method for measuring viral genome titer to determine therapeutic dosage. However, this method requires a good standard curve for process quantification. Digital PCR offers absolute quantification without the need for a standard curve. 1D ddPCR has been widely used to measure viral genome titer by targeting a single site within the viral genome, usually at the GOI region. However, 1D ddPCR cannot provide information on viral genome integrity.

FIGURE 12

Identification of high producer clones compared to transient transfection process.



2D ddPCR, which has two targets at the end of the viral genome, can be used to assess genome intactness. A study was conducted where primers and probes were designed targeting the CMV enhancer/promoter and the Poly(A) region. Through 2D linked analysis, the percentage of full-length partial AAV genomes over total genome population can be calculated. However, due to the design of the targets at both ends of the viral genome, it was not possible to confirm the identity of the GOI.

3D ddPCR FOR rAAV GENOME INTEGRITY AND IDENTITY

To further advance analytical methods, a 3D ddPCR assay was developed, which aims to provide a more comprehensive picture of the AAV viral genome. By adding one more target in the middle of the viral genome to detect the GOI region, it is possible to perform a 3D ddPCR assay that provides both integrity and identity information. While the setup of the multiplex high-dimensional digital PCR is straightforward, analyzing the higher-dimensional PCR data presents a challenge. The graph generated from 3D ddPCR shows different droplet populations (Figure 13). Within the triple-positive droplet population (orange group), all three targets are present in different formations, making it challenging to characterize this triple-positive population.

FALSE-POSITIVE DROPLETS CAN BE IDENTIFIED USING A 3D LINKAGE MATHEMATICAL MODEL

Due to the random partitioning of DNA fragments in a digital PCR setting, a triple positive cluster is not equal to triple-linked DNA molecules. This is simplified in the diagram below, which shows three targets named A, B, and C (Figure 14). The digital PCR machine outcome can provide triple-positive droplet information; however, the 3D linkage model is designed to identify the true linked ABC droplet.

Examples of false positive droplets include when single fragments or double-linked fragments join in one droplet, however A, B, and C are not linked together in one DNA molecule. The aim of the 3D linkage model is to identify different false-positive droplet scenarios, thereby providing an accurate concentration of intact viral genomes for all three linked targets.

The model also provides an accurate distribution of linked ABC fragments, as well as the DNA concentration of each viral genome fragment.

FIGURE 13

(A) rAAV genome integrity and identity (B) 3D ddPCR analysis.

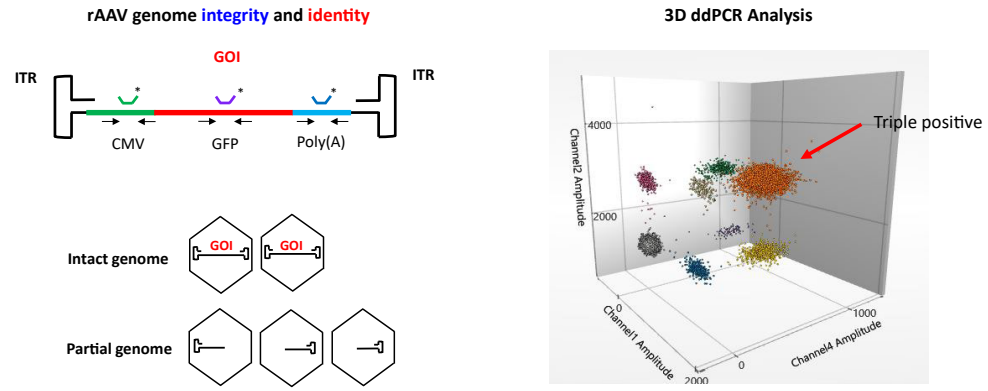


FIGURE 14

The identification of false-positive and true-positive droplet results using digital PCR.

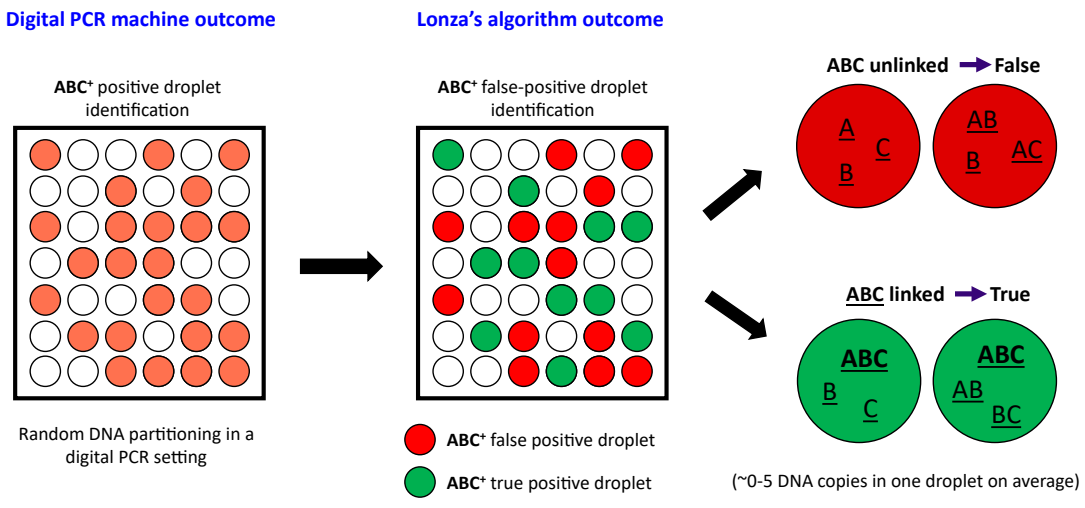
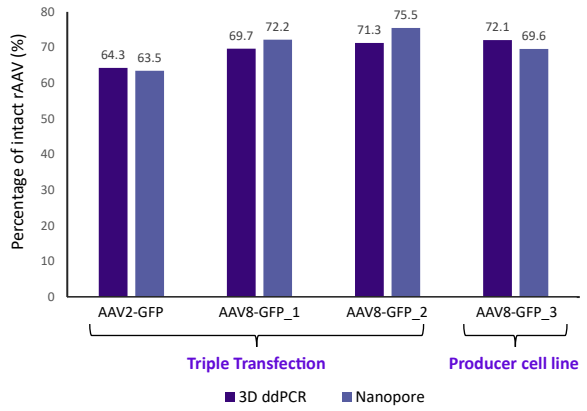


FIGURE 15

A comparison of the percentage of intact viral genome using 3D linkage analysis and nanopore sequencing.



3D ddPCR LINKAGE ANALYSIS ON INTACT AAV VIRAL GENOME POPULATION IS ALIGNED WITH ORTHOGONAL NANOPORE SEQUENCING ANALYSIS

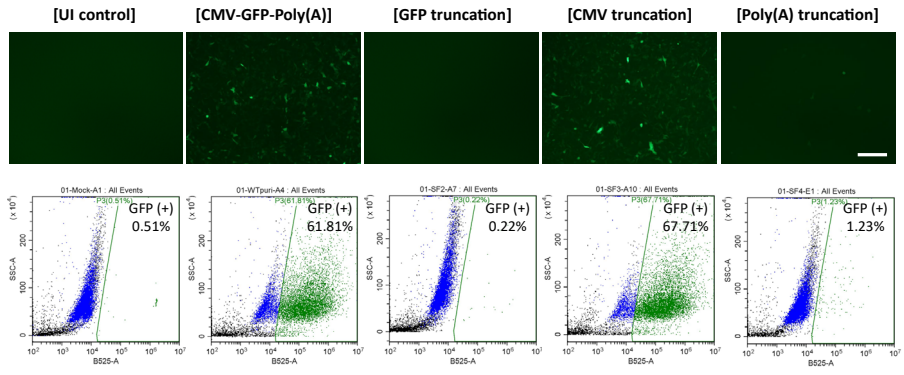
The 3D linked analysis method was further verified by comparing it with nanopore sequencing, which is another orthogonal method. Two different AAV serotypes, AAV2 and AAV8, were tested and the percentage of intact AAV viral genomes was measured. The results obtained from the 3D linked analysis were very similar to the nanopore sequencing result, showing alignment of the two different methods (Figure 15). In addition to different serotypes, there was also consistency in the AAV produced by two different platforms- the traditional triple transfection platform and the new AAV PCL platform.

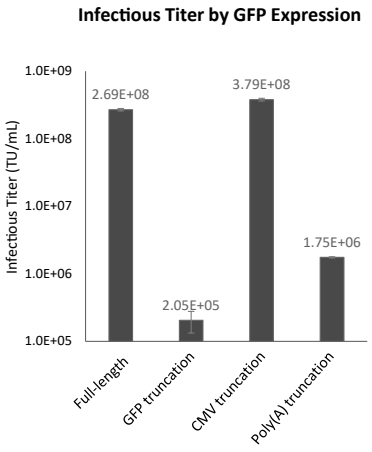
CORRELATION OF TRANSDUCED GOI/GFP EXPRESSION WITH INTEGRITY OF rAAV VIRAL GENOME

The infectivity of full-length AAV and AAVs truncated in different regions were analyzed using a cell-based assay. Strong GFP expression was observed in the cells treated with full-length AAV (Figure 16). As expected, there was no GFP expression in cells infected with GFP–truncated AAV. Truncation in the selected CMV enhancer region minimally impacted GFP expression, whereas Poly(A) truncation dramatically impacted GFP expression levels. Flow cytometry analysis further quantified the percentage of GFP-positive cells, which is used to calculate the infection titer. There was a correlation between transduced GFP expression and

FIGURE 16

Measurement of GFP expression and infectious titer in cells infected with full-length and truncated AAVs.





