Cell and Gene Therapy: Hope, Hype and Political Upheaval

The sector has come a long way since the 1970s, but does political upheaval threaten progress?

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Kite, CAR Ts, and Access for Patients

Depending on the country, only about two in 10 eligible patients, on average, receive CAR T-cell therapy.

Featuring Cindy Perettie, Executive Vice President and Global Head of Kite, a Gilead Company

What first inspired your interest in science?
I attribute it to my high school biology and chemistry teachers. They did such a great job teaching science. It made me realize how complex cells are, and how they communicate with the rest of the body through chemistry using nerves and other systems. I absolutely loved it. When you start thinking about it in the context of disease – and we've all had family or friends impacted by illness – it becomes even more fascinating. You just want to get in there and make a difference in the world.

Why did you join the pharma industry?
I did basic research in academia at Johns Hopkins for several years, and while I loved it, I realized something important: basic research is foundational and is where everything starts, but if you really want to see its impact on patients, then you need to take it further.

I watched others move into the pharma industry, and I saw how they were able to translate that foundational research into something tangible for patients. That's when it clicked for me. I wanted to have that broader impact too.

You've worked in several companies over the years. What are the most memorable milestones or rewarding moments?
One of the earliest milestones in my career was when I was doing basic research on VEGF (Vascular endothelial growth factor); at the time, I was focused on it from a research perspective, but about five or six years later, I joined a pharma company and had the opportunity to develop anti-VEGF approaches into an actual therapy. Seeing it go from a scientific concept to something that was helping patients was incredible. That therapy ended up being approved in 19 different indications. It was amazing to witness that journey from research to real-world impact.

I've also been able to work on potentially curative therapies at Genentech and now at Kite. It's incredibly fulfilling to be part of something that can profoundly change cancer treatment, especially for patients who might not have had options before. When you get the chance to work on something that truly changes lives, it's a privilege and a career highlight.

How did you join Kite?
I hadn't worked directly with cell therapy before, but I had worked with therapies in the blood cancer space. Before joining Kite, I reached out to some physicians to get their perspectives on

cell therapy and the different companies in the space – without mentioning Kite specifically. What really stood out to me was that all of them, independently, said the same thing: "If you're going to go into cell therapy, you need to join Kite." They told me that Kite is the global leader in cell therapy and praised their reliable manufacturing capabilities.

When I finally spoke with Gilead and Kite leadership, it became clear that it was the right place for me. Why you join a company comes down to three things: the people, the culture, and the science. Without question, Kite had all three.

How was the learning curve of jumping into a new field?
Because I'd been following cell therapy from a distance, I thought I understood it. After I started at Kite, however, I realized how complex cell therapy really is – everything from the treatment paradigm to the manufacturing process.

One thing that really stood out to me was the way people at Kite work together. The company refers to their work as a "team sport." Every company says they value teamwork, but at Kite I truly understand what this means. Without a collaborative mentality, we wouldn't be able to get these therapies to patients. The learning curve has been incredible. I'm 20 months in, and I'm still learning every single day.

What is Kite working on at the moment?
Depending on the country, only about two in 10 eligible patients, on average, receive CAR T-cell therapy. These are potentially curative therapies, so a major focus area for us is realizing the full potential of CAR T and ensuring more patients have access. This means meeting patients where they are. For instance, how do we treat someone in their town, rather than have them travel all the way to a treatment center in a far-away city?

Beyond that, Kite has an incredible pipeline. We have approved therapies for lymphoma and leukemia, and we recently completed studies for an investigational multiple myeloma therapy. We're also expanding into solid tumors. We are looking at glioblastoma and neuroblastoma, and we have research underway in hepatocellular cancers. At the end of last year, we filed an IND for our first program in autoimmune disease. We are also working on several therapies that are next generation, including dual targets and armoring – and we are seeing improvements in both efficacy and safety.

At the same time, we continue to improve our manufacturing process. We're in nearly 30 countries already and we're working hard to reduce turnaround times for patients. In the early days of cell therapy, it would take several weeks to get therapies to patients. In the US, we've brought that down to just 14 days. Outside the US, we're at 17 days. This is a massive improvement, and it's all thanks to automation, advancements in manufacturing processes, and enhancements in quality testing. This is very important as the patients have aggressive disease and need the therapies as soon as possible. During the COVID-19 pandemic, the industry learned a lot about rapid sterility testing, which continues to help us shorten timelines.

Why are CAR Ts so compelling for autoimmune diseases?
Think about conditions such as lupus or multiple sclerosis. We've already seen the same targets used in cancer – particularly with monoclonal antibodies – being applied to these diseases. So why not do the same with CAR Ts?

Professor Georg Schett in Germany has already taken that step, and the results are promising. For patients living with a chronic disease that requires life-long treatment, a CAR T treatment – even if it's not fully curative in the first version – could still offer a lasting impact. It might take a few iterations to get to that point, but even being treatment-free for five or six years would be life-changing. If we can develop a treatment that makes those diseases no longer feel chronic, that would be incredible.

Read the full article online.

