CELL AND GENE

From The Medicine Maker

Presenting our special supplement to celebrate the fast-growing field of cell and gene therapies

Time Machine

Freezing time in cell and gene using cryopreservation

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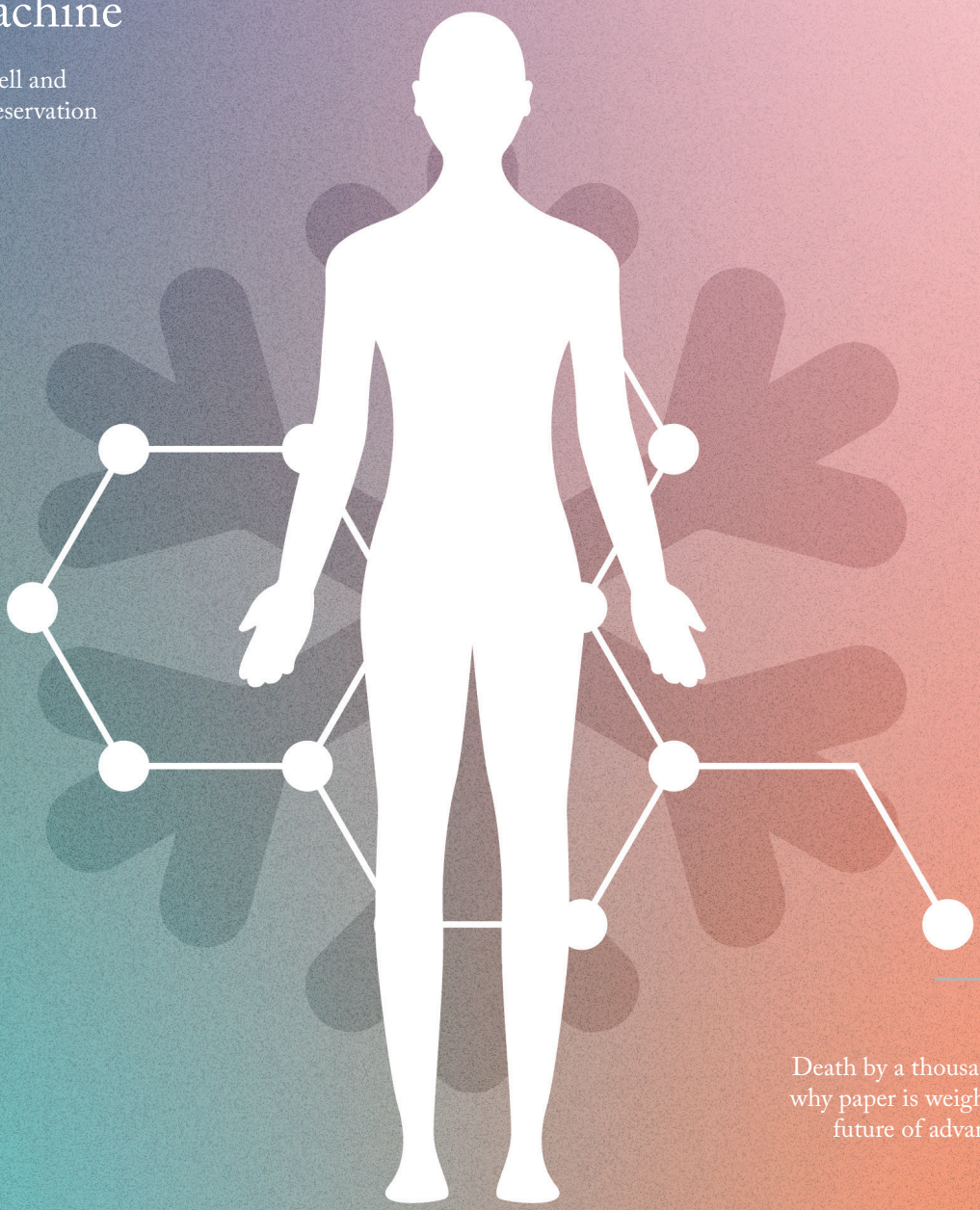

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CGT: A True 21st Century Industry

The digital age arrives in cell and gene manufacturing

Cell and gene therapy manufacturing continues to mature and transform. Scalability, accessibility, cost reductions, and increased safety have all been key priorities. To this end, many manufacturers are embracing automation, digitalization, and AI.

AI is creeping into every industry; in some cases causing great controversy (particularly in creative sectors). However, the use of AI in drug development is something that everyone can get behind. Automation and robotics are not only reducing the manual labor required for processes like cell expansion and final product formulation, they're also ensuring greater consistency and precision. AI-powered predictive analytics are being deployed to optimize supply chains, providing manufacturers with insights to predict and address potential bottlenecks before they occur, ensuring smoother production workflows.

Furthermore, advanced AI applications such as digital twins are transforming process development and quality control with virtual replicas of manufacturing systems. These digital replicas allow manufacturers to simulate, test, and refine processes without halting production, thereby reducing risks and saving time. AI-driven data analytics further enhance process monitoring by identifying subtle patterns that may indicate inefficiencies or quality issues, enabling proactive intervention.

It has often been said that the pharma and biopharma industries are slow to embrace new technologies and processes, but in cell and gene therapies, there is little room for error – and nextgen approaches can make a big difference. As uptake of AI and automation continues, cell and gene therapy manufacturing is becoming a true product of the 21st century. Let's hope that the industry and its regulators continue to adapt with the changing times.

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Advanced Therapies, Archaic Hardware: the Perils of Paper

Here's how paper is weighing down the future of advanced therapies

By Matt Todd, Head of Digital and Data, Ori Biotech

The phrase "death by a thousand paper cuts" can be aptly applied to advanced therapeutics manufacturing.

Makers of the first wave of cell therapies leveraged existing processes to reach patients as quickly as possible. This meant following a path based on manufacturing approaches that are efficient for scaling up large batches of small molecules or monoclonal antibodies, rather than applying bespoke processes to individual patient-derived cells for each therapeutic dose.

Multiple autologous cell therapies are now on the market, but there remain many opportunities in other therapeutic areas. However, there are obstacles to reaching patients in need; namely, the high costs, long timelines, and large manufacturing facilities needed to make cell therapies.

One lesser discussed limitation is the use of paper-based records. A 1,000-page batch record isn't so daunting when it represents millions of therapeutic mAb doses, but it's a different story when the same type of paper record is required for each dose of an autologous cell-based therapy. After completing a commercial clinical dose, the batch record must be stored in a secure, fireproof cabinet until a document management company collects and stores it for years.

Paper batch records present significant obstacles to obtaining critical data insights, which are essential for accelerating process development and enhancing quality assurance in manufacturing. The inherent

inefficiencies and lack of real-time data access delay decision-making and hinder the ability to quickly identify and rectify process deviations. Moreover, the manual nature of paper records increases the risk of errors and complicates the task of ensuring compliance and traceability across multiple production cycles and facilities.

A combination of digitization and integrated hardware is key to cutting the paper out of cell therapy manufacturing. Digitized data can easily be aggregated and used to refine processes. It can be integrated across different steps of the process, accessed across geographically disparate sites, and – crucially – shared with partners. Collaboration remains a critical part of cell therapy development, particularly for reducing the time it takes to make a dose and get it back to patients. Cloud-based research and development platforms will play a critical role in industrializing advanced therapy manufacturing.