- Equal multiplicity of infection (MOI) in the potency analysis based on conventional 1D ddPCR titers
- Truncation in the selected CMV enhancer region minimally affects GFP expression

the integrity of the AAV viral genome. This case study demonstrates the importance of obtaining comprehensive viral genome information from 3D linked analysis, which correlates well with functional assays at early stages of process development.

Q&A


Suparna Sanyal (left), **Peng Wang** (right)

Q During process development, do you utilize newly developed analytical methods?

PW Yes. We have developed analytical methods for all steps within process development. For example, with genome integrity, we are currently looking at how our upstream processes can help improve the integrity of the genome.

Q Does Lonza use mass photometry or AUC for fill versus empty ratio for QC release testing?

SS Mass photometry is currently used in our process development setting to ensure that we hit the right target for percent full. The mass photometry and the AUC, which is the method we typically use for our QC release testing, are well correlated. In the future, we will consider having both methods available.

Q You showed a great correlation in titer between shake flask and bioreactor. Do you have to spend a lot of effort to optimize the parameters for the two systems to match?

SS No—a lot of work has happened behind the scenes in identifying the optimized parameters for the feasibility assessment. In general, when we insert a new GOI and AAV serotype, we can quickly identify the condition needed to move on to 3 L, with the caveat that AAV, GOI, and capsid can have a variable response. If it does not meet the target criteria, then we will consider whether a full DoE is required or if there are one or two parameters that can be adjusted relatively quickly. Usually, going from shake flask to 3 L is a fast process.

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Q Would Lonza accept the use of a customer cell line for AAV production using Lonza's transient transfection platform?

SS Absolutely. If a customer is bound to using a specific cell line for their AAV production, we can utilize that with our platform. We can also discuss with the client to see what plasmids they would like to use, whether their own plasmids or ours. We are flexible when it comes to working with our customers.

One thing to keep in mind with a customer cell line or plasmids is that we would not know how that combination would play out versus an optimized component plus process that we already have with our platform. For these customers, we could do a side-by-side comparison on a small scale to show what is working and let the customer decide how to proceed. In a nutshell, we can use customer elements as a starting point, but it may impact what additional optimization may be needed, both from a process and analytics perspective.

Q For the transient triple transfection, has Lonza compared the use of synthetic DNA and conventional pDNA for transfection?

SS Yes. We have looked at a synthetic DNA system for two serotypes, AAV2 and 9. The general output showed that the titers were similar, using both conventional pDNA as well as the synthetic DNAs, but the packaging efficiency for the synthetic DNA was significantly lower. If that is something that our customers are interested in, we may need further optimization of the design to get comparable results on all fronts.

Q We are interested in your AAV producer cell line feasibility offering. Could you elaborate on how to collaborate with Lonza for this project?

PW It is quite straightforward. All we need is your GOI sequence, your construct, and your CAP sequence. We will drop these sequences into our plasmid and start work. At every stage, we jointly decide with you on whether to proceed to the next step or not.

Q How would the feasibility assessment work if we wanted to test three GOIs, and how long would that take?

SS We often have customers asking how long the feasibility assessment would take with multiple GOIs. It all depends on how quickly you can give us all the starting materials that are needed. If we can have them all at the same time, then we can maximize efficiency by running these in parallel. It will not be 3 months sequential, meaning 9 months to obtain three different readouts. Rather, it would be closer to 4–4.5 months.

Q Your AAV platform is impressive. Do you also have platforms for LVV?

PW Yes. We have platforms for both AAV and LVV. We will share more details on this in one of our upcoming seminars.

Q What factors do you take into account when scaling up transfection complexation mixes?

PW Yes, we have a very broad DoE design. This would give a full picture on how to adjust the upstream parameters. We are building a small-scale visibility study, which we can verify using 3 L bioreactors, although this could be scaled up to 250 L. Using our platform design and our infrastructure we can help improve AAV titer and quality.

Q Is the Xcite clonal cell line free of T antigen?

SS Yes, it is. We are using a suspension cell line, which is a HEK-293 cell line without the T antigen. We use this for both the transient transfection and the stable producer cell line.

Q What transfection reagent do you use in your platform?

SS For the transient transfection platform, we usually use FectoVIR AAV.

Q For triple transfection, did you use electroporation or transfection reagent?

SS Transfection.

Q What affinity resin do you use for the process?

SS We generally use an AAVX resin in our platform.

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Q Is your transfection reagent Lonza proprietary or commercially available? As Lonza proprietary reagent, do you have assays for it? Is your 3D ddPCR method validated from final product release?

PW We are in the process of transferring 3D ddPCR to be used at later stages of development. Currently, the 2D ddPCR is in use, particularly at early stages of process development. After the necessary paperwork has been completed, we will see 3D ddPCR used in a GMP environment.

BIOGRAPHIES

Suparna Sanyal has over 15 years of broad pharmaceutical and CDMO experience driving innovation, drug discovery, product and service development for CNS, oncology, and cell and gene therapy. Suparna works closely with the commercial, innovation and operations teams to develop asset strategy, commercial offerings and capabilities to ensure meeting the changing landscape of cell and gene customer needs. In her role, she supports sales and marketing teams for pipeline development and new business acquisition. Previously to this role, she was the Innovation and Commercialization Manager at Lonza, with a focus on driving development, prioritization and commercialization of their innovation portfolio. Suparna's background is in neuroscience and she earned her PhD from the University of Toronto, Toronto, ON, Canada in Neuropharmacology.

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Peng Wang earned his doctorate in Chemical and Biomolecular Engineering from UCLA, Los Angeles, CA, USA. After his postdoctoral training at Harvard University, Cambridge, MA, USA he worked as Senior Research Scientist at MD Anderson Cancer Center. Before transitioning to Lonza Business Development as Associate Director, he worked as Associate Director in the R&D to develop viral vector platforms.

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AUTHORSHIP & CONFLICT OF INTEREST

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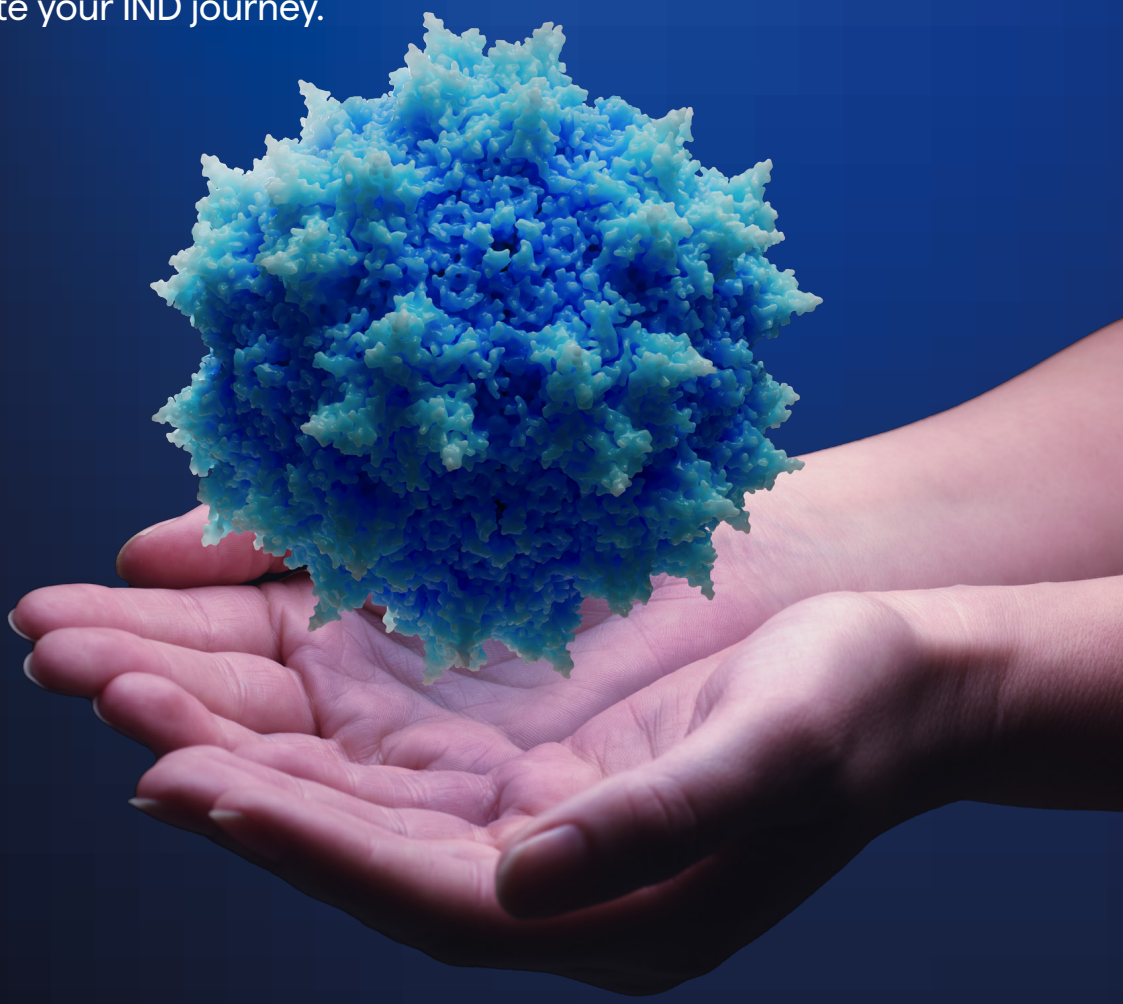

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CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

Navigating the transition from research to clinical-scale cell therapy manufacture

Johannes Fruehauf, Steven Feldman, and Mary Ann Santos

Collaboration is essential to bringing cell therapies to market, helping to overcome key hurdles in process development such as cost and scalability, transitioning products from academic research to the clinic, and optimizing cell therapy workflows to maximize efficiency. In this article, we extract learnings from two different ongoing collaborative initiatives, each of which is aimed at addressing cell therapy development challenges.