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Political Upheaval Forces Medical Centers to Adapt

Academic medical centers are racing to adapt as political turnover and funding uncertainty threaten the future of cell and gene therapy research.

By Heather Purvis, Director of Clinical Operations at Title21

Academic medical centers are positioning themselves to deal with the changing times. Since funding cuts and significant regulatory leadership turnover were announced by the Trump-Vance administration, hospitals, and medical centers working in cell and gene therapies are under a new set of pressures that could impact the future of the space.

Academic medical centers in the US are driven by two things: their patients and the future. Patients treated at academic medical centers have the most complex diseases and are often in search of novel treatments for their specific conditions. That is why the future is so important: the next generation of care providers training there will bring new ideas and treatments, pushing the science of healthcare even further.

Funding creativity

The expansion of cell and gene therapy (CGT) technologies is constrained by the number of trained scientists and funding available, and we have seen massive upheaval on both sides of that equation. Changes announced to National Institutes of Health (NIH) funding (and even more so, uncertainty about what changes are yet to materialize) are forcing universities to focus and get creative.

In instances where NIH grants for promising research are no longer as accessible as they had been, sponsors are being asked to invest more in the early phases. There will, of course, be new strings attached in order to fund the whole ecosystem this way. That will mean more exclusivity considerations.

Right now, programs are seeing a high level of project churn – the frequency at which resources and team members change throughout any on project – from very calculated investments by sponsors that cut treatments that do not progress on schedule. Academic medical centers, however, require budget sustainability. On the funding side, they may explore bundled research projects or multi-project deals with sponsors at pre-negotiated rates to keep sponsor funding more stable. Those deals would raise concerns about the institutions' credibility, so partners will need to draw clear lines around the research phases.

Medical centers are also exploring creative new ways to share costs and create funding streams. These include supply-oriented networks with shared GMP laboratories for complementary products across organizations. This additional networking will likely result in more standardized regulation processes, supplies, governance, standard operating procedures (SOPs), quality, and reach of distribution. They are also exploring efficiencies in lab practices and supplies, and opportunities to serve more customers.

Staffing competition

The primary constraint on the growth of CGT treatment has always been trained staff. We have seen hundreds of layoffs at NIH and Centers for Disease Control and Prevention (CDC), and projects cancelled at academic research centers. While some institutions have been hit harder than others, the pressure has swept across the largest names in medical research. On the surface, this could be an opportunity in a

"Paper won't work – it is increasingly critical to move away from paper and towards management systems that direct users in compliance."

market where highly trained researchers have long been hard to find: there is a new influx of researchers in the talent pool.

However, according to a 2025 survey, while workforce mobility may increase, the shift would not be straightforward. For one, a postdoc who has devoted years to a certain disease or therapy may be more willing to change geographies than specialties. Canadian and European research centers are openly recruiting US researchers and staff – and the UK recently reorganized regulations to make it easier to get clearance for certain research. These countries, and the pharma units based there, see the opportunity and are increasing funding for their projects, making themselves more attractive to American researchers.

There are still too few bench technicians available, and there was already tremendous competition for program leadership, medical directors in particular. Staffing – and steady leadership – may be the biggest challenge ahead for CGT treatment development.

Logistics

Another hot topic for CGT labs at academic medical centers is how to balance the practical supply chain, quickly evolving regulatory standards, and data collection needs for multiple projects in research that need rapid solutions. There are physical space constraints for GMP labs, and the supply chain is still maturing – even as a treatment moves into approved manufacturing, it is still a relatively small batch compared to other university programs. Researchers examining such challenges in California conclude simply that, "Facilities that fail to adapt risk losing their competitive edge."

That may be the bottom line on all the issues related to CGT treatment and research: academic medical centers and related labs must adapt quickly. Driven by their patient-centered mission and professional ambition, we should expect US academic medical centers and the worldwide community of CGT experts to change rapidly.

Projects come and go quicker than they used to, and the new pressures will only accelerate that churn. It means research centers need a highly adaptive supply chain, and a highly adaptive way to manage both incoming and outgoing inventory. The reality is, paper won't work – it is increasingly critical to move away from paper and towards management systems that direct users in compliance. Furthermore, automation will be a key attribute for attracting funding, signaling a commitment to eliminating waste.

Collaboration will be the key driver of advances needed to maintain momentum in CGT. Biopharma will need to work more closely with academic medical centers to ensure they have the resources necessary to support all the infrastructure that goes into bringing these therapies to patients. That includes systems to allow for quick onboarding, as well as key resources including training, equipment, and tailored management systems.

That collaboration needs to go well beyond the walls of one organization, one sector, or even national borders. There must be a new push to use data to focus and refine these partnerships to find new ways of creating a functional CGT business ecosystem. To get there, sponsors need to better understand the challenges that academic medical centers are facing – and be full partners in addressing them.

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Harnessing Synthetic DNA for Safer, More Efficient AAV Manufacturing

Adeno-associated viruses (AAVs) have emerged as one of the most promising vectors for gene therapy, offering efficient and targeted gene delivery with a favorable safety profile. However, traditional AAV manufacturing methods often face challenges related to production efficiency, safety, and regulatory compliance. One of the primary obstacles stems from the reliance on plasmid DNA (pDNA).