During the early stages of development, drugmakers often don't recognize the scope of challenges that paper represents for scale-up. What may work for tens of patients in an early-stage clinical trial is an untenable obstacle for a field aiming to treat tens of thousands of patients per year in the near term. It is common to hear early-stage developers say they plan to transfer processes to digital in time, but most realize – too late – that this change is not a minor consideration. It is a process transformation – and most of the challenges are difficult to predict.

Attempting to squeeze digitization into more mature workflows tends to add rather than remove complexity; building it in from the beginning is crucial to ensuring a smooth, sustainable scalability. Moving away from paper also means automating and integrating connectivity into manufacturing technologies. In many fields, the Industry 4.0 trend of smarter machines improves efficiency and productivity in several ways; for example, making it clear when preventative maintenance is required. When a batch takes weeks to produce and where a single failure can mean life or death for the patient, equipment uptime is critical.

Especially for autologous cell therapies, complex supply chains are required to ship patient biological material from hospitals to manufacturing sites and back. In a paper-based system, manufacturing can be a black box, meaning doctors do not have the necessary information to make key decisions on patient care in the moment. Given that clinicians are managing patients in critical care, having access to data on the product and its estimated time of arrival, quality, and release time during the end-to-end manufacturing process can be invaluable. Hardware integration will be even more important as more patients need to be served at more distributed sites.

Smart manufacturing requires early investment in a different set of priorities and capabilities than today's common approaches. For example, new closed and automated platforms need fewer human operators and less cleanroom floorspace, meaning drugmakers might not need large manufacturing facilities. On the other hand, robust internet connectivity becomes a much higher priority for maintaining and monitoring the Internet of Things-enabled device fleet.

Though many drugmakers wait to think about automation and smart manufacturing, those that adopt and initiate them early will see more significant impact. Early adoption lays the groundwork for resilient manufacturing and logistics models, robust and streamlined scale-up, and the flexibility to constantly learn and improve.

The Elite Athlete Concept for Cell Therapy

How metabolic conditioning could improve cell therapy potency and persistence

By Yelena Bronevetsky, Director of Product Management at Xcell Biosciences and James Lim Chief Scientific Officer at Xcell Biosciences

Efforts to improve the performance of cell therapies inevitably focus on boosting potency through genetic engineering. The rationale is obvious; if we could just design tumor-targeting constructs and perturb exhaustion signaling pathways, surely, the resulting therapies would have the desired effect. In our view, however, there's a more reliable and straightforward approach. Scientific evidence supports the idea that incorporating metabolic conditioning, whereby cells are exposed to oxygen and pressure levels found in tumor microenvironments, during the development and production of cell therapies will give patients the best chance at healthy outcomes.

Let's take a step back to consider the specific improvements needed in the cell therapy space. First, existing therapies targeting cancer tend to work well in just a small fraction of patients and we need this success rate to be higher (1); lack of response to a cell therapy should be a rare event. Second, current therapies have been predominantly approved for treatment against blood cancer, but with liquid malignancies representing just 10 percent of cancers, there is a pressing need to expand the utility of cell therapies to solid tumors.

To address both of these challenges (improving efficacy rates and addressing a broader range of cancers), we should develop cell therapies with greater potency and persistence. Reaching solid tumors, for example, has proven difficult because cell therapies have to travel long distances to get from the bloodstream to the tumor site – and often arrive depleted. Any cancer-killing function that remains cannot be put to work until the cells overcome suppressive forces, such as low oxygen, high pressure, and the presence of cell populations designed to block T cell function.

Though conventional wisdom says the answer is to genetically engineer cell therapies to withstand these forces, plenty of existing data indicates that something as simple as fine-tuning cell culturing conditions may offer the solution we need. Here's the theory; cells facing a hostile environment will function best if they've been trained to survive in that environment already. We like to think of this as the "elite athlete" concept; elite athletes train for the conditions they know they'll face, whether that's training at high altitudes for elite cyclists or running steep hills for marathoners preparing to race in San Francisco.

For cell therapies, that training occurs in culture as the cell population expands. Though culturing is typically performed under conditions designed to keep cells happy and dividing as quickly as possible, scientists have run a number of studies showing that harsher conditions may lead to better outcomes in vivo. Restricting the availability of glucose in culture, for instance, leads to cells with enhanced antitumor function (2). Growing cells under hypoxic conditions during the T cell activation period results in stronger cytotoxic function in vivo (3). Other changes to metabolic conditioning regimens have shown promise in boosting cell therapy efficacy – even for solid tumors (4, 5). The cytokine composition of cell culture media also has an important role to play. Though the standard IL-2 regimen leads to better growth in culture, shifting to other cytokines, such as IL-7, IL-15, and IL-21, reduces in vitro expansion but leads to increased potency and persistence once infused.

Taken together, the evidence suggests that the efficacy challenge with cell therapies may not be a genetic engineering weakness, but a conditioning one. The focus on giving cells culturing conditions that solely prioritize rapid expansion leads to cells that thrive only in perfect conditions, but become depleted and ineffective in the harsh reality of a tumor microenvironment. Growing cells instead under the kind of low-oxygen, high-pressure conditions they will experience at the tumor site may not produce ideal results in vitro – cells can divide far more slowly – but once in the body, they are more likely to exhibit potent anti-tumor activity. Toughening up cells in culture provides the training they need to excel in harsh solid tumor microenvironments.

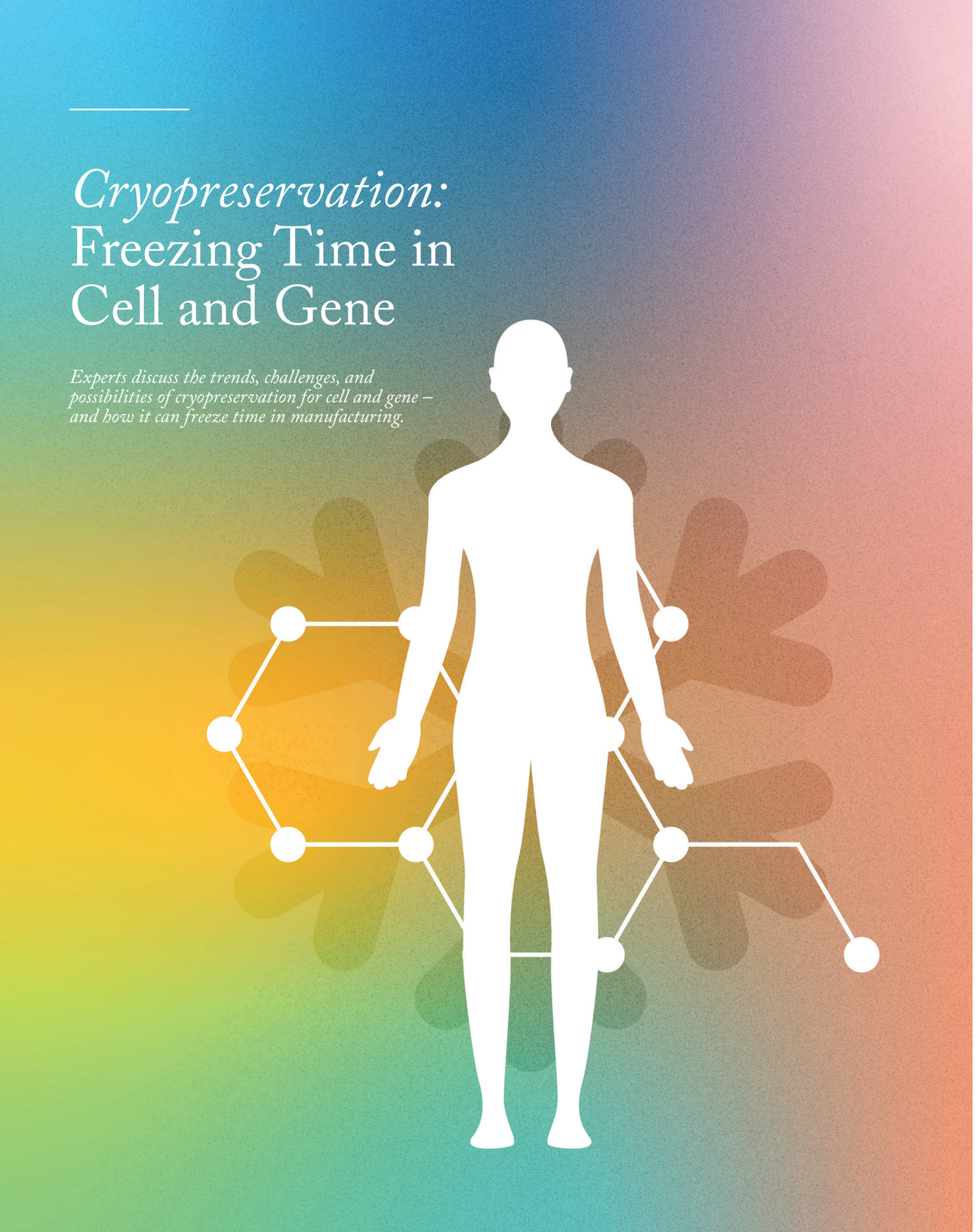
This idea, too, has been supported by research studies. Scientists have demonstrated that CAR T cells targeting the ROR1 protein appear to have excellent tumor-killing potential based on in vitro assay performance conducted under ambient oxygen conditions (6). But when introduced in humans, this function is significantly reduced. Animal studies demonstrated the ability of ROR1 CAR T cells to traffic to the tumor site, but also found they exhibited poor anti-tumor activity and persistence leading to disease progression. Had those cells been cultured under conditions more like the tumor microenvironment, they may have exhibited improved potency and persistence, leading to better patient outcomes.