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INTRODUCTION

The cell therapy field faces many challenges, including escalating costs in process development, difficulties in scaling academic research to clinical applications, and navigating an evolving regulatory landscape. In addition, cell therapy process development scientists face the challenge of accessing specialized equipment, while those at early-stage biotech companies must contend with time pressures due to limited cash runways.

Collaboration is an important tool in addressing each of these obstacles. Here, we summarize and draw lessons from two real-world examples where different forms of collaboration have helped deliver broader, long-term success in cell therapy development. The first example is of a large-scale initiative, the focus of which is to support biotech startups in developing their early-stage therapies and production processes through the sharing of laboratory space, equipment, and technical expertise. The second example looks at how an academic center worked with Thermo Fisher Scientific to bring about incremental improvements in a CAR-T cell therapy process workflow. Both of these collaborative efforts address the imperatives of cost control and ensuring scalability to enable the efficient clinical translation of cell therapies.

CASE STUDY 1: LabCentral & BioLabs

Purpose of LabCentral and BioLabs

- Both organizations aim to enable early-stage innovation in the biotech sector

- Lab Central focuses on supporting high-potential biotech startups by providing resources to accelerate their growth and innovation
- BioLabs operates as a network of shared, fully equipped laboratory and office facilities, allowing biotech startups to develop and test their ideas

Impact

- LabCentral and BioLabs have supported over 1,000 companies between them to date
- Approximately 500 of these companies are currently working on novel therapy development
- More than 250 clinical trials have been launched to test therapeutics developed in their labs, highlighting the significant clinical impact of their support

LabCentral profile

- Based in Cambridge, MA, USA, LabCentral has supported both small and large biotech companies for more than a decade
- Notable success stories include Affinivax, which developed a breakthrough pneumococcus vaccine and was acquired by GlaxoSmithKline for nearly $3 billion
- LabCentral has evolved from its initial focus exclusively on startups

FIGURE 1

Manufacturing workflow of at-scale cell culture process

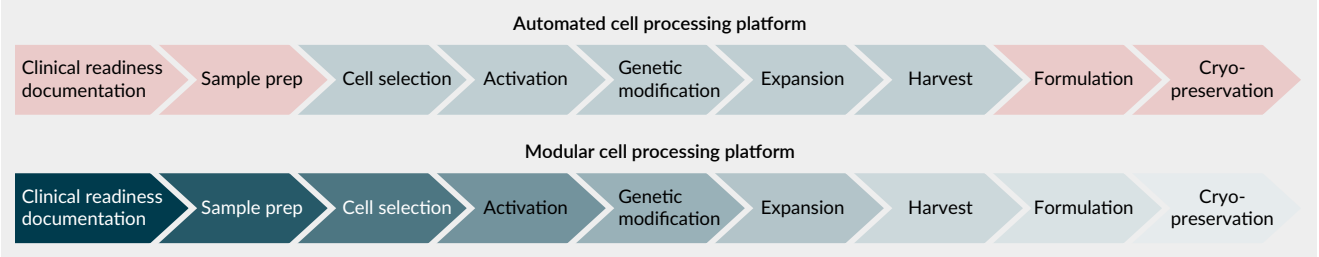

TABLE 1

Advantages and limitations of utilizing individual manufacturing instruments in a modular cell process workflow

Limitations of a singular manufacturing instrument	Advantages to a modular approach
Sole-source reagents for enrichment and activation	Reagent independence and customization
Constrained to working on a pre-defined customized application	Can easily develop custom workflows per clinical program
Limited cell expansion capacity	Enhanced expansion capabilities
Preventative maintenance costs	Enables used of surface coatings for transduction enhancers
Difficult to scale-up	Increased scalability
	Reduced COGs per run

COG: cost of goods.

to providing lab space for companies scaling up to 20–25 employees

- LabCentral 238 is a specialized facility designed to support cell and gene therapy companies with unique process and equipment requirements. It includes 100,000 ft^2 of lab and office space, individual suites, shared labs, and a full complement of equipment
- Partnerships with Astellas Pharmaceuticals, Thermo Fisher Scientific, and Waters provide specialized equipment and technical support, enabling biotech companies to scale faster and more cost-effectively

BioLabs profile

- BioLabs is a global platform that offers coworking labs and startup support across the USA, Europe, and Asia
- BioLabs Philadelphia was established in 2018, a city known for breakthroughs in cell and gene therapy
- BioLabs has supported many notable cell and gene therapy companies
- BioLabs has collaborated with Thermo Fisher Scientific to launch the BioLabs Center for Advanced Therapeutics in Philadelphia. This facility will provide comprehensive workflow solutions and a process development suite with onsite technical support from Thermo Fisher scientists and engineers
- The collaboration will provide essential support to biotechs in developing their processes from initial ideas to products, enabling them to transition into GMP manufacturing

Summary

The LabCentral and BioLabs models demonstrate that shared infrastructure can play a key role in addressing the high costs of cell and gene manufacturing. It allows early-stage biotech companies to develop their processes in a cost- and time-efficient way, mitigating bottlenecks in the manufacturing process and ultimately facilitating patient access to life-changing cell therapy products.

CASE STUDY 2: STANFORD UNIVERSITY LABORATORY FOR CELL AND GENE MEDICINE (LCGM)

Stanford University LCGM profile

- The LCGM is Stanford University's FACT accredited, cGMP-compliant facility for process development, manufacturing, release, and storage of cell therapy and viral vector-based gene therapy products intended for Phase 1/2 clinical trials
- 23,000 ft^2 facility with separate controlled spaces for cell and viral vector production
- The facility features highly skilled and trained professionals, a dedicated development space, six ISO-7 manufacturing suites, and three ISO-7 viral vector manufacturing and fill-and-finish suites

Purpose and goals of the LCGM team

- Overcome cost barriers in process development
- Navigate the transition from academic research to clinical-scale manufacturing

- Harness modular process technologies to enhance efficiencies
- Understand and enable incremental process improvements in order to help advance cell therapies

CAR-T cell manufacturing workflow

The LCGM utilizes automated cell processing technology for clinical-scale CAR-T cell manufacturing process, conducting cell selection, enrichment, activation, transduction, expansion, and harvest steps on a single closed, automated platform. However, there are clear benefits to adopting a modular approach where individual modules at each process step are interconnected in a sequential workflow (see Figure 1). Table 1 lists some key pros and cons of a modular process workflow versus an integrated automated workflow.

Collaboration with Thermo Fisher Scientific

- Bead removal is a requirement for CAR-T cell processing. LCGM collaborated with Thermo Fisher Scientific to harness Gibco™ CTS™ Detachable Dynabeads™ for this purpose in a modular CAR-T cell process workflow
- Collaborative evaluation of detachable beads for CD3 depletion and CD56 enrichment for NK cells

Summary

- Developing a modular process for CAR-T cell manufacturing can help to:
  - Improve manufacturing flexibility
  - Reduce Cost of Goods
  - Enhance scalability
- For academic centers such as the Stanford University LCGM, leveraging partnerships with tool and service providers such as Thermo Fisher Scientific is crucial in providing access to tools that can improve manufacturability
- Through such collaborative initiatives, it is possible to make incremental improvements to process workflows and enhance efficiency, ultimately providing better outcomes for patients

Q&A



Johannes Fruehauf (left), **Steven Feldman** (center), **Mary Ann Santos** (right)

Q **MAS:** How do you see the future of cell therapy industry collaborations evolving in light of current regulatory and market trends?

JF I think we all need to be realistic and admit that in the current environment, it is hard to predict where we will be in 6–12 months' time. I would certainly reassure people working in the space that cell therapy solutions are still needed; if your science is good, then it will be needed. There will be guidance and pathways at the US FDA that we can count on. Right now, there is some uncertainty, but we will get through this.