Challenges of Plasmid DNA for AAV Manufacturing

In the early stages of development, when using pDNA for AAV manufacturing, the main challenge is the production of a master cell bank (MCB). This can be an extremely challenging and time consuming step, but is highly important because it can impact yields and sequence integrity. Furthermore, pDNA manufacturing relies on bacterial fermentation, which often raises safety concerns in AAV manufacturing because of the presence of a bacterial backbone. This can lead to unwanted packaging of exogenous sequences and influence the efficiency of the final AAV vector.

The process of large-scale plasmid production is time-consuming and can lead to inconsistencies in yield and purity. As gene therapy developers transition to large scale AAV manufacturing, issues may arise around the quality and concentration needed to progress. Usually, three different plasmids are required for transfection, meaning the amount of pDNA required for AAV production is substantial, which creates further hurdles. These limitations not only slow down manufacturing but also pose potential safety and regulatory concerns for clinical applications.

Introducing hpDNA: Ideal construct for AAV Manufacturing

With various challenges associated with pDNA manufacturing, there's a growing need for reliable alternatives. 4basebio's synthetic DNA is manufactured using a fully cell-free process, which means that the resulting DNA is free of bacterial sequences. 4basebio's synthetic DNA platform produces application-specific DNA constructs to suit a number of therapeutic applications. hpDNA is ideally suited for viral vector manufacturing, as it is a double-stranded, linear construct, which is covalently closed with single strand hairpins at the 5' and 3' ends.

Why Synthetic DNA is a Game-Changer for AAV Manufacturing

One of the most significant advantages of using synthetic DNA for AAV manufacturing is the drastic reduction in lead times. Traditional plasmid-based approaches require time-consuming processes, which can extend production timelines. Synthetic DNA, on the other hand, is produced enzymatically, which eliminates the need for bacterial fermentation processes. This accelerates the production process, allowing for faster turnaround times in gene therapy development and clinical applications.

Regulatory requirements for gene therapy products continue to evolve, with increasing emphasis on the purity and safety of AAV vectors. Synthetic DNA minimizes the risk of contamination from bacterial endotoxins and antibiotic resistance genes due to the lack of the bacterial backbone. This also eliminates the risk of reverse packaging, where undesired elements are mistakenly incorporated into the AAV capsid.

Maintaining high and consistent viral titers is essential for the efficacy and scalability of gene therapies. AAV vectors produced using synthetic DNA achieve comparable titers to those produced via plasmid-based methods. There are significant cost reductions because less DNA is required to achieve comparable titers, due to the linear construct lacking a bacterial backbone.

The integrity of inverted terminal repeats (ITRs) is crucial for maintaining AAV vector stability and function. Plasmid-based methods are prone to recombination events during bacterial fermentation that can lead to deletions or mutations within the ITRs, negatively impacting vector efficacy. Synthetic DNA offers greater sequence stability and precision, eliminating the risk of recombination and ensuring a higher-quality AAV product.

Learn more about hpDNA for viral vector manufacturing and how 4basebio can support your needs.

Learn more

Fear Replaced by Understanding, Optimism, and Miracles: Part I

Cell and gene therapies have come a long way since the 1970s. Technology, combined with knowledge, will take them even further.

By Daniel Eisenman, Executive Director of Biosafety Services at Advarra

For decades, cell and gene therapies (CGT) seemed elusive, relegated to the world of science fiction. In the 1970s, in fact, TIME magazine featured a cover story titled, "The DNA Furor: Tinkering With Life," which heightened public fears over the nascent field of genetic engineering, human gene transfer, and the creation of virulent microorganisms.

In 1975, these concerns culminated in the Asilomar Conference on Recombinant DNA, discussing the potential biohazards and regulation of biotechnology. The first-of-its-kind conference marked the beginning of an extraordinary era for science and for public discussion of science policy. It's also where researchers proposed an oversight framework that later became NIH Guidelines for oversight of research involving genetic engineering, gene therapy, and gene editing.