Incorporating more biologically relevant conditions during cell culture is clearly an important avenue to pursue, but it should not be left to the final stages of cell therapy manufacturing. We believe that an early and lasting focus on cell conditioning could greatly enhance the performance of cell therapies. From preclinical to process development to manufacturing, a focus on conditioning cells to the tumor-specific environment – rather than on the absolute number of cells grown – may provide the best chance to improve potency and persistence. Ultimately, this alternative approach could help us address some of the biggest challenges in the cell therapy field today.

References available online at: tmm.txp.to/elite-athlete-concept

Cryopreservation: Freezing Time in Cell and Gene

Experts discuss the trends, challenges, and possibilities of cryopreservation for cell and gene – and how it can freeze time in manufacturing.



From advanced supply chains and personalized medicines, to interplanetary exploration, cryopreservation could have a profound impact on the future of healthcare and therapeutics.

Advanced therapy developers and researchers are doing their utmost to improve and accelerate the journey of their products from the bench to the bedside. The supporting transport, logistics, and storage specialists tasked with the preservation and delivery of those products are working just as hard to improve their own products and services – and keep pace with a rapidly developing modality. Cryopreservation is seen as a key technology for advanced therapy supply chains, but it's a technique with many challenges. Here, three experts from the cryopreservation field discuss what is happening now, and what could happen in the future.

How has the demand for cryopreservation changed with the development of advanced therapies?

Stella Vnook: It has significantly increased. For instance, the global market for preservation equipment was around $2.5 billion in 2014 and is now projected to reach over $8 billion by 2025. This growth has been driven by expansion in cell therapies and regenerative medicine.

We spend so much time and passion launching new therapeutic products, and we want them to be available and accessible. We can scale up manufacturing, but the cost of transportation and logistics is skyrocketing. We need to start solving this before it hits the budget line, which would put us at the mercy of liquid nitrogen transportation.

Priya Baraniak: As we see more and more cell and gene therapies launch, one thing I think we're all very passionate about is their global accessibility and democratization. While we still see a strong preference amongst many cell therapy developers for fresh tissues and cells – especially nascent biotechs – fresh cells pose a real logistics challenge. The transportation and storage of these materials runs against the clock. Cryopreservation enables extended storage and global transport. We're essentially freezing them in time.

Cryopreserved products have already been embraced by large pharma and established biotech companies. Until we have better processes for lyophilization, or next generation solutions to circumvent cryopreservation, it's going to continue to be the path forward – even to the point of the cryopreservation and transplantation of entire organs.

As we see cell and gene therapies continue to expand in their indications, we're going to continue to see the increased need for cryopreservation technologies, but cost is definitely a major consideration, along with any regulatory hurdles that might exist. The industry, as a whole, needs more standardization and decentralized manufacturing. Cryopreservation does offer some standardization, but the regulations are going to be very important.

Trevor Smith: There's certainly an increase in demand for cryopreserved products and, as we learn more about these treatments, the more they resemble the very definition of personalized medicines. It's "table stakes" in the operational process, collection, shipping, manufacturing, and reshipping back for reinfusion, but it's no small feat to do all of that. Logistically, it's challenging: aligning schedules for different sites whether in centralized and decentralized manufacturing, but cryopreservation gives you a path forward so these things can get to the patient in time and with the required quality.

Can you elaborate on the advantages of cryopreservation over conventional methods?

TS: Conventional methods merely keep the materials fresh or chilled so they remain as close to the native cell and tissue populations as possible. However, they then forego viability risks inherent to the normal freeze-thaw cycle for cells. Cryopreservation stops the clock in manufacturing, easing the pressure of scheduling at the collection site from the patient to better align with the manufacturing availability downstream for more seamless transitions into the manufacturing process. Cryopreservation also enables different dosing strategies, such as multi-dosing, which gives more flexibility for advanced therapy developers to create a product that's more beneficial to patients.

SV: A decade ago, we had very limited cryopreservation tests. Now that cryopreservation is becoming standardized, we expect to optimize it, and testing can go further. We can include cell survival rates, cellular damage tests; we can extend storage duration without compromising efficacy, and we can test at every step how cells are functioning in that environment. A precise and reliable preservation method is critical to ensure therapies that patients receive will have maximum therapeutic benefit.

PB: The IVF field is a major driver of cryopreservation in healthcare and medicine, but beyond fertility, biobanking is still something we do routinely. We have newer options coming to market now, and ideas about first line treatments for patients versus second, third, fourth, fifth line treatments. Today's immunotherapies follow chemotherapy, radiation, monoclonal antibodies or combinations thereof. Many of these patients' bodies are ravaged by the time we are able to go in and perform leukapheresis. Prophylactic apheresis at the point of diagnosis is an emerging idea, and when nothing else has worked, we can try CAR-T therapy using material from the patient from when they were healthier. The hope is that these therapies become first line therapies, rather than last hope chances.

Meet the Experts

Priya Baraniak is a co-founder and Chief Business Officer of OrganaBio, a biotechnology solutions provider enabling the development and commercialization of cell therapies. Baraniak's biomedical engineering expertise has culminated in a broad understanding of the cell therapy supply chain, various laboratory techniques, QA/QC measures, GMP lab design & manufacturing, regulatory filings, and technology transfer.

Stella Vnook is the CEO of Likarda, a biotech company developing technologies to improve cell therapy delivery, potency, and sustainability. After helping to develop and commercialize a method of coating cells with inert hydrogels to maintain cell viability, Vnook earned a place on our 2024 Power List.