I would ask you, the scientist, to focus on your science and be an advocate for science, because we need you to be. Your solutions are valuable because they help cure patients. Having said that, if you are working in cell and gene therapy right now, the investment climate is not favorable. Do try and find different ways to get through this phase. If you look at previous cycles, we are now in a dip following a period of hype. We witnessed an unprecedented influx of investment into cell and gene therapy technologies during and immediately following the height of the COVID-19 pandemic, and now we are paying the price for that. Typically, a savvy investor knows that this is a great time to invest because you get great technologies at low valuations. So, if you have a technology that has the potential to provide a solution then stay with it, try to hibernate and survive this phase. You may need an industry collaboration or a co-development partner in a pharma company to help you see this phase through. That's my glass-half-full advice regarding the current situation, although I am still trying to navigate it myself!

Q **MAS:** What advice can you give to startups and early-stage biotechs to translate their therapies into reality, including on how to form meaningful partnerships in the cell therapy space?

SF There are a lot of startups that have good ideas. However, I think there is a general feeling that industry can translate therapies better than academia. Startups in particular have the advantage of being able to explore collaborations such as those with academic centers. As we mentioned earlier, the advantage of collaborating with academic centers is the deep knowledge and understanding they possess on what it takes to develop and transfer a process for a commercial product. They can also provide access to the clinical infrastructure, which is key given that the central question for an early-stage biotech to answer is, how are you going to manage and run your Phase 1 trial?' You

" I cannot emphasize enough how important it is to keep track of your timelines."
Johannes Fruehauf

need that data to be viable as a company. I think all types of collaboration are important, however, the collaborative mentality needs to be a little more pervasive.

Q MAS: What are the metrics or indicators that show that a partnership or collaboration is working, and that it is meaningful and mutually beneficial for all parties involved?

SF It is not possible to engage in a collaboration without clearly defined and measurable objectives or goals. Success really comes from understanding the critical quality attributes (CQAs) of the product manufactured using a particular process and setting the appropriate specifications and ranges, etc. accordingly. It's important to have a robust process that can be moved to the clinic. As I mentioned earlier, I think the ultimate measure of success is positive Phase 1 clinical trial data and to achieve this almost always involves some level of collaboration.

JF I work with dozens of companies at this juncture—preclinical to clinical transition. I cannot emphasize enough how important it is to keep track of your timelines. If you are working in collaboration, it should accelerate your timelines. If you have a collaborator that slows you down, then it is the wrong collaborator.

From a venture capital point of view, it is very important that you generate the *in vivo* proof-of-concept data, that you get your manufacturing right, and that to make your clinical trial material, you work with a CDMO or academic center that understands your goals and what you're working on. I completely agree with Steve: ultimately, clinical trial data is what we all want to have. If you have good Phase 1 data in cell therapy, where there is usually less attrition than in other modalities, it's likely going to translate well at later stages.

In terms of collaboration, I don't know a single company that doesn't have a collaboration in this field, because no one group can have all the expertise to solve the daunting technical challenges that are involved in making cell therapy products. However, make sure that you thoroughly vet your collaborators and have a backup plan if something fails. Don't let their inefficiency slow you down.

Q MAS: It is important to be ready for the clinical success of your therapy and the subsequent process scale-up that comes with it. How do you prepare for this?

JF I think the key is knowing what lies beyond your process. Often, you work with first-time biotech founders who are experts in one thing. For example, they are experts in a particular receptor, genetic mutation, or pathway, yet they have little experience

of pharmaceutical development, for example—of what happens on the other side of an IND or a successful Phase 1 trial. Unfortunately, what frequently then happens is the scaling of an academic process that wasn't optimized to begin with. These efforts are often focused on scaling rather than innovation within manufacturing. This is something that we as a field are challenged to think about: are there ways in which we can innovate the manufacturing process? Often, what I see is that the incentives are not well aligned; the incentives of any given startup are to bring their process forward and into the clinic as quickly as possible, and to then seek to give it to somebody else to scale up. There is no real focus on how to improve the manufacturing of cell therapies because once you have a process, it is hard to go back.

SF I agree with Johannes. I think there needs to be a focus on scalability from the beginning. If you look at the technologies available, the field has migrated towards closed automated platforms or modular closed systems for manufacturing cell therapies such as CAR-Ts, and automation is one way to improve scalability.

We are always working to achieve a faster, more efficient process. In fact, there are now 3-day and even 1-day CAR-T manufacturing processes. There are also discussions around *in vivo* CAR-T, where you just bypass cell therapy manufacturing altogether. Technology is moving in that direction. So, CAR-T cell therapy manufacturing will become more efficient and scalable. Nonetheless, it is important to continue to bear scalability well in mind when starting out with a process. Even in an academic setting, we communicate with our investigators who are interested in moving a therapy forward to make sure they understand right from the beginning what it takes to develop a process to support a clinical trial. I think everybody in the cell therapy field is more forward-thinking now, but we have not overcome the scalability issue just yet.

Q **MAS:** What is on your wish list in terms of next steps for automation?

SF I wish that I could automate every process that I start with in order to be able to manufacture at scale and increase my throughput. However, this may or may not be possible depending on the type of automated platform being used. If it's a closed, single-use automated platform, can it be used in series with another robot running all the machines? Or is it necessary to change the process to match another technology? This is also a challenge: if you have clinical data generated using a single-use, closed, automated platform and you then switch to another platform, you won't be able to leverage that data. This is why it is important to understand what it is you want to manufacture and how you want to manufacture it before you commence development, so that you can plan for automation. I think the key question with any existing process is: is it automatable, or do I need to make a change?

"I think the key question with any existing process is: is it automatable, or do I need to make a change?"
Steven Feldman

Q **MAS:** I think that's the key term—'automatable'. At the 2025 ISCT Annual conference, there was a speaker who stated that for early-stage companies, the process doesn't have to be automated; it just has to be automatable. Similarly, it doesn't have to be scaled at that point; it just has to be scalable.

How do you see collaboration between early-stage companies and CDMOs—what are some success factors there?

JF I think it's useful for teams who are in the early phase of development, such as academic teams and biotech startups, to work closely with CDMOs—in particular, to help with how to think about scaling their processes. I hope that the BioLabs Center for Advanced Therapeutics in Philadelphia, where developers will work closely with Thermo Fisher Scientific scientists on their process development and scale-up, will ultimately allow early-stage biotechs to accurately predict how their products can be commercially produced at scale and in multiple locations.

If you are a scientist reading this article, I want to challenge you to think like a commercial drug manufacturer. Think about how the process that you use within your lab to make a few billion cells to treat a mouse needs to be scaled up to treat hundreds or even thousands of patients. Think about working closely with people who can advise on scalability early on in your workflow, and on how to reduce bottlenecks. It's important to address these points as early as possible and before the process gets approved by the regulator, as it is difficult to go back afterwards and re-engineer a process.

Q **MAS:** Steve, the LCGM team is addressing many different diseases, including cancer, rare diseases, and other indications. Can you elaborate on how the team plans for scalability?

SF The LCGM is the GMP manufacturing facility that supports Stanford University, so various centers use it. For example, we have gene correction facilities for rare disease groups and CAR-T manufacturing facilities for cancer and more recently, autoimmune diseases. In each case, it's mainly about setting up the workflow, however, it is necessary to be able to offer different methodologies, e.g., CRISPR-based editing of CD34 cells for gene correction; engineering CD4s into a specific type of regulatory T cell; novel graft generation; making CAR-T cells, etc.

What we try to do as standard practice is to work with investigators early on to understand what they have achieved in the lab, their goals for their therapy, and what they need to do to manufacture the cells they need. There is knowledge transfer and some small-scale process feasibility studies are conducted. Then we embark on an effort to close and

scale up the process for clinical manufacturing. During this entire process, we keep scalability and automation in mind.

I think it's important to focus on educating upstream with the investigators in order to come up with solutions for how to achieve the best possible process workflow. There also has to be some flexibility in considering alternative solutions. Again, it comes down to education and an understanding of what it takes to commercialize a product. We now address questions on scalability at the beginning of the process, whereas a decade ago this wasn't the case; we didn't care how the product got to the clinic or what the process looked like! That is not the culture today among industry professionals and academics alike—today, development is always done with scalability in mind.

BIOGRAPHIES

Johannes Fruehauf is a physician-scientist and life-science entrepreneur. He is the Founder and CEO of Biolabs and LabCentral, the national network for biotech incubators and the largest co-working spaces for life-science startup companies. Together, Biolabs/LabCentral have helped launch over 850 venture funded startup companies in the life sciences in 16 different cities and a presence in the USA, Germany, France and Japan. The concept of these facilities is built around openness, transparency and shared resources and has changed the way biotech companies are built in the USA. Companies launched at Biolabs/LabCentral have raised over $30 billion in venture capital financing since 2010. Dr Fruehauf is a Founding General Partner at Mission BioCapital, an early-stage venture capital fund providing capital to start-up companies in the life sciences. Dr Fruehauf studied Medicine in Germany and France. He practiced medicine (internal medicine and OB/Gyn) for several years in Germany before coming to Boston for a post-doc at Beth Israel Deaconess Medical Center/Harvard Medical School. He is an author of 30 peer reviewed articles in the medical literature and inventor on numerous issued and pending patents.