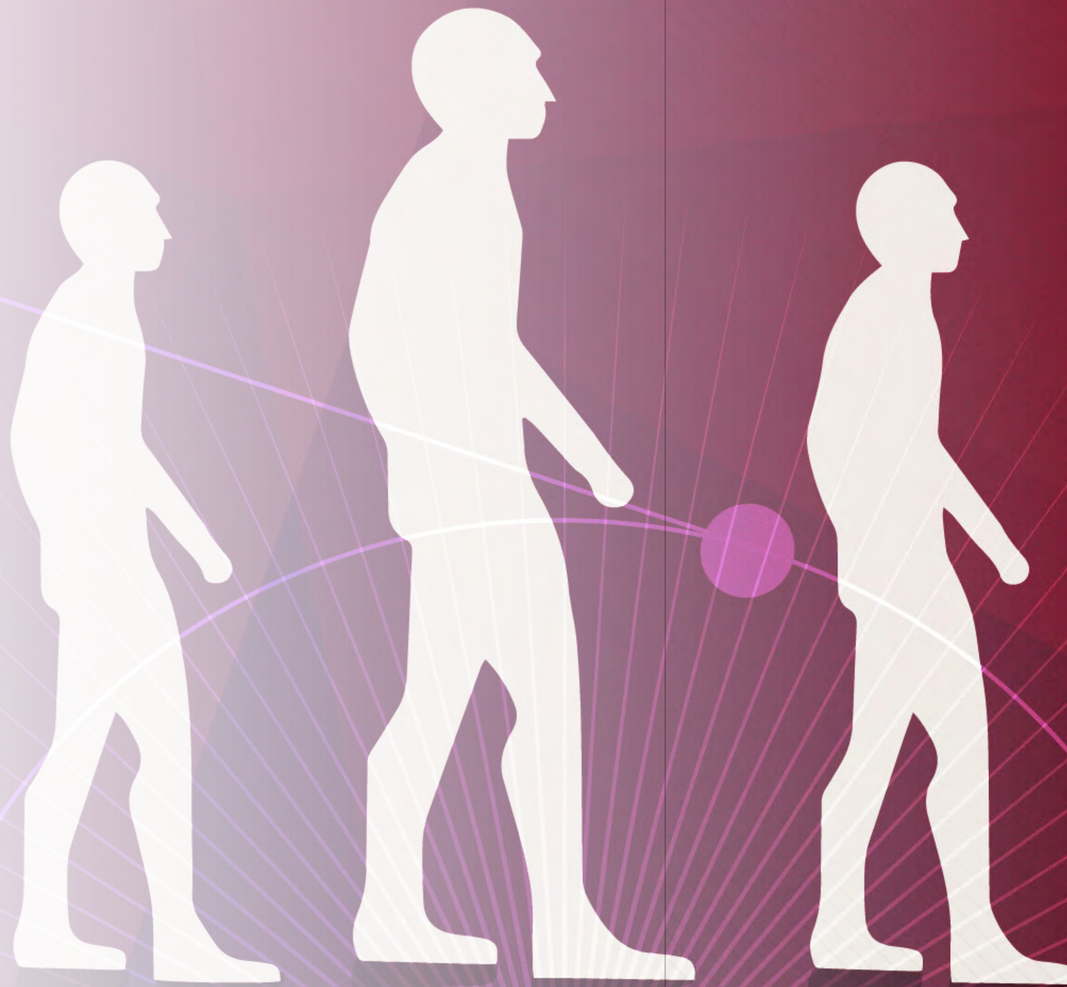
With new regulatory foundations, CGT work persisted, but not without some highly publicized setbacks in the late 1990s and early 2000s, including the French SCID trial where pediatric subjects developed leukemia, and the death of Jesse Gelsinger. Since the turn of the century, however, much progress has been made in developing safety features for gene transfer technology. The FDA, for instance, has established guidance documents for CGT research. Advancements in biotechnology, an emphasis on translational medicine, and increased investment have also helped lay the groundwork for a CGT clinical trials boom.

In March 2023, the Journal of Gene Medicine had entries for 3,900 CGT clinical trials in 46 countries. Most trials focused on cancer (68.3 percent) or inherited monogenic diseases (13.1 percent), with the US leading the world in the most trials undertaken: 2,054 (52.7 percent). As of September 2024, the FDA has approved 38 cell and gene therapies versus seven in 2023. But it's not nearly enough, given the life-changing potential in these curative therapies for the 7,000 rare diseases without treatment.

"It would be a shame if all we manage to do is approve another two or three gene therapies a year – that's a failure," said Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER) in a 2023 Biospace interview. "Success would be that we start to watch what should be, if not exponential, at least some logarithmic progression toward more and more gene therapies being approved."

Great promise, greater hope

In 2015, Investigational New Drug (IND) applications for gene therapies sharply increased with the first FDA approval for a



"With new regulatory foundations, CGT work persisted, but not without some highly publicized setbacks in the late 1990s and early 2000s."

gene therapy, a genetically engineered herpesvirus intended to treat melanoma. In 2017, came the first two approvals for chimeric antigen receptor (CAR) T cells, a type of gene-modified cellular therapy. CAR-T cells start as white blood cells typically obtained from the patient and genetically reprogrammed to target and kill the patient's cancer. This approach has been successful in B cell leukemias and lymphomas where previously refractory or resistant cases are now seeing overall response rates as high as 90-pus percent.

Researchers pushed this approach forward to B cell-mediated autoimmunity to treat conditions such as lupus, where the aim is to suppress the abnormal immune activity causing disease symptoms. Researchers at UC Davis Health were able to eliminate or reduce lupus symptoms with a single infusion of CAR-T cells with no relapses among the study's patients after two years of monitoring.

"CAR-T cell therapy paved the way for success in oncology, and now technologies like gene replacement therapy, gene editing, and RNA editing hold tremendous promise as a treatment or cure in many rare diseases where there is significant unmet need," said Meagan Vaughn, associate clinical director at Krystal Biotech.

Krystal is a gene therapy biotechnology company focused on developing and delivering medicines to patients with genetic life-threatening or rare diseases. The company's Vyjuvek is the first and only re-doseable gene therapy for the treatment of dystrophic epidermolysis bullosa.