Trevor Smith is the Senior Marketing Manager for Cell & Gene Therapy at Terumo Blood and Cell Technologies. He has expertise in T cell expansion on automated bioreactor systems, process development, GMP lab design, training, and optimized cell collections.

Are there any inhibiting factors that developers might face in accessing or utilizing cryo-based solutions?

PB: Bringing automation in will drive down costs and boost standardization. Until then, equipment and equipment costs are definitely an area of limitation. Workforce development is another that needs further attention. Cryobiology is a very specific field; there aren't many cryobiologists out there with the very distinct knowledge of what it takes to cryopreserve cells, tissues, and living materials. You need someone who understands cell biology and the physics of freezing, temperature changes, and nucleation. It's a multidisciplinary field that requires more technical experts to drive it forward.

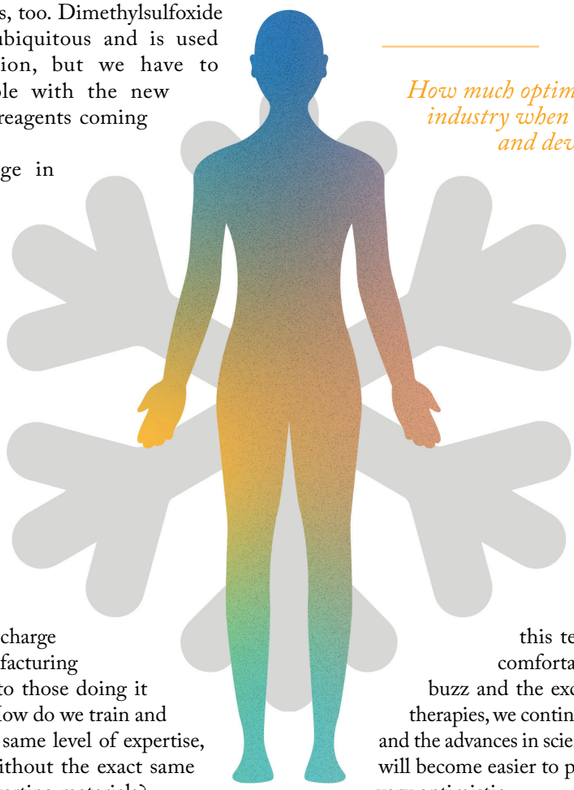
There are regulatory hurdles, too. Dimethylsulfoxide (DMSO) has been quite ubiquitous and is used routinely in cryopreservation, but we have to make regulators comfortable with the new technologies, materials, and reagents coming to market.

TS: The biggest challenge in adopting automation is that there are so many other areas to focus on during therapeutic development. The final fill and finish step is often deemed a lower priority when compared to expansion or transformation. There is a strong desire to automate and standardize processes, but the timeline for adoptions is often later in clinical trial process development. The primary manufacturing process often gets the most attention.

Priya's access to expertise point is certainly valid; those in charge of cryopreservation after manufacturing are in a different talent pool to those doing it immediately after collection. How do we train and make it so that both have the same level of expertise, the same consistency, even without the exact same cryopreservation process and starting materials?

SV: There are four factors that are critical. First, the complexity of logistics costs; the infrastructure requirements, temperature control equipment, and backup systems. Second, regulatory and safety concerns. Handling liquid nitrogen comes with risks, as does DMSO. We need to do better as an industry to educate ourselves and our colleagues in the FDA about what we're doing now and where we need to go, and there needs to be more educators. Third, the sustainability factor. How do we create a sustainable solution without excessive energy consumption? And fourth, the environmental impact of the production, transportation, and utilization of liquid nitrogen. Cryopreservation, logistics, and transportation was always thought of as somebody else's headache, until you get to phase III where you start to realize that those costs, implications, and technological hurdles are yours.

A company launching a product has little interest in going back to the beginning to figure out a new way of cryopreserving it. They just want to launch it and make it available. There needs to be an integration of the knowledge accumulated and embedded into earlier stages of the R&D process.

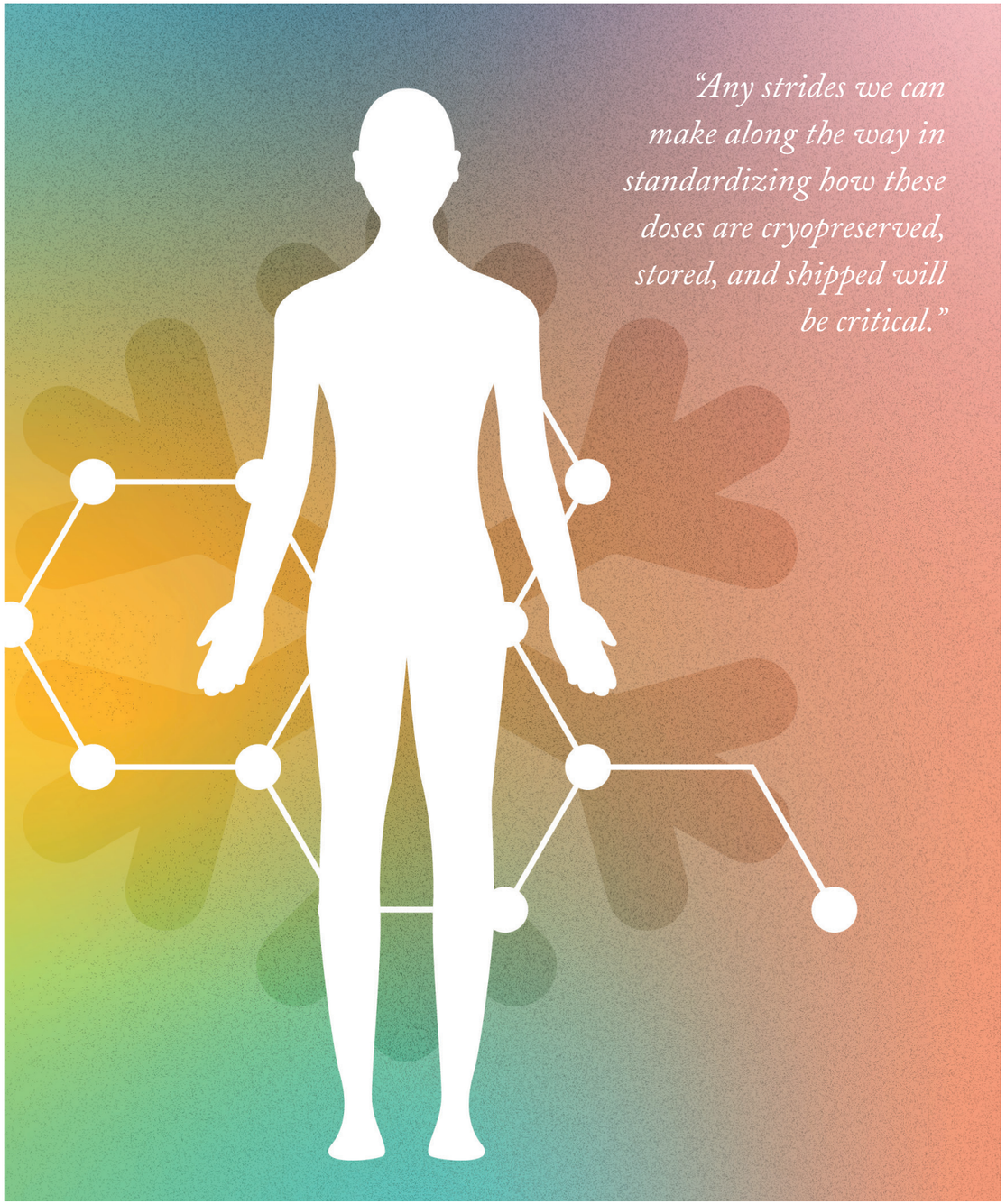


How much optimism is there in the industry when it comes to attracting and developing new talent?