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Steven Feldman is the Site Head and Scientific Director for Stanford's Laboratory for Cell and Gene Medicine, Stanford's GMP Cell and Gene Therapy Facility. He directs process development and manufacturing for the Stanford Center for Cancer Cell Therapy, Stanford Center for Curative and Definitive Medicine and all other users of the facility, be it Stanford faculty or Industry partners. The group develops novel cell and therapies for the treatment of cancer and rare diseases and will begin efforts to manufacture gammaretroviral and lentiviral vectors to support investigator-initiated clinical trials. Dr Feldman's research interests include development of retroviral and lentiviral packaging cell lines and novel strategies for the large-scale closed cell culture processes to support production of clinical reagents. As a result, the lab is focused on identifying novel tumor-associated antigens and developing T cell receptors and chimeric antigen receptors to re-direct T cells to target specific tumors. Recently, research efforts have also focused on individualized cell therapies utilizing mutation-specific TIL, as well as mutation-specific TCRs to engineer T cells, targeting immunogenic mutations presented on breast cancers. In addition, as we characterize our clinical products we have efforts to modulate cell function and phenotype by manipulation of cellular pathways.

Steven Feldman, Site Head and Scientific Director of the Laboratory for Cell and Gene Medicine, Stanford Center for Cancer Cell Therapy, Stanford, CA, USA

Mary Ann Santos is a Global Senior Manager at Thermo Fisher Scientific focused on strategic collaborations for cell, gene and advanced therapies. She has over 27 years of experience in the biotechnology industry with expertise in cell biology and life sciences. This includes working with biotechnology, bioindustrial and biopharmaceutical companies in addition to academic institutions in North America and across the globe. She has also led research project teams with a focus in next generation cancer therapeutics as well as experience in process development prior to joining Thermo Fisher Scientific.

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AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

Exploring asprosin: how AAV vectors are advancing hormone research

INTERVIEW

"I do believe AAV vectors will become more widely used, not just for CGTs but in other applications as well."

Lauren Coyle, Editor, BioInsights, speaks to **Bijoya Basu**, MD-PhD Candidate, Case Western Reserve University School of Medicine, about the potential of AAV vector technology in hormone research and translational science, particularly when studying asprosin, a hormone with roles in metabolism, appetite, and thirst regulation.

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Q Why has asprosin captured the attention of researchers across multiple disease areas?

BB The asprosin hormone was discovered around a decade ago by Dr Atul Chopra, the principal investigator in our laboratory. It was found serendipitously—there was a patient with a unique disease called neonatal progeroid syndrome (NPS), and at the time, nobody knew what was causing it. Then, simply by studying the genetics of this rare condition, we discovered the asprosin hormone exists in all bodies.

"Ultimately, we adopted AAV vectors as a robust research tool to stably express asprosin in animal models and study its downstream effects. Unlike adenovirus, AAV does not induce illness in mice and provides long-term expression."

Asprosin is part of a class of hormones called caudamins [1], which are C-terminal cleavage products of unrelated proteins. Profibrillin is cleaved into two distinct products: fibrillin-1 from the N-terminus, which contributes to the extracellular matrix, and asprosin from the C-terminus [2].

What made asprosin interesting in the beginning was that it gave insights into human biology and metabolism. However, since it is a hormone, it also raised new questions of how it can be targeted and sequestered for therapeutic purposes. One of the early questions following its discovery was whether downregulating asprosin could lead to a potential therapy for type 2 diabetes and obesity [3].

As asprosin biology continues to unravel, more information is being revealed that this hormone is involved in significantly more than just metabolism. For example, a recent study found that it controls thirst in the brain through the cerebellum [1]. These studies are helping us not only to understand asprosin but also human biology, as a whole.

Q One major challenge in cell and gene therapies (CGT) is the variability of recombinant protein production. How has this impacted efforts to study asprosin, and how has this led your team to explore AAV as a solution?

BB One issue often seen with recombinant proteins is significant batch-to-batch variability. We have experienced this firsthand—after purchasing recombinant asprosin from different vendors, we found that its efficacy was inconsistent, and it only worked as expected in some cases. Rather than investing time troubleshooting or attempting to produce our own recombinant protein, we began considering alternative tools to study asprosin.

When studying asprosin, our goal was to modulate its pathway by either upregulating or downregulating. To this end, we employed various tools and strategies, including the use of genetic models and monoclonal antibodies [4,5] Ultimately, we adopted AAV vectors as a robust research tool to stably express asprosin in animal models and study its downstream effects manufactured and produced by Vector Biolabs. Unlike adenovirus, AAV does not induce illness in mice and provides long-term expression. Based on our observations, injecting mice with AAV allows for asprosin to be upregulated for several months. This has been instrumental in not only advancing our understanding of asprosin biology, but also in optimizing a variety of tools.

In our paper on the discovery of specific monoclonal antibodies [3], we utilized AAV to elevate circulating asprosin levels and subsequently neutralized them using the antibody. More recently, we have focused on optimizing the ELISA method we use to measure circulating asprosin [6]. The AAV was used as a tool to both elevate levels of asprosin and to demonstrate that our ELISA technique can reliably detect those changes.

Q How does AAV-mediated overexpression of asprosin overcome the reproducibility issues seen with recombinant approaches, and are there any specific benefits to using AAVs in hormone research more broadly?

BB As with any biological tool, there is always the possibility of batch-to-batch variability. However, in our experience using AAV over the past few years, we have found that almost every batch produced by Vector Biolabs has worked consistently. Our AAV-based tool enables stable overexpression *in vivo*, allowing for more consistent mechanistic studies. This results in consistently stable and elevated levels of the hormone.

In contrast, recombinant proteins typically involve administering a single dose. However, these are rapidly cleared from circulation, requiring administration of multiple doses to maintain physiological effects. AAV addresses reproducibility challenges by enabling chronic overexpression.

While AAVs are commonly associated with gene manipulation, typically for diseases involving defective or absent gene expression, our use of AAV in asprosin research is different. We are not editing a faulty gene but rather increasing the levels of a naturally occurring hormone in mice. It allows us to use AAV as a powerful way to learn more about biology itself.

According to our analyses, AAV administration results in approximately a two-fold increase in circulating asprosin. Interestingly, this mirrors the elevation observed in patients with obesity, who typically show around double the asprosin levels compared to individuals with normal weight. By replicating this condition in mice, we are able to study the hormones effects in a controlled and targeted manner. The mice do gain weight following AAV-mediated asprosin overexpression, but not to the extent seen in diet-induced obesity models [3]. This distinction allows us to isolate the effects of asprosin from other factors associated with obesity, such as systemic inflammation or metabolic dysregulation.

All things considered, AAV is a valuable tool in hormone research. It enables the hormone of interest to be elevated without significantly disturbing other physiological systems, thereby enhancing both experimental reproducibility and biological insight.

Q What has the use of AAV vectors revealed about asprosin's role in regulation that previous methods could not capture clearly?

BB With the AAV, we have seen increases in both blood glucose and body weight [3]. This has been shown across multiple studies from our laboratory over several years. We used multiple tools to prove this, including knockout models, monoclonal antibodies, and the AAV. Across our work, we have also demonstrated that when asprosin is downregulated in a mouse model, and we reintroduce it using AAV, certain physiological responses could be replicated upon reintroduction.

By chronically increasing asprosin levels with AAV, we have repeatedly observed rises in water intake, body weight and blood glucose. Importantly, we have also shown that these effects can be reversed—when we neutralize asprosin using tools like the monoclonal antibody, those phenotypes come back down [3]. In contrast, we would not necessarily be able to demonstrate this as clearly with recombinant protein, as we cannot be sure how long it remains elevated or how consistently it is being sequestered.

"I see firsthand how rapidly the field of CGT is evolving."

Furthermore, we have found that asprosin also increases appetite, and it does so through AgRP neurons [5]. Similarly, we have observed that mice injected with the AAV not only have higher body weight and blood glucose, but they also exhibit increased food intake, indicating a higher appetite [3].

Q Given your success with AAVs in asprosin research, do you see this platform being applicable to other emerging hormones or bioactive molecules, and what makes it suited for understudied targets?

BB I do believe AAV vectors will become more widely used, not just for CGTs but in other applications as well. Using it as an overexpression tool is very beneficial, especially when trying to uncover new biological insights. When asprosin was first discovered, there was some pushback—certain people did not believe that a hormone could come from the C-terminus of another protein.

It was necessary to have all these layers of proof because we were challenging what was already known in biology. AAV is a valuable tool for that, as it allows you to overcome some of the issues we discussed with recombinant proteins. It also enables chronic expression, which can be targeted later. Additionally, it helps optimize other tools, such as antibodies and ELISA. Therefore, I truly believe AAV will be an invaluable tool for researchers in the future.

Lastly, as mentioned earlier, asprosin forms during the specific cleavage process of profibrillin, which could explain why recombinant proteins sometimes present issues. As we continue to discover not only new hormones but also new ways hormones are secreted, having tools to overexpress them could be crucial for the field, instead of just relying on recombinant proteins.

Q Looking ahead, how do you see the role of AAV-based tools evolving in translational science, especially as CGTs continue to gain traction in both research and clinical settings?