"Right now, our focus is on re-doseable gene therapy using a viral vector to deliver the therapeutic gene. We are working towards this as a treatment for Cystic Fibrosis, for patients who do not have any other treatment options," added Vaughn. Gene therapies typically involve a viral vector, a genetically engineered virus used as a delivery vehicle for a potentially therapeutic gene.

When it comes to rare diseases, CGT offers hope to those who feel the most hopeless, such as the family of Evelyn Villarreal. She was born with spinal muscular atrophy (SMA) – a recessive disease that gradually paralyzes and kills children by the time they are about two years old. Tragically, the Villarreals already had one daughter die of the same disease at 15 months. So, the parents quickly enrolled Evelyn in a clinical trial for an investigational, one-time gene therapy when she was just eight weeks old.

Not long after, doctors saw progress. Evelyn was the first baby in the clinical trial who was able to roll over – a big breakthrough. "Our neurologist just cried," recalled Evelyn's mother, Elena, whilst speaking with the CDC. "As Evelyn progressed, she was the first one to walk. It brought so much hope." Now, Evelyn goes to school, enjoys science and art, writes stories, swims, and flies kites. Miraculously, Evelyn has beaten the odds and grown into a flourishing ten-year-old – a marvel never before possible in SMA1 patients – as documented in Science.

Overall, the disease areas seeing the greatest success and FDA approvals from novel CGT science are oncology (10 approvals), infectious disease vaccines (8 approvals), and rare diseases (11 approvals). As science evolves, the life sciences industry will likely start to categorize cell and gene therapies not according to disease area but, rather, according to technology. Recharacterizing CGT based on its science can open doors to eventually treating a wider range of diseases.

Read part II here, where Daniel Eisenmann delves into the clinical trial initiation process and how modern technologies, such as decentralized approaches and AI, can help accelerate research in cell and gene therapies.

6 Common types of CGT approaches:

- Gene-modified cellular therapy
- Genetic vaccines
- Gene transfer
- Oncolytics: reprograming viruses to kill cancer
- Gene editing
- Gene-modified bacteria or phages

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more from Daniel Eisenman

Getting Cell Lysis Right in Gene Therapy Manufacturing

As viral vector production scales, cell lysis becomes a balancing act – efficient enough to release vectors, but gentle enough to preserve them

Cell lysis is often seen as just another step in the upstream workflow for gene therapy production, but it's anything but routine. This moment of breaking open cells determines not only how much vector is released, but how pure and consistent the final product will be. As gene therapy manufacturing processes scale to meet broader clinical demand, many teams discover too late that their lysis method doesn't scale or comply.

Here, Avantor's Beth Kroeger-Fahnestock explores the technical and operational challenges of cell lysis, from reagent selection to large-scale implementation, as well as optimizing the cell lysis step and key considerations for selecting the best reagent to ensure scalability and meet environmental and regulatory standards. As well as working within industry, Kroeger-Fahnestock has served on the ISPE task force responsible for writing the ISPE Guidance: Cleaning Validation Lifecycle – Applications, Methods, and Controls Good Practice Guide, published in 2020 and was an Adjunct Lecturer, Temple University, School of Pharmacy, RA/QA Graduate Program for several years.

Give us an introduction to the cell lysis step in gene therapy manufacture…

Cell lysis is a critical step in upstream gene therapy manufacturing, particularly for viral vectors such as AAV, where viral particles remain intracellular post-production. To release viral vectors from the producer cells during upstream processing, a lysis step is needed to rupture and break down the cell membrane, leading to the release of intracellular content. An often-underappreciated component within the upstream workflow, cell lysis may, in fact, constitute its greatest vulnerability, potentially compromising the integrity and reliability of the entire process. The primary objective of the lysis step in the viral vector workflow is to efficiently release high yields of intact viral vectors while minimizing vector damage and impurity load, which directly affects downstream processing and overall product quality.

If the lysis step is inefficient, a significant portion of the viral vector may remain within the producer cells, reducing recovery. A poorly optimized lysis process can shear viral particles under uncontrolled chemical or mechanical stress, or release an excessive amount of host cell impurities (e.g., host cell DNA, proteins, lipids), increasing the complexity and cost of downstream clarification and chromatography, and potentially compromising product quality.

The approach to cell lysis must be tailored to the vector system. For example, AAV and adenovirus require active lysis. Detergent-based chemical lysis of the cells producing AAV vectors is common and typically followed by enzymatic digestion with an endonuclease to degrade host cell and plasmid DNA. In contrast, lentiviral vectors are released into the culture medium, so the harvest typically involves clarification without the need for cell lysis.

The gene therapy field continues to grow, addressing a broader

"The primary objective of the lysis step in the viral vector workflow is to efficiently release high yields of intact viral vectors while minimizing vector damage and impurity load."

range of indications for larger patient populations. With this growth, the need to scale processes and deliver greater consistency and efficiency is essential. This imperative includes the cell lysis step; having a solution that offers effective lysis and one that ensures complete cell disruption, vector integrity, and easy removal during purification, all while meeting environmental and regulatory standards.