TS: The fact that talent is being attracted is a vindication of how compelling the industry is. In 2017, with the first FDA approvals for CAR-T cell therapies, people realized that cell therapies were real, which generated a lot of interest that has compounded in the years since.

However, we need to simplify the training to guide people through the process of pre-programmed protocols. This would lower the barrier to adopting this technology and getting people comfortable with using it. Between the buzz and the excitement around cell and gene therapies, we continue to attract curious individuals, and the advances in science, technology, and automation will become easier to perform and function. Yes, I am very optimistic.

SV: In the past we were looking for people with MDs and PhDs to develop new protocols and systems. What's more important now is attracting people earlier on; people with bachelor degrees in biochemical engineering or any pharmaceutical process can be motivated by the changes made in the lab. Now these processes are more optimized,



we have opportunities for the younger generation earlier in their careers.

They can see how an expansion process translates into a lifesaving medication, as well as how their everyday role translates into saving a life. And if they're passionate about it, they can continue with their master's and doctorates.

PB: To get the type of workforce that we need for the growth that this industry could see in the next 10 to 25 years, we need to look at programs at the community college level, such as the vocational technical programs we have for other trades. You don't need a full degree; you can learn basic skills on aseptic technique, cryopreservation, and other elements without one. Traditional schooling is not for everyone and we're seeing more and more that a PhD is not paramount. What's more important is attention to detail, hunger and drive, and the need to continue to make science "sexy".

We've seen a lot of hardship in the industry since 2022, including brutal layoffs and a hard funding landscape. It's incumbent upon leaders in the industry to keep that optimistic outlook and to remain bullish on this, even in the face of adversity. We need to make sure the younger generation isn't turned away. We need to show passion – that inner fire – in our personal missions.

TS: I remember a mentor saying how the next stage will be taking cells out of the body, enhancing them, and putting them back. I remember another professor saying "That's crazy! It's like science fiction." But then it happened. The work in this space will be rewarding in the future, and the onus is on us to make people see the connection between manufacturing, collections, and the patient impact. The patient stories are going to become more and more valuable for the field – not just in terms of recruiting, but in keeping the energy and excitement alive.

What do you think cryopreservation is likely to continue to contribute to the advanced therapy sector in the future?

SV: It already helps patients in, for example, rural clinics who may not be able to drive to more central locations. Cryo brings the product to them. My mission is to make the treatments available to every person who needs them. Cryo is about removing barriers to access new technologies.

TS: In the near term, I'm hopeful that developers' aspirations for adopting new solutions become a reality. As allogeneic therapies advance into the clinic and beyond, we'll see more "off-the-shelf" options become readily available, but scale is going to become the next frontier, and the next problem to solve. Any strides we can make along the way in standardizing how these doses are cryopreserved, stored, and shipped will be critical.

DMSO, a main component of cryo-protected media use, could be phased out. We are looking closely at the emergence of non DMSO-containing media – it's definitely a good space to keep an eye on.

PB: Personalized medicine and the ability to bank cells for future use will become more and more popular. Will we be able to cryopreserve ourselves? Walt Disney has, supposedly! Personally, I wouldn't want to, but some do!

I can foresee applications in space exploration, and sending cells to space, which is being done by SpaceX and others to discover the effects of microgravity and radiation on different cell types. How might this affect life on the moon or Mars? Maybe someday we will have to leave Earth, or choose to leave Earth. There's a whole new frontier out there in the realm of science fiction, but maybe 50 or 100 years from now, it's conceivable that we might need cryopreservation for things like that.

SV: There's a lot of good we can do with where we are too. Maybe we will reduce the reliance on chemical cryopreservation and move into the era of physical insulators so we can work on better ways of getting blood and organs to those living with conflict. The reality, now, is the instability in the world, and the people facing different challenges. Their priority is to stay alive. If they need blood or any kind of treatment to do that, there are therapies out there. The question is, how do we, as an industry, evolve to be able to deliver?

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In Support of the Supply Chain

From automation to integration, there is huge room for improvement in supply chain management systems for cell and gene therapies

By Fiona Withey, CEO, TrakCel

Stakeholders across the cell and gene therapy space are unanimously stressing the urgent need for establishing standards in response to the industry's rapid growth. There is a particular need for improvement in chain of identity (COI) and chain of custody (COC) tools because these form the backbone of the complex supply chain process for advanced therapies. This need is especially true for autologous therapies where biological material must carefully be moved from a patient's location to the site of production and back to the correct patient – without error and within tight timeframes.

Developers of advanced therapies may often feel that top-to-bottom, bespoke solutions are needed to fit their unique needs when it comes to supply chain management, but experience tells us this tends to be short-term thinking that ignores the challenges of scalability, interoperability, and long-term costs.

Here, I present five recommendations for supply chain orchestration and IT platform selection.

1. Digitize early

In the early days, cell and gene therapy developers started out with paper-based tracking workflows – and some early-stage projects still rely on this method. Unfortunately, processes that are workable in early development become unwieldy at scale-out. As the field has matured over the past decade, more and more companies are recognizing the limitations of a paper-based system and seeking out digital solutions.

Tracking the progress of a therapy on paper with multiple external partners is prone to human error – rendering it increasingly risky and onerous during scale-out. Well thought-out digital systems with development that meets the GAMP-5 standard can facilitate scale-out far more easily. These systems can also be validated within a quality system and against relevant regulations to ensure they are secure and compliant.

Despite the obvious advantages of digital orchestration, some companies still start with a paper-based system, with every intention of moving to a digital system when the time is right. But delaying implementation of a more robust digital system until later in drug development is likely to add unnecessary risk, as well as be a false economy. The earlier the switch to an appropriate digital solution, the better.

2. Be cautious of custom approaches

Conventional wisdom has coalesced around digital approaches to COI and COC, but many developers understand that they require flexibility to match the unique workflow they are creating. A custom-built system may seem like an effective approach, but does not always provide the expected flexibility.

Many first-wave cell therapy developers learned this the hard way after creating their own platforms in house to meet specific needs that were then unable to cope with scale up. I've seen developers begin with a custom-built orchestration solution before realizing that they need a complete rebuild. Many designers of the earliest commercial platforms had similar experiences: after launching with traditionally coded software solutions that had to be re-coded for each new deployment, the need for constant testing made them unscalable. The leading options have switched to configurable solutions built on cloud platforms, which enable quicker configuration, testing, validation, and deployment to support clinical trial and commercial therapy supply chains.

The upfront investment of time and effort to launch a custom solution can seem straightforward to estimate, whether it's an outsourced or in-house build, but it means bearing the full task of ongoing testing and validation. Therapy developers often don't realize the degree of future costs, particularly as longer-term maintenance and changes are generally not factored into the scope or roadmap. Furthermore, custom-built solutions tend to be based on a company's experience to date – often just a small number of clinical-scale runs – which can be severely limiting.

Some developers have also found their bespoke systems are ill-prepared for the complexity of expanding into new geographies; language translations and regulatory/data privacy requirements vary from country to country, for example. It can be difficult to make sure your workflow is meeting all territory-specific requirements – and to adapt when rules, standards, or regulations change.