BB One of the main advantages of AAV over vectors such as an Ad5 virus is its favorable safety and durability profile. While Ad5 can express transgenes more rapidly, it often induces immune responses and can make animals ill. In contrast, AAV tends to be well-tolerated and supports long-term expression, making it particularly valuable for both research and therapeutic applications.

As someone currently doing a PhD in genetics, I see firsthand how rapidly the field of CGT is evolving. New therapies are being approved at an accelerated pace, and the momentum in this space is significant. I believe AAV-based approaches will continue to contribute to both research and clinical understanding. This is particularly relevant as AAV becomes increasingly common in neuroscience and endocrinology research.

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BIOGRAPHY

Bijoya (Bijou) Basu is an MD-PhD candidate at Case Western Reserve University, currently pursuing a PhD in Genetics and Genomic Sciences. Her research, mentored by Dr Atul Chopra at the Harrington Discovery Institute, focuses on the hormone asprosin. Bijou's work has earned recognition through national presentations and publications, including in *Nature Neuroscience* and *Trends in Endocrinology and Metabolism*. She's received multiple accolades, including awards from the American Academy of Neurology and Society for Neuroscience. Bijou is committed to a career at the intersection of neuroscience, translational research, and patient advocacy.

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From Mystery to Discovery

AAV Makes It Clear

Harnessing AAV to Uncover the Biology of Asprosin:

A CASE STUDY IN **Hormone Research**

Bijoya (Bijou) Basu

Key Speaker

CELL & GENE THERAPY INSIGHTS

From innovation to access: bridging gaps in scalability and cold chain precision logistics for advanced therapies

INTERVIEW

"...trade disputes, wars, and natural disasters are creating new regulatory hurdles, that require navigation."

Rohin Iyer, Senior Director, Global Cell and Gene Therapy Operations, Marken, speaks to **Jokūbas Leikauskas**, Editor, BioInsights, about addressing the complex logistics of cell and gene therapies through global infrastructure, precision, and advanced technologies. They also discuss evolving cold chain needs, regulatory and geopolitical challenges, and the need for scalability.

Cell & Gene Therapy Insights 2025; 11(6), 755–762 · DOI: 10.18609/cgti.2025.084

Q What recent innovations or regulatory shifts are having the biggest impact on how CGTs are developed, transported, and delivered?

RI CAR-T cell therapy began more than 10 years ago, with the first patient, Emily Whitehead, who remains completely cancer-free to this day. However, there is so much that has changed since this first therapy was administered.

The biggest innovations have come over the last 5 years, and even more recently in the past 2 years, with the advent of shorter manufacturing times. We now see examples of CAR-T cell manufacturing in only 2 or 3 days, whereas previously it took 8–14 days, or even up to 21 days. Nowadays, cells can be manufactured 2 days after apheresis, and the patient already has a drug product ready to be collected and delivered. While this is great for the patient, it compresses the logistics timeline significantly and adds complexity that must be managed carefully and with precision.

There is also *in vivo* CAR-T cell therapy, which promises to take the cells out of the equation entirely by using either mRNA-loaded lipid nanoparticles or viral vectors as the therapy. That changes the temperature range over which these therapies are shipped, as well as the packaging, moving from liquid nitrogen shipments to -80 °C or dry ice shipments. In essence, these changes not only impact manufacturing, but also logistics and the cold chain.

Another example is armored CAR-T cells, which are sometimes used when CAR-T cells have not been effective or when patients have relapsed after treatment. These armored CAR-T cells have secreted payloads that can now treat previously intractable cancers and are even outperforming conventional CAR-T cell therapies.

Beyond innovations in cell therapies, there have also been regulatory shifts. Although there has been a noticeable increase in commercial approvals for CGTs and advanced therapies in general, geopolitical climate shifts, such as the introduction of new tariffs and other disruptions, have introduced more complexities. Additionally, trade disputes, wars, and natural disasters are creating new regulatory hurdles, that require navigation.

Furthermore, getting something from one country to another is no longer as easy as it used to be due to customs clearance. Government institutions are also under increased scrutiny regarding how much they spend and how much they receive. All of this has a direct impact on the end product—and ultimately, on the patient.

Q As the complexity of CGT logistics continues to grow, what are the most pressing bottlenecks or vulnerabilities in today's cold chain infrastructure, and how can we start to solve them?

RI There are many bottlenecks in the cold chain infrastructure. One of the biggest is around packaging and the slow evolution of data loggers used to track and trace these shipments and therapies. This is not just to ensure life-critical therapies are getting from point A to B, but also ensuring that they are maintained at the correct temperature and that there have not been any significant shock events or similar issues. There is a growth in innovation in that area but it has also been a bit of a slow crawl. These shipments contain very sensitive payloads and must be kept at the correct temperature. If they are not, we need to know when they are likely to exceed those nominal temperature ranges. As I mentioned

"...there have been all kinds of disruptions along the cold chain. At Marken, we have seen everything from car fires to airline delays, labor strikes, IT outages, and even missile strikes at airfields."

earlier, there have been all kinds of disruptions along the cold chain. At Marken, we have seen everything from car fires to airline delays, labor strikes, IT outages, and even missile strikes at airfields.

Furthermore, the statistics show that only ~78% of flights are on time. Yet in this field, 78% on-time performance is simply not acceptable. The expectation in cold chain and specialty logistics is to be 95–99% on time as the room for error is too high and could potentially result in patients suffering serious, even life-threatening, consequences. In essence, we must be more perfect than the industry typically allows. The way we achieve that is by having a team that supports the infrastructure through relentless planning, conducting lane risk assessments, and building contingency upon contingency into our route planning. Therefore, when things go wrong, we already have a way to respond and work around the issue.

Q How does Marken define 'precision' in this context, and what technologies or processes are central to achieving that level of control, visibility, and responsiveness?

RI My personal definition of precision comes from the scientific concept of consistent reproducibility. The analogy I like to use is of an arrow hitting a bullseye. If an arrow always hits the center on the bullseye, that is known as accuracy. However, if the arrow lands very close to the center, that is still a precise outcome. It may not be the perfect result, but it is consistent, and everything is landing within a small margin of error around the target. That is where we aim to be with precision logistics. We do not expect perfection, but we do expect to stay within our defined margin of error, aiming to be a minimum of 95%, and in many cases our clients, and the patients they serve, demand even higher precision than this.

With advanced therapies such as CGTs or radiopharmaceuticals, any significant delay can compromise the product. This might lead to temperature variations if the product is left out too long, or exposure to pressure or shock. In turn, that can result in the loss of cell viability, payload, or packaging integrity if the product is left at the wrong temperature for too long.

When that happens, the cells, nucleic acids, radioisotopes, or other components, such as proteins, will inevitably lose potency and creates other issues. For example, if packaging integrity is lost, contamination can occur. If the radioisotope has a short half-life, the therapy could be rendered useless. Therefore, we must be extremely careful not to let those things happen. Precision is no longer optional—it is essential.

These therapies are typically being dosed in critically ill patients or those with rare diseases, and in many cases, these patients have failed all other prior lines of therapy. For some, this can be the difference between life and death, which is why we design for robustness. We focus on strong central planning and precise cold chain management. Additionally, we leverage smart technology, such as real-time or near real-time monitoring via specialized data loggers and through our control tower. This is technology we

"...to scale successfully, we must also maintain strong visibility into our operations, especially in an uncertain world."

incorporate into our packaging with visibility tools and sensors that can measure temperature and GPS coordinates.

Regarding Marken's definition of precision, we have strategically unified under a single umbrella with UPS Healthcare, bringing together our legacy partners—including MNX, Bomi Group, Polar Speed, RH Logistics, BPL and other industry leading UPS organizations. Together, we are Marken, UPS Healthcare Precision Logistics—a global standard for cold chain excellence. This allows us to leverage our own internal resources in a way that was not previously possible. For example, we leverage the UPS air network with priority, and we are capable of fully utilizing this resource for advanced therapies. It is just one example of how Marken applies the concept of precision more effectively as we continue to support the growing number of advanced therapies entering the pipeline.

Q Scale is often a limiting factor for emerging therapies. What do scalable logistics look like in the CGT space, especially when dealing with personalized, patient-specific treatments across borders?

RI Currently, scalability is a common theme in the CGT field, as it is one of the biggest bottlenecks. Many people are building new gadgets designed to pump out more cells or viral vectors.

Looking a few years back, some evidence suggested that ~25,000 CAR-T cell therapies had been dosed in patients at that time. Today, the estimate is significantly higher with ~50,000 patients dosed with CAR-T cell therapies [1,2]. That illustrates the exponential growth happening in this space. For example, there are now around 139 approved cell, gene, and RNA-based therapies, and greater than 4,400 in the clinical pipeline. That number grew by 10% in just the past year. When looking at the industry growth, it is exponential. Market forecasts suggest a 20–30% compound annual growth rate (CAGR) over the next 10 years, which is a conservative estimate.

This kind of growth is what concerns many developers, as we need to scale these operations to treat more patients. At Marken, we improve scalability by developing and adopting new tools and technologies, including automation, better cross-disclosure, and the integration of AI and machine learning. These are not only integrated in manufacturing, but also in logistics, particularly to improve day-to-day tracking and tracing. At the same time, we have live operators in control towers, who are available 24/7 by phone within 15 seconds or less to solve problems as they arise.