What makes cell lysis particularly challenging at large scale, and what are some of the most common failure points?
At large bioreactor volumes, it is essential to ensure consistent and complete lysis. Factors such as mixing efficiency, reagent distribution, and contact time are difficult to control at larger scales, potentially leading to uneven lysis, reduced vector recovery, or increased product variability. Another concern is the shear sensitivity of vectors. The lysis method must be aggressive enough to release intracellular vectors but gentle enough to preserve their structural integrity. This balance is more difficult to maintain in large-scale systems, where mechanical stress and process parameters, including temperature or pH, can fluctuate more widely.

Impurity management also becomes more critical at scale. Larger batch sizes mean greater quantities of host cell proteins. DNA and lipids are released during lysis, placing a heavier burden on downstream purification steps. Excessive impurities can foul filters, reduce chromatography efficiency, and lead to lower overall yields if not adequately controlled.

Additionally, lysis reagents used at large scale must be highly consistent, scalable, and compatible with regulatory expectations, including requirements for low endotoxin levels, animal-origin-free materials, and validated removal in the final product. Operationally, the lysis process must be easy to integrate into automated, closed systems to support aseptic manufacturing and reduce contamination risk.

Ultimately, effective large-scale lysis depends on selecting reagents and protocols that are robust, reproducible, and optimized not only for vector release, but for downstream compatibility and regulatory compliance.

Are there "rules of thumb" or design considerations you recommend for optimizing lysis without damaging viral particles?
Once the viral particles are released from the cell during the lysis process, the detergent lysis step must not have any effect on the integrity, infectivity, or yield of the released viral particles -- particularly from shear stress due to agitation. The viral vector may denature and unfold as a result of shear stress and adsorption to surfaces during the downstream process. This shear stress and resulting viral particle damage can lead to a decrease in downstream yield, and low yields can create a dosing problem. If the vector concentration in a gene therapy batch is too low, developers would have to increase the dose volume to an unreasonable level.

To avoid this, mixing speeds, temperature, and incubation time during the lysis step must be carefully controlled. Gentle agitation, combined with a well-optimized lysis solution concentration, can promote efficient lysis while minimizing physical stress on the viral particles. In addition, choosing a lysis solution that preserves capsid integrity and can be effectively removed in downstream purification is essential for both product quality and regulatory compliance. Ultimately, process development teams should balance lysis efficiency with product protection, using small-scale models to test and tune conditions before scaling up.

Read the full article online.

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From R&D to GMP Manufacturing: Accelerating Cell Therapy Development with Evotec

Cell and gene therapies (CGTs) are transforming the therapeutic landscape, offering new hope for patients with previously untreatable conditions. Yet, the journey from discovery to clinical application is complex, requiring a coordinated approach across scientific, technical, and regulatory domains. Success depends not only on innovation, but on integration – bringing together the right expertise, infrastructure, and strategy from the earliest stages of development.

Building strong foundations with PD/AD

A robust CGT program begins with early integration of process and analytical development (PD/AD). Guided by Quality by Design (QbD) principles, this approach helps define the building blocks of a scalable and compliant manufacturing process. Early process design, coupled with fit-for-purpose analytical methods, enables developers to embed quality from the start – identifying and controlling key product and process attributes. This foundation is essential for overcoming common manufacturing challenges such as variability, raw material quality, and scalability.

Implementing a PD/AD feedback loop allows for continuous optimization of quality, safety, and scalability throughout the product lifecycle. When cross-functional teams are aligned from the outset, development accelerates, and regulatory risks are reduced. This proactive strategy ensures that therapies are not only scientifically sound but also technically and operationally ready for clinical advancement.

Ensuring continuity through technology transfer

Technology transfer is the critical bridge between product development and GMP manufacturing. Success depends on thorough preparation: Clear documentation and close alignment between sending and receiving units to ensure the process and associated analytics meet product specifications under GMP requirements.

Flexibility is essential. Teams must anticipate and adapt to the unique challenges of transferring cell-based manufacturing processes into a GMP environment. These challenges may include qualifying research-grade raw materials, managing equipment differences between facilities, and translating manual laboratory procedures into workflows compatible with cleanroom operations.

Navigating a complex regulatory landscape

Equally vital is regulatory strategy. Developers must navigate a diverse global regulatory landscape, where frameworks differ significantly across regions. Understanding how these differences shape development and approval pathways is essential. For example, while both the EMA and FDA provide guidance for advanced therapy medicinal products (ATMPs), their expectations and review processes can vary in meaningful ways.

Proactive regulatory engagement, starting early in development, can streamline progress and prevent costly delays. Strategic planning, clear documentation practices, and alignment with evolving regulatory expectations are key to preparing robust IND submissions. Actionable steps taken early on not only support regulatory readiness but also position therapies for long-term clinical and commercial success.

The power of integration

What distinguishes high-performing CGT programs is the ability to integrate these elements into a cohesive development pathway. Rather than relying on fragmented, multi-vendor approaches, a unified strategy enables faster decision-making, reduced risk, and greater operational efficiency.