In short, custom builds can also be a false economy, with inflated costs over time. Though the largest pharmaceutical companies may have the resources to iteratively rebuild their orchestration platforms, many smaller companies and earlier-stage biotechs risk getting trapped in a situation that will be resource- and cash-intensive – conflicting with the core strategy of progressing the development of their therapy.

3. Harness the power of automation

Automation makes standard cases exceptionally easy to handle with minimal intervention. For CGTs, the reality is that a surprising amount of time is spent managing scenarios that don't follow the ideal process. Technology can help by automatically identifying exceptions and managing escalations. Automation also accelerates development, which is crucial given that the patients enrolling in trials

come with many potential variables. They are typically very unwell, often seeking third- or fourth-line treatment following the failure of standard-of-care approaches. This might mean that something as trivial as catching a cold can delay immune depletion, severely disrupting the tight schedule. And, of course, dealing with biological material also presents potential points of failure – from temperature deviations to limited cell yield. In short, your supply chain platform must be able to consider and address therapy-specific, patient-specific, and process-specific variables.

4. Consider long-term support and user training

As with any software, maintenance is an ongoing necessity and adoption and utilization are critical. User interfaces and other key components tend to get dated very quickly. For COI and COC, it can be advantageous to integrate solutions with partner systems, such as courier portals or software, to form a highly connected ecosystem from patient to therapy infusion and beyond. Any update to these systems or connectivity methodologies, such as application programming interfaces, must be accounted for. If the owner of a custom system can't make rapid updates, there's a risk the integration will fail – regardless of which party is responsible for the change. Given the health circumstances of most patients in CGT trials, the impact of delays due to system failures can be significant.

"In short, custom builds can also be a false economy, with inflated costs over time."

In general, IT system management must be forward-looking to anticipate changes and improvements in technology, particularly in an industry that is evolving as rapidly as the CGT space. For example, new technologies arise regularly in fast-developing fields, such as artificial intelligence. Assessing how these could be leveraged to improve a system is a mammoth task. This is before you have acted to incorporate the latest technological advances into a solution – a process that is never complete, if you are always keeping an eye on what's coming next.

Commercial solution providers form their own partnerships with these vendors and have the resources to appropriately monitor and prepare for upcoming changes. Their solutions also have the advantage of bulk and can leverage their broad user base for better responsiveness, pushing external vendors to prioritize fixes. A mature provider with a large network of connected vendors can empower developers to adapt quickly if, for example, a courier of choice was unavailable and an alternative must be used.

5. Ease the pain for healthcare staff

As they move forward with clinical trials, cell therapy developers are no longer working in a vacuum. They need constant feedback from users at all points of the value chain to make sure their supply chain approach remains relevant. Through regular industry working groups and other outreach efforts, we understand that portal fatigue is a growing pain point at patient sites. For centers of excellence working with dozens of therapies, they may be grappling with a variety of shipping, manufacturing, and patient information portals for each therapy. Dealing with that complexity falls on the shoulders of healthcare practitioners, such as nurse navigators. These people don't want different logins and workflows for each therapy. Integrated systems, with the ability to manage all of the therapies from a specific developer, can start to address this issue.

It takes a huge investment of time to manage the many integrations required for the suite of ecosystem partners, including logistics, enterprise resource planning solutions, manufacturing execution systems, benefits verification, and patient services. Throughout the rapidly evolving CGT space, everyone is coming to realize that – across all domains – the go-it-alone approach is untenable.

DEPARTMENT

Advanced Transformation

Software development and CDMO experts share their key tips for choosing the right digital technologies and partnerships

Digital transformation is a key phrase buzzing among modern pharma companies. Although there can be benefits for any enterprise, cell and gene therapy manufacturing is, arguably, where companies stand to gain the most. This area of the industry continues to mature and needs every edge it can get to optimize manufacturing. However, the digital journey is not an easy one, which is why many companies turn to partnerships. Here, we speak with software expert Alexander Seyf, CEO and co-founder of Autolomous, and David Smith, VP of Development at CDMO BioCentriq, to get their take on the digital future of the sector and tips for success in choosing the right technologies and partnerships.

How can advanced digital platforms benefit manufacturers?

David Smith (DS): There are a number of points to highlight including reduced cost, faster response time, improved communication across stakeholders, robust chains of identity and custody, and improved efficiency and visibility on delivery times. Supply chain management interfacing digitally to the warehouse ensures stock levels are maintained based on usage – and even supplier stock levels.

The difficult part is that these benefits are often not fully realized until organizations are fully digitized, where logistics is talking to warehousing, supply chain, operations, quality control and quality assurance – all the way up to management (and even to the patient). But even without full digital integration throughout, there are still wins to be made by dividing the entire vein-to-vein process into small bites and tackling individual focus areas to improve consistency and reduce costs. Introducing automation in certain areas, for example, can reduce the cost of labor by removing operators from manual, open processes. On the manufacturing floor, there can be a lack of communication between equipment and other departments. The ability to move data from a local instrument to a batch record electronically immediately opens up greater insight into how the manufacturing process is performing, where we stand in the manufacturing process, and the potential to predict what will happen next, such as maintenance requirements or long-term trends.

Alexander Seyf (AS): Digital platforms offer real-time monitoring for process control, automated data collection for ironclad audit trails, and insights that can help drive continuous improvement. These tools are essential for both efficiency and scalability. They should – and do – exist to revolutionize how partners book, manufacture, and deliver vein-to-vein cell and gene therapy treatments.

What factors should companies consider when choosing the appropriate tech?

DS: The first point of call is to look at the critical quality attributes and critical process parameters of your product. Does the technology have the ability to provide a service within those limits? From there, a user requirement specification (URS) can be drawn to highlight the key requirements of the technology. It's important that this URS be future-proof based on your needs. Is the technology needed for a pipeline of therapeutics or just one? The answer to this question can vastly change the URS. Also, when generating the URS make sure that someone with a GMP background has reviewed it. A 21CFR Part 11 compliant technology, for example, is not required in development but will be for GMP manufacturing.

Your URS should look specifically at the problem you are trying to solve. Remember: digitization is not the only answer to many problems faced by manufacturers today, indeed there are often far simpler, less time-extensive ventures that can be undertaken. Digitization can help, but it is important to not discount other options too early.

AS: Adopting digital solutions comes with a unique set of challenges. I advise manufacturers to prioritize flexibility and scalability, process optimization, automation potential, quality and regulatory rigor, and an open technology ecosystem. Also, look for a partner that will champion a partnership-first ethos across all endeavors – and one that will remain steadfast in their conviction that the full promise of cell and gene therapies is realized not in solitude but in unity. It is by forging strong partnerships that we will unlock the transformative power of cell and gene therapies.

And what about when choosing a CDMO?

AS: For therapy developers at any stage, choosing a collaborative partnership with a CDMO is a pivotal decision. It's not just about planning for success; it's about being equipped to navigate the unforeseen. Choose a CDMO with a demonstrated track record in your therapy area. Look for strong process development capabilities to optimize your manufacturing and accelerate your path to market. You also want them to have a true understanding of the regulatory landscape to smooth the path to approval.

A forward-thinking CDMO should either be capable of scaling with you to commercial production or have a reliable network to support your growth. If a CDMO can't take you all the way to commercial scale, they should have an established network that can. The right CDMO convinces you to stay through unparalleled value, not through the inconvenience of change.