Additionally, to scale successfully, we must also maintain strong visibility into our operations, especially in an uncertain world. We must also invest in our people who carry out daily operations, packaging preparation, lane mapping, and inventory management. It is an expansive ecosystem across logistics and manufacturing that requires various operational hubs.

As mentioned earlier, we have a fantastic, dedicated team, including project managers, operational excellence coordinators, and investigators where each one of them is

dedicated to doing the right thing. These people are not just trained in logistics, but also in the biology behind CGTs and manufacturing, which helps them grasp their impact on patients and gives them the confidence to speak the language necessary to address these very complex challenges.

Q Looking at Marken's role in the cell and gene therapy (CGT) ecosystem, how does your team support the unique logistics needs of CGTs, particularly when it comes to ensuring global delivery with uncompromised product integrity?

RI Marken has a specialized Advanced Therapies Division with over 100 employees. There is enough infrastructure to be situated globally in strategic locations and regions where patient and client needs are the greatest, which allows for more agility and flexibility.

The infrastructure includes a global control tower comprising a 24/7 monitoring team. Additionally, there is a packaging department, an operational excellence team, an operational readiness team, as well as dedicated project managers. These teams help support the unique logistics needs in CGT, while also being precise, lean, and agile enough to make key decisions in the moment and act on them. This helps remove some of the mystery for the client and customer when things may be going sideways, as they often do in logistics.

Q Looking ahead, the CGT pipeline is only getting more crowded and complex. What trends or disruptions do you foresee over the next 3–5 years, and how is Marken evolving to stay ahead of those changes?

RI We are seeing the greatest impact due to the current geopolitical climate, as well as climate change. Natural disasters seem to be becoming less 'natural' and more extreme as time goes on. The rise of more authoritarian governments is also creating political strife the world over. While these types of disruptions are not necessarily new, their frequency has increased. As a result, our ability to use certain airports or roadways is increasingly impacted.

We rely on outside service providers to help us do this work, and they are often at the mercy of these uncontrollable events. Many people in the logistics field might say some of these events are considered controllable. That is because we choose which carriers we use and which service providers we partner with. For example, if one provider fails to deliver the right solution in a moment of crisis, we can choose not to work with them again.

Logically, we are listening to our customer feedback and demands. We are making real investments in our people, as well as in owned vehicles, better tools, and advanced technologies, such as AI and real-time data loggers. For instance, it is crucial to consider whether our data loggers can track GPS location in an app, point to the shipment's location, alert us if it is heading in the wrong direction, or trigger a push notification if it enters or exits the wrong geofence.

We often use this information in unconventional but crucial ways. For example, if a shipment is marked as 'tendered' at the airline cargo desk and the flight has departed, but the GPS still pings on the tarmac, we know something is wrong. Conversely, if the GPS stops pinging once the shipment exceeds a certain height threshold or altitude, we know the package has been uplifted.

Additionally, if we face a severe weather disruption, flights are cancelled, there is an IT outage (such the CrowdStrike incident), or a war that is completely out of our control, we will do everything possible to communicate transparently and get the therapy to the patient despite these obstacles.

We know there is a sick patient out there whose life might depend on us. Therefore, we must do everything we can to ensure that the patient's family, their medical team, the manufacturers, and the researchers who have invested countless hours and millions of dollars into developing these therapies. They can all count on us to deliver, because failure is not an option for us.

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BIOGRAPHY

Rohin Iyer leads Marken's advanced therapies division, managing the critical distribution of both clinical and commercial personalized medicines. Leveraging Marken's unique cell and gene therapy (CGT) portfolio as its flagship premium service offering, he oversees the complex logistics across a diverse array of advanced therapeutic modalities ranging from nucleic acid therapies to CAR-T therapy, as well as the raw materials used to manufacture them. Dr Iyer's team provides specialty logistics solutions to both emerging and highly established biopharmaceutical developers in the field and leverages an extensive global cryogenic and operational network, specialized control tower oversight with advanced visibility and interventional tools, and dedicated project management and operational excellence staff to deliver innovative solutions for clients and patients. His leadership expertise includes over a decade in CGT development and over 15 years of hands-on laboratory work focused on stem cells, tissue engineering, immunotherapy development and regenerative medicine at large pharma organizations. With extensive experience in portfolio management, process development and bioprocess optimization in CGT and immunotherapy, he has played an instrumental role in supporting the clinical research and development of regenerative medicines. Rohin obtained his Bachelor of Applied Science and his PhD in Biomedical Engineering at the University of Toronto, Toronto, ON, Canada.

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EVENT PREVIEW

Advanced Therapies Europe 2025

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As part of our ongoing coverage of major gatherings in the advanced therapeutics space, *Cell & Gene Therapy Insights* presents a preview of Advanced Therapies Europe 2025. Scheduled for September 2–4, 2025, in Barcelona, Spain, this conference will see 500 senior leaders from biotech, pharma, academia, investment, manufacturing, and solution provider sectors gather together to explore the latest advancements in cell and gene therapy.

The event includes deep-dive workshops, strategic roundtables, the Women in Advanced Therapies Congress, the Investment Summit, and the Innovation Exchange showcasing the biotech breakthroughs shaping our future. Confirmed speakers include leaders from Takeda, Novartis, Johnson & Johnson, Kiji Therapeutics, and more.

EMERGING TECHNOLOGIES: FROM CONCEPT TO DISRUPTION

Advanced Therapies Europe 2025 will spotlight the technologies poised to redefine the CGT landscape. In the panel 'Emerging Tech in CGT—What's Next?', leaders including Åse Rosenqvist (Nordic Cell Therapy Business Unit Lead, Johnson & Johnson), David Sourdive (Co-founder, Executive Vice President CMC & Manufacturing, Cellectis), Carolina Pola (CEO, STAb Therapeutics), and Oliver Dovey (Senior Director Functional Genomics, bit.bio) will explore the frontiers of CRISPR, gene editing, and cell engineering. The session will examine the next wave of *in vivo* and *ex vivo* therapies, and ask which breakthroughs are most likely to shift the clinical and commercial paradigm.

In addition, the 'Innovation Exchange' will offer a dynamic platform for biotech start-ups to pitch novel solutions to a panel of investors including Sven Kili (Partner, Saisei Ventures), Rahul Khetan (Venture Associate, UCB Ventures), Laura Rodriguez Gallego (Partner, Invivo Partners), and Malgorzata Rogalska (Analyst, Ysios Capital). This session promises a window into the technologies that may soon move from the edge of possibility to the center of practice.

MANUFACTURING, ANALYTICS, & SCALE-UP

As CGT products move from lab to clinic, the challenges of manufacturing,

characterization, and realistic development timelines remain front and center. In the panel 'Bridging the Characterization & Analytics Gap in CGT', experts including Eleuterio Lombardo (Director, Cell Therapy Characterization, Takeda), Lindsay Davies (Chief Scientific Officer, NextCell Pharma), and Damian Marshall (VP, Analytical Development, Resolution Therapeutics) will explore why robust analytics remain a bottleneck, and how collaborative, cross-functional approaches are beginning to close the gap.

Furthermore, 'From Discovery to Development—Creating Realistic CGT Timelines' brings together voices from biotech, academia, and clinical translation. Speakers Anne Douar (Principal & Founder, Ad hoc Biologics), John Campbell (Chief Scientific Officer, Swarm Oncology), Elena Matsa (Professor, University College Cork), Alessandra Magnani (Head, Advanced Therapies and Immunotherapy Platform, Hospital Sant Joan de Déu), and Claudio Santos (CEO, Gyala Therapeutics) will discuss how to align CMC, regulatory, and development planning from day 1.

REGULATORY AFFAIRS: NAVIGATING COMPLEXITY WITH CLARITY

As the regulatory landscape for advanced therapies continues to evolve, two sessions at Advanced Therapies Europe 2025 will provide essential insights for developers seeking clarity and strategic foresight. In 'CGT Regulations Uncovered: New Rules, New Realities', Alexander Natz (Secretary General, EUCOPE) and Paolo Morgese (Vice President Public Affairs Europe, Alliance for Regenerative Medicine) will unpack recent legislative shifts across the EU, USA, and other key regions. From the EU Pharmaceutical Legislation reform to the implications of the FDA's evolving stance on accelerated pathways, this session offers a practical lens on compliance in a fast-moving field.

The panel 'Engaging Regulators Early—The Key to Accelerating ATMP Development' will explore how early, proactive dialogue with agencies like the EMA, US FDA, and MHRA can de-risk development. Anna Koptina (Head of Regulatory Affairs, Elicera Therapeutics) and Benjamin Dewees (Senior Vice President of Regulatory Affairs, Artiva Biotherapeutics) will share lessons from the front lines of regulatory engagement—highlighting what works, what doesn't, and why timing is everything.

A LOOK TO THE FUTURE: WHERE ARE WE HEADING?