Ultimately, accelerating CGT innovation requires more than cutting-edge science – it demands a development model that is agile, scalable, and regulatory-ready. By aligning process development, technology transfer, and regulatory strategy from the outset, developers can move confidently toward IND submission and clinical success. Altogether, integration enables a reduction in investments and fixed costs, lowering the high entry barriers that are currently limiting innovation to take off – especially for the small biotech and academic spin-offs.

To further understand how integration overcomes key challenges in cell therapy development and accelerates innovation, **read our whitepaper series.**

Learn more

Complex DNA; No Compromises

How can you ensure your gene therapy research won't be slowed down by synthesis problems?

By Daniel Lin-Arlow, Co-founder and CSO of Ansa Biotechnologies

Gene synthesis, the construction of DNA molecules longer than a few hundred base pairs, is essential for the discovery, development, and manufacture of cell and gene therapies, as well as for assay development, target validation, and model organism development. For gene therapies, researchers rely on gene synthesis for constructing transgene payloads, modulating their expression in cells, and engineering viral vector delivery systems. For cell therapies, synthetic genes are also used to build transgene expression constructs and more complex genetic circuits that can sense and process multiple signals to trigger a context-sensitive therapeutic response within the patient.

Designing these sequences on a computer is often considerably more straightforward than actually obtaining the needed DNA constructs. However, once you input your designed sequences into the order form of traditional gene synthesis vendors, you'll often immediately encounter limitations around guanine-cytosine (GC) content, homopolymers, repeats, and many other elements that fall under the broad category of "complex DNA." Across the board, synthesis vendors seem to have convinced scientists that they have no choice but to accept suboptimal practices such as redesigning sequences to meet manufacturing constraints, abandoning desirable sequences for being too complex, or resorting to tedious, labor-intensive, and failure-prone workarounds to build the constructs in house from small pieces.

This should never have become acceptable. When it comes to the development of critically needed cell and gene therapies, nobody should have to compromise their science just because synthesis vendors aren't up to the challenge. From rejected or failed orders to long turnaround times and delays, researchers should expect more from vendors who play such a pivotal role in the process of therapy discovery and development. After all, we cannot realize the full potential of cell and gene therapies without being able to explore a broader design space – and reliably get the actual DNA we want to test all of those interesting ideas.

I am a former synthetic biologist who grew frustrated by being unable to access the DNA I needed to conduct experiments, which is why I set up my company. Based on my experience, below are the important considerations when evaluating a gene synthesis vendor.

Complexity

As the most common reason sequences are rejected or eventually failed by legacy vendors, the ability to build complex DNA

"When it comes to the development of critically needed cell and gene therapies, nobody should have to compromise their science just because synthesis vendors aren't up to the challenge."

sequences is probably the most important factor to consider. Most gene synthesis vendors build DNA constructs by stitching together dozens of chemically synthesized oligos that are roughly 80-150 bases long, but the assembly process struggles with complex sequences. By contrast, enzymatically synthesized oligos can be much longer – 600 bases or more – enabling vendors who use them to produce a much broader range of sequences than can be reliably manufactured starting from short, chemically synthesized oligos. If exploring a larger design space would be helpful for your cell and gene therapy work, look for a synthesis vendor that not only claims to build complex DNA, but also backs it up with specific parameters for how they define (and consistently deliver on) complexity.

Quality control

Synthesizing complex DNA isn't the only tough task for vendors – sequencing the resulting DNA can be challenging too. Short-read sequencers can be stymied by extreme GC content, repetitive DNA, and other hallmarks of complex sequences. Sanger sequencing and other conventional tools, such as gel electrophoresis, often aren't precise enough for high-confidence quality control. If your order involves complex DNA sequences, make sure the vendor has a robust workflow to validate the purity of the products, ideally with long-read sequencing that can get through difficult DNA elements. Even for clonal DNA, this is the only way to know for sure that your synthetic DNA is homogeneous and matches the sequence you ordered.

Turnaround time

Faster is almost always better when you're trying to get a new therapy into the clinic. Consider the financial impact of a delayed program because the DNA constructs you need take weeks or months longer than expected to arrive. Were your cells or animals ready to receive a product by a certain date, but then your DNA got delayed? You could find yourself in a situation that feels like missing a connecting flight and ruining your vacation.

With most existing gene synthesis vendors, the chance of delays and failures increases with the length and the complexity of the sequences requested. This again can be traced back to the limitations of chemical DNA synthesis; in building DNA from short oligos, one low-quality oligo could sink the build of the full-length sequence.

Some new gene synthesis approaches that rely on longer oligos can help reduce turnaround times, especially for long and complex DNA, but make sure you're looking at the time to receive some constructs, as well as the time it takes to receive your complete set. It's often not worth beginning an experiment until you have all the constructs, so getting half your order in the promised amount of time, and half your order a month later, can still be a costly issue. Check with vendors about their success metrics for the percentage of orders shipped complete within the committed delivery window.