DS: The CDMO market today is stronger than ever in terms of available capacity, which used to be a key determining factor in who to choose. Now the gears have shifted, so too have CDMOs. Experience is my leading metric. A CDMO that has done it before can leverage their knowledge to keep things on track and succeed. But it's not just about management, it's also about the team on the ground, including material handlers, operators, quality control, and quality assurance. These are the personnel that will directly impact the success of your therapeutic, so visit them, ask them questions, and find out if they have the background to manufacture your therapeutic. Also, identify turnover rate and the likelihood of that team still being your team in nine months' time. The role the therapeutic company can take in praising the team for successes is often overlooked. Making them feel part of the company can improve the success of a project.

Beyond experience, flexibility and quality are crucial. During the process, the entire team will be learning about the therapeutic, so it's vital to find a CDMO that can be flexible to your changing needs – not only for the services rendered, but also in how to communicate with your stakeholders. Ensure you visit the site and speak with the manufacturing team. Although flexibility is crucial, it has to be conducted within the confines of quality, so ensure the CDMO has the appropriate knowledge, documentation, and protocols to identify the rigidity of the quality system.

Autolomous and BioCentriq will be working together to streamline development and manufacturing using digital technologies. How will both companies benefit?

AS: True innovation cannot happen in isolation. Our partnership with BioCentriq will provide us with insights that will allow us to continuously refine our digital platform. This collaborative approach helps ensure that our platform remains fit-for-purpose and supports our partners as their requirements change.

With a focus on data capture, operational logistics, quality release by exception, instant tech transfer, and powerful data analytics, what we bring is a solid foundation upon which BioCentriq can operate. Capabilities such as automated batch release, integrated inventory management, patient support, and AI-driven insights align perfectly with BioCentriq's vision for the future. We have a shared goal of making transformative therapies accessible to every patient in need.

DS: As a CDMO, we are keen to reduce the timeline and cost of technology transfers. We want to digitize a large proportion of the technology transfer process, starting with electronic batch records (eBR). Suppliers today provide eBR software to build records for use within GMP manufacturing. The aim of this work is to move the process upstream and into a development scenario, so building off executed protocols, data collection, and process knowledge that will already have been written in development. By creating protocol-based eBR for use in development, Autolomous can increase its market share by working with researchers as well as manufacturers in deploying their system. This move is crucial to help standardize processes and gain valuable insights into how manufacturing processes are developed. Armed with this information, the partnership will help provide knowledge and enhanced tools into the industry to increase patient access through improved manufacturing.

Give us a bold prediction of the near future of cell and gene therapies…

DS: Therapies are moving towards first-line treatment for larger indications. I expect this trend will continue with the need to manufacture more lots than ever before. This trend will once again put a constraint on manufacturing expertise, but can be offset with more automation and digital solutions.

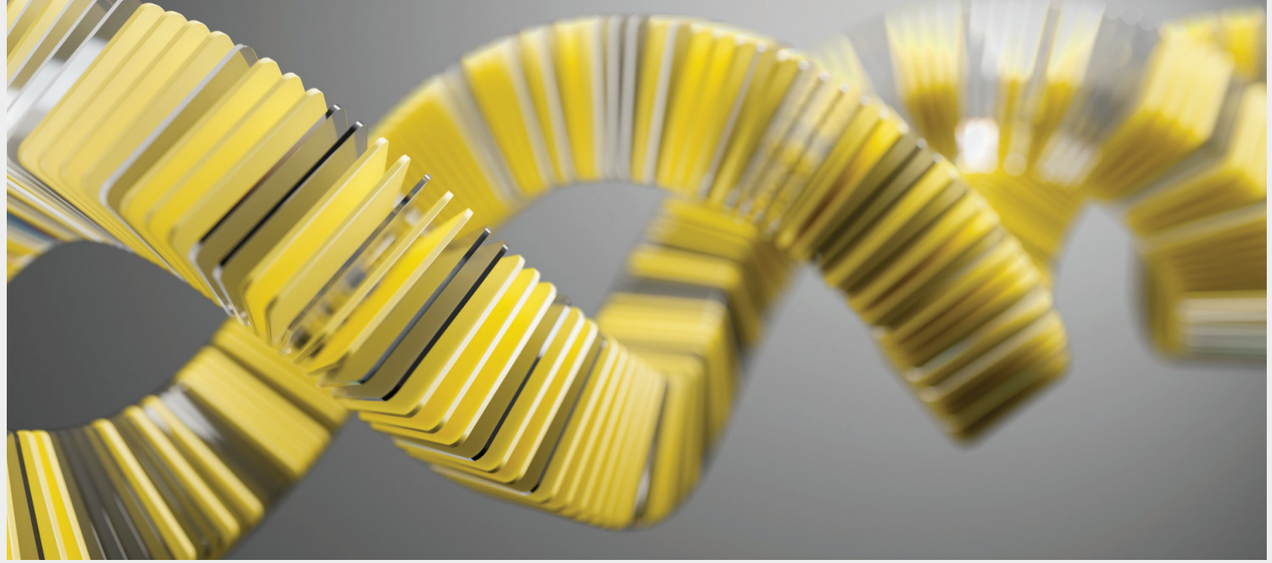
AS: The future is where a fully automated, regulatory-compliant manufacturing and release process becomes a reality, ensuring that life-changing therapies can be delivered swiftly and safely.

The future of CGT manufacturing is intrinsically linked to the industry's ability to continually innovate, merging cutting-edge scientific research with the latest technological advancements. By proactively aligning scientific endeavors with emerging technologies, we can enhance the precision, efficiency, and scalability of therapies. This commitment to innovation ensures that, as we move forward, our journey is illuminated by the brightest minds and the most advanced tools at our disposal, driving the evolution of therapies that can transform lives.

Navigating the Challenges – and Opportunities – of Lentiviral Vectors

Lentiviruses are growing in popularity within the gene therapy and gene-modified cell therapy landscape, but their production comes with unique challenges, including scalability, performance optimization, and regulatory considerations. Here's what experts at Sartorius have to say on the matter.

Featuring Marcel Fueger, Product Manager for Separation Technologies - Filtration, and Geraldine Guérin-Peyrou, Head of Product Management for Advanced Therapy Solutions, both at Sartorius



What are the biggest trends and conversation points in cell and gene therapies (CGT)?

Marcel Fueger (MF): Although CGT is a relatively new field, there have been many breakthroughs, but to meet increasing patient demand there are several key challenges to address, including the need to reduce costs and improve scale. Viral vectors are essential for CGT, which is why their manufacture using efficient and scalable production methods is a key topic in the industry. The most commonly used viral vectors are adeno-associated viruses and lentiviruses, but each vector has its own characteristics and advantages/disadvantages. It's our job at Sartorius to help our customers overcome all types of bioprocessing challenges, including those related to viral vector production.

Geraldine Guérin-Peyrou (GG-P): Viral vectors are definitely a big talking point in CGT. The manufacture of viral vectors – particularly on a commercial scale – is a complex process with many steps that require a high level of expertise. Safety is also paramount. You have to ensure that your vectors are not carrying unwanted gene insertions or other risks that could lead to cancer or life-threatening illnesses.

Why are lentiviruses receiving increasing attention?

MF: Lentiviruses are highly effective at delivering therapeutic genes to cells and can permanently integrate genetic material into the host cells' genome to provide long-term and stable gene expression, which is highly beneficial for treating chronic diseases. Unlike many other types of viral vectors, lentiviruses can transduce both non-dividing and dividing cells, expanding their applicability to a wider range of cell types, including T-cells. They also have a large packaging capacity to deliver genes of interest. In short, they have many unique capabilities compared with other viral vectors – and will only improve with further innovations in vector design.