As the conference draws to a close, the plenary panel discussion 'Charting The way Forward: Where Are We Heading?' will see Angela Vollstedt (Director, Global Cell & Gene Therapies Portfolio, Novartis), Miguel Forte (CEO, Kiji Therapeutics and President, ISCT), and Montse Daban (Executive Director, BIOCAT) debate the future trajectory of advanced therapies. This panel of trailblazers from across the field will reflect on 2 days of deep discussions on the current state of the European CGT landscape, and look forward to the future of the space. Attendees can expect discussion on Europe's global competitiveness in CGT, the role of AI and automation in reshaping development pipelines, and how to build a more resilient and equitable innovation ecosystem.

As a reader of *Cell & Gene Therapy Insights*, you're entitled to a **20% discount** on delegate tickets—just use the code **INSIGHTSBIO20**. You can use the **link here** to register for Advanced Therapies Europe 2025.

Additionally, to find out what other cell and gene therapy events are upcoming, you can find our online Events Calendar **here**.

CELL & GENE THERAPY INSIGHTS

EVENT PREVIEW

Cell and Gene Therapy World Asia 2025

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As part of our ongoing coverage of key gatherings in the cell and gene therapies space, *Cell & Gene Therapy Insights* presents an event preview of Cell and Gene Therapy World Asia 2025. Taking place on September 10–11, 2025 in Singapore, the knowledge-sharing conference will showcase the latest advances, technologies, and collaborative opportunities in regenerative medicine in the APAC region, including CAR-T technologies. This preview offers readers a glimpse into the sessions, speakers, and themes that will shape the discussions of Cell and Gene Therapy World Asia 2025.

2025 SPEAKERS

Esteemed voices from the CGT industry across Taiwan, China, Japan, Singapore, India, Australia, South Korea, Indonesia, Thailand, and more, will gather in Singapore in September to share insights on the latest developments in this dynamic field. Speakers include Jimmy Chang (CEO, TaiMed Biologics), Paula Lam (CSO, BioCell Innovations), Richard Wang (Founder & CEO, Neukio Biotherapeutics), Julio Lin (Vice President, Blue Blood Biotech), Rebecca McQualter (CEO, Chimeric Therapeutics), Maloy Ghosh (CSO, Zumutor Biologics), Andrew Bruce (CEO, Medisix Therapeutics), Jennifer Kuan (VP of Taiwan Operations, Bora Biologics), and Ivan Horak (Founder & CEO, Tikva Allocell).

CAR-T ADVANCEMENTS

CAR-T cell therapy will be a key focus at the 9th Annual Cell and Gene Therapy World Asia 2025, reflecting its growing clinical and commercial relevance across the region. The agenda includes in-depth discussions on CAR-T development, manufacturing, and clinical translation. Attendees can expect insights into the evolving CAR-T landscape in Asia, including case studies and regional trial experiences. With participation from leading organizations such as Legend Biotech and SCG Cell Therapy, both active in CAR-T innovation, the conference offers a platform for stakeholders to exchange knowledge and explore collaborative opportunities.

Sessions include 'The Revolution of CAR-T Therapy: Current Frontiers and Future Horizons', in which an expert panel of leaders will discuss the latest advancements in CAR-T engineering to improve efficacy and safety, as well as how regional collaborations can accelerate market access. Tools and technologies to enable CAR-T manufacturing will also be explored, in the sessions 'Revolutionizing CAR-T Production: The Role of Automation' and 'AI and Next-Generation Bioreactors for Scalable CAR-T Manufacturing'.

VECTOR MANUFACTURING STRATEGIES

Vector manufacturing will be another critical theme at Cell and Gene Therapy World Asia 2025, addressing one of the most pressing challenges in the cell and gene therapy pipeline. The agenda includes focused sessions on upstream processing and vector design, in addition to innovations in vector analytics and characterization services. As the APAC region continues to expand its footprint in gene therapy, these sessions will provide a timely platform for knowledge exchange in advancing vector manufacturing capabilities.

On the agenda, a presentation entitled 'Scalable Production Solutions for AAV Vector Manufacturing' will explore suspension-based bioreactor systems for improved scalability and reduced production costs, in addition to the benefits of templated platforms for AAV production. 'Advancements in Bacterial and Viral Vector Platforms for Gene Therapy' will explore the potential of bacterial vectors as alternatives to viral-based systems, as well as current innovations in improving the safety profile and therapeutic efficiency of viral vectors like AAV and lentivirus.

COMMERCIALIZATION

With the Asia-Pacific CGT market projected to reach US$4 billion by 2027, the region's growing role in translating advanced therapies from bench to market will also be explored. Discussions will cover critical enablers such as cryogenic logistics, supply chain management, and regional regulatory harmonization. Sessions, such as 'Digital Transformation in CGT Supply Chains', will highlight case studies from emerging biotech hubs such as China, India, and Southeast Asia, offering insights into successful commercialization pathways.

The closing plenary session, 'Charting the Next Decade: Transforming Cell and Gene Therapy in Asia', will explore the most critical investments needed to advance manufacturing and infrastructure capabilities in the region, in addition to achieving regulatory harmonization across Asia to accelerate approvals.

CELL & GENE THERAPY INSIGHTS

EVENT PREVIEW

Cell and Gene Therapy East Asia 2025

Cell & Gene Therapy Insights 2025; 11(6), 843–844 · DOI: 10.18609/cgti.2025.095

As part of our ongoing coverage of major gatherings in the advanced therapeutics space, *Cell & Gene Therapy Insights* presents a preview of Cell and Gene Therapy East Asia (CGTEA) 2025. Scheduled for September 25–26, 2025, in Incheon, South Korea, this conference will spotlight breakthroughs in gene-modified cell therapies, scalable manufacturing, and evolving regulatory frameworks across East Asia. In this preview, we highlight key sessions, speakers, and themes that will shape the conversation at one of East Asia's most anticipated CGT events.

NOVEL MANUFACTURING STRATEGIES FOR COMMERCIALIZATION

Regional leaders will explore commercialization, regulation, and collaboration in the development of cell and gene therapies (CGTs). A panel including Ryu Kang (CSO, Vaxcell-Bio), Kenji Nakamaru (VP, Head of R&D, Optieum Biotechnologies), and Phil Huang (Technical Director, Stemcyte) will showcase how East Asia's innovation hubs can drive therapy development and commercialization, while addressing regional supply chain challenges and fostering cross-border collaboration in research, clinical trials, and patient access. Furthermore, Bryan Choi (ISCT Asia Regional Vice-President and Professor, Inha University) will present on Asia's evolving regulatory landscape and infrastructure supporting CGT growth. Phil Huang will highlight REGENECYTE, showcasing the expanding potential of cord blood stem cell therapy beyond oncology.

SCALING UP CGT MANUFACTURING

The conference will also highlight advancements in scalable manufacturing for next-generation CGTs. KwangJun Yoon (Managing Director, CHA Biotech) will share strategies for risk management and regulatory alignment, while Sungjun Yoon (CEO, Fortuga Bio) will explore the clinical translation of dendritic cell immunotherapies. Kazuchika Furuishi (Board of Director, CellFiber) will discuss innovations in

encapsulation technology and overcoming manufacturing challenges to ensure quality and GMP compliance.

CAR-T & CAR-NK CELL THERAPIES IN ONCOLOGY

This event will also cover innovative CAR-T and immune cell therapies for solid tumors and hematologic malignancies. Lee Heon Ju (CEO, CarBio Therapeutics) will present innovative fifth-generation CAR-T platform technology targeting challenging solid tumors. Kenji Nakamaru (VP and Head of R&D, Optieum Biotechnologies) will discuss scFv-CAR optimization to enhance T cell function. Manh-Cuong Vo (General Manager of R&D, Vaxcell-Bio) will highlight NK cell and CAR-based therapies showing promising clinical activity. Cheng-Yi Jerry Kuo (Vice General Manager, UWELL Biopharma) will cover clinical development and trials of CAR-T cell therapies for blood cancers.

INNOVATIONS IN GENE EDITING & DELIVERY SYSTEMS

The conference will highlight innovations in gene editing, delivery systems, and extracellular vesicle (EV) therapeutics. Jaesuk Lee (CSO, nSAGE) will present the discovery and engineering of a novel Cas12a base editor with enhanced efficiency and multiplex capabilities. Seokjoong Kim (CSO, GenEdit) will discuss advances in polymer-based delivery technologies for genomic medicine. Chaemin Lim (Assistant Professor, CHA University) will explore therapeutic engineering of EVs, focusing on cell source screening, functional enhancement, and drug formulation strategies to boost stability and efficacy.

Cell and Gene Therapy East Asia 2025 is set to be a pivotal event showcasing the latest breakthroughs in gene-modified therapies, scalable manufacturing, and regulatory innovation across the region. Bringing together top industry leaders, researchers, and regulators, the conference will explore strategies to accelerate commercialization, overcome manufacturing challenges, and foster cross-border collaboration. Key sessions will highlight cutting-edge CAR-T and immune cell therapies, advanced gene editing tools, and novel delivery platforms, offering unparalleled insights into the future of cell and gene therapy development and precision medicine in East Asia.

As a reader of *Cell & Gene Therapy Insights*, you're entitled to a **15% discount** on delegate tickets—just use the code **BIOINSIGHTS**. You can find out more about the Cell and Gene Therapy East Asia 2025 events **here**.

Additionally, to find out what other cell and gene therapy events are upcoming, you can find our online Events Calendar **here**.