In conclusion, cell and gene therapies represent a burgeoning field with incredible opportunity to address or even cure diseases and conditions that have never been targetable with traditional drug classes. For the best chance at success, however, the scientists creating them shouldn't be limited by arbitrary technical constraints in the DNA synthesis process. New types of synthesis are entering the market, ready to fill these gaps. It's time for scientists to have the freedom to focus on their research without being limited by their DNA synthesis vendor.

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Making Solid Progress: Sitting Down With 2025 Power Lister John Maher

We discuss the journey of John Maher, co-founder and CSO, Leucid Bio, from Michel Sadelain's New York lab to King's College London.

What drives your passion for developing therapies for hard-to-treat cancers?

It's the unmet clinical need. Back when I was training in oncology, I saw firsthand how tough things were for patients. That stayed with me. Cancer is poised to become the world's leading cause of death – it affects people of all ages and walks of life. The scale of the problem is what motivates me.

What inspired you to focus your research on CAR-T cell therapy, especially targeting solid tumors?

Originally, I thought I might pursue a career in medical oncology, but back when I started out, treatment largely revolved around high-dose chemotherapy, which was incredibly toxic. This really put me off, so I switched to immunology as a clinical specialty but remained passionate about cancer and the potential for the immune system to play a role in therapy.

In those days, immunotherapy wasn't really a thing. It just didn't work! But I was fascinated by the potential of T cells, which

naturally recognize virus-infected cells. The idea of retraining them to identify and destroy cancer cells was compelling. This led me to CAR-T.

How did your experience at King's College London influence the formation and direction of Leucid Bio?

A UK fellowship gave me the opportunity to join a lab in New York, led by Michel Sadelain, who was pioneering CAR-T development at the time. The 18 months I spent in Michel's lab convinced me this was the direction I wanted to take my career.

After returning from New York, I established a CAR-T lab at Guy's Hospital with a focus on treating solid tumors. As time passed, we started to see exciting clinical data showing how effective CAR-T could be in certain blood cancers. That momentum gave me the confidence to spin out a company from King's – what is now Leucid Bio – with a focus on adapting CAR-T technology to treat solid tumors.

I had great support early on – particularly from Mike Garrison, who was then heading up the King's Commercialization Institute, and Anthony Walker, who went on to become Leucid's first CEO. Both were instrumental in helping me make the leap into biotech, a world I was completely unfamiliar with.

What are the main obstacles currently limiting the broader application of CAR-T therapies for solid tumors?

The challenges are numerous. First, there's the issue of target selection. With blood cancers, we can target molecules unique to a specific cell type. Even if we kill both malignant and healthy cells – like healthy B cells when treating B cell cancers – we can manage the side effects with, for instance, antibody replacement therapy. However, we can't play those kinds of tricks with solid tumors.

Second, it's a delivery problem. CAR-T cells can access blood cancers directly via the bloodstream, but to reach a solid tumor, they have to exit the bloodstream, penetrate organs, and identify tumor sites – an extremely difficult journey.

Third, and perhaps most intractable, is the tumor microenvironment. It is incredibly hostile. Anthony Walker once joked that solid tumors build a "Donald Trump-style wall" to keep the immune system out – and honestly, it's a great analogy. Tumors recruit healthy cells, like fibroblasts and white blood cells, to build a protective barrier of cells and collagen that shields them from attack. Overcoming that is essential.

How important are partnerships and collaborations in advancing research and clinical trials?

They're absolutely critical, especially in translational research. I've benefited from many productive collaborations over the years. You can exchange ideas, share technologies – it accelerates progress for everyone involved.

There's a saying: "If you want to go fast, go alone. If you want to go far, go together." That's the spirit of collaboration in this field.

How do you see CAR-T therapies being integrated into standard cancer treatment protocols?

We are already seeing this happen with blood cancers. Initially, CAR-T was used only in terminally ill patients as a last resort. But as the efficacy became clear, trials began exploring its use earlier in treatment. Now, CAR-T is being used earlier and earlier in the patient journey.

I believe we'll see the same trajectory with solid tumors once we develop effective CAR-T therapies.

What advice would you give to young scientists looking to translate their research into clinical or commercial success?

I've made plenty of mistakes myself. One key piece of advice: be commercially aware from the start. Much of my early work wasn't properly protected with patents. At the time, CAR-T wasn't seen as commercially viable, and universities didn't want to fund patent applications.

But if you believe in your technology, protecting it through patents is essential. Investors and pharma companies want exclusivity. So, be more commercially savvy than I was!

Reflecting on your career, which achievement are you most proud of?

I'd say it goes back to my time in Michel Sadelain's lab. Before I joined, I read a paper by Helene Finney, who described what we now call a second-generation CAR – an artificial receptor built from different protein components. She showed it worked in a model cell line but didn't have the tools to test it in real T cells.

Michel did have those tools. Using them, I recreated Helene's receptor in human T cells and showed it worked just as well. That architecture – the second-generation CAR – is now used in all seven FDA-approved CAR-T therapies.

So we can count Helene and Michel among your biggest influences. Anyone else?

Funnily enough, I've never actually met Helene. I just know her work! But Michel was definitely a key mentor. And I must mention Farzin Farzaneh at King's College London. He's been a tremendous supporter of my work in CAR-T.

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