What are the manufacturing considerations for lentiviral vectors?

GG-P: You first need to transfect HEK 293 cells, typically using three or four plasmids to express the different components of the vectors, including your gene of interest. After the cells have been cultured, you can proceed with collection and purification – both of which can be tricky because of the sensitivity of lentiviruses.

Scalability during the transfection step is also a significant challenge. You must mix the plasmids with the transfection reagent before adding them to your cells – and that means the stability of transfection complexes is critical to ensure you have enough time for mixing, especially when working at industrial scales.

Even at the earliest stages, you need to be considering how you will achieve the process quality and robustness required for the commercial scale. In reality, it is not at all straightforward to go from a flask to a bioreactor; key aspects, such as mixing and oxygenation, are very different. However, there are plug and play solutions available that can be used early on to facilitate later scale up.

MF: From my perspective as a clarification and filtration expert, it is interesting to see how approaches used in the production of mAbs are being employed for viral vectors. But the challenges are not the same. Lentiviruses are large particles, around 100 nm in size, and are very sensitive to shear stress, temperature, and time. Additionally, the feed stream often consists of high-density cell cultures, and therefore shows demanding turbidities and is processed in volumes of around 200 liters. In other words, scalability is essential – especially during the clarification steps. One common issue with filtration, particularly in prefiltration, is the potentially low capacity of filters when it comes to challenging feed streams. Low capacity can result in high cost of goods. Not choosing the optimal filter chemistry leads to product loss caused by adsorptive effects, which is a frequent challenge when filtering lentiviral feeds.

What about regulatory considerations?

GG-P: There is a lack of clear regulatory guidelines and standards for producing lentiviral vectors. For example, there is no guidance on the quality grade of transfection reagents or plasmids; however, many people in the industry expect regulatory scrutiny to increase in the coming years as the CGT field matures, and the focus will almost certainly be on higher-quality materials. Even in the absence of guidelines, using the highest quality plasmids and transfection reagents possible is a wise choice. I recommend GMP-compliant – and ideally ICH Q7 compliant – components to improve consistency and to reduce the risk of introducing impurities or contaminants that may affect the safety or efficacy of the final product. And by using high quality components and working to the highest standards, you don't have to worry about regulations changing in the future.

How can Sartorius help customers with lentiviral vector production?

GG-P: Sartorius has acquired several specialist businesses to build out a full portfolio in CGT, including transfection reagents, plasmids, filters, bioreactors, and beyond. We have solutions that span from the bench all the way to commercialization. We also have a strong regulatory affairs team that can support customers, as well as technical support specialists that can help set up design of experiments (DOE) and optimize processes. Scaling a process can be tricky – but you don't have to do it alone!

Sartorius has successfully tackled all types of projects over the years. Sometimes, customers come to us after they've started working with products that aren't GMP-compliant at larger scales. In those cases, we help them revamp their entire process to ensure GMP compliance. We can also support customers right from the start of their projects, which is recommended. After all, when we are involved early, it's much easier to streamline the scaling-up process because we can use the same products at larger volumes.

MF: Lentiviral vectors will remain a key cornerstone of CGT for the foreseeable future. However, as the field is relatively new, many biopharma companies may find that their internal expertise is lacking or still developing. Our team has the knowledge to support in finding the best fitting solutions and overcoming challenges. Since a lentivirus is handled as Biosafety level 2 material, many customers come to us for closed, single-use solutions. This approach protects the user and the environment from exposure to harmful agents, while also minimizing the possibility of cross-contamination.

For this procedure our filter trains are a popular solution. For example, a first step may use Sartopure® PP3, a highly porous, polypropylene-based filter that minimizes product loss caused by adsorption, while accommodating large particle sizes. This could be followed by Sartopore® 2 XLG, a sterilizing-grade filter to ensure the removal of smaller contaminants. Together, these filtration steps protect subsequent processes, especially the expensive chromatography stage, by preventing clogging and maintaining product integrity.

What are your top tips for success?

GP-P: As I noted earlier, optimizing the transfection step is crucial but often overlooked. Many people tend to use a single plasmid ratio, a fixed amount of DNA, and a standard volume of transfection reagents without considering alternatives. I strongly recommend adopting a DOE approach to optimize conditions. The Sartorius Ambr® system is a powerful tool for this purpose because it allows simultaneous analysis at different points. And when combined with Sartorius' MODDE® software, it becomes an even more effective solution. It's important to remember that all parameters should be optimized together; if you are changing the media, you need to re-optimize. And if you are changing the gene of interest, then you need to re-optimize.

As a side note, I came to Sartorius through the acquisition of Polyplus. And when I was at Polyplus, I would not shy away from recommending certain Sartorius products, such as MODDE, because I knew they were so good!

MF: The goal for clarification is low turbidity, but high yields are needed for the complete manufacturing process, which should be robust with the right production and purification techniques. As Geraldine explained, optimization is really important – and you need a process that can be scaled. I recommend testing and trialling alongside partners to find what works best for your application. Manufacturing and filtration processes used to produce one viral vector may not work for another because viruses behave so differently.

As the CGT field continues to mature, there will be more innovation – and more regulatory changes – aimed at increasing safety and manufacturing efficiency. Right now, we don't know what the gold standard will be. But what I do know is that Sartorius will be at the forefront – continuing to investigate and invest in new solutions so that we are ready to support our customers.

SARTORIUS

Be a Little Different

Sitting Down With… Luigi Naldini, Director, San Raffaele Telethon Institute for Gene Therapy, Milan, Italy

How did it feel to receive the Lifetime Achievement Award at Phacilitate 2024?
It was very rewarding – as with any award! Gene therapy has been neglected for so long, but now there is appreciation from all over the scientific industry. Early on, there were very few of us working and believing in what could be done with gene therapy. Now, there is much better recognition. Although an award goes to a single person, that person doesn't deserve all the credit. This award really goes to a whole team of people who have been involved in different stages.

Have you always wanted to be a scientist?
I always loved science, but early on it was more about nature and wildlife. In high school, I became more familiar with the emerging concept of molecular biology. At that time, there was no real understanding of DNA and RNA, so it was like an entirely new world was opening up – I found that very attractive. I ended up going to medical school, which, at the time in Europe, was a common path if you were interested in a research career in the biomedical area. Although I am an MD, I rarely practice or conduct clinical work. I am more interested in basic science and translational research.

How did you get into gene therapy?
After my MD and PhD, I started work on signal transduction. Back then, we were uncovering the basics of growth factor receptor tyrosine kinase, but I wanted to take a new route. I came across a review about the emerging area of gene therapies by Richard Mulligan (Harvard). After the early hype of gene therapies and the lack of results, he explained that we needed to go back to the hard science.

I was attracted by this idea and I wanted to join the field. I went to the US and I applied to Richard Mulligan's lab, but I didn't get the role! Over the years, I became very close to him and he always said, "Too bad you couldn't come to my lab."

And I would reply, "I could have come to your lab, but my application was rejected!" Fortunately, I was also interviewed at the Salk Institute and ended up in the lab of Inder Verma.

Why focus on lentiviral vectors?
At the time, there was discussion around current vectors, such as the gamma retroviral vector, not being very efficient. On the floor above me was the lab of Didier Trono working on HIV. We thought, why not try creating a vector from HIV? I was interested in starting something from scratch in gene therapy rather than joining something that was already going on, so building a new vector was very appealing. Though we never dreamed it would become so useful!

"I always loved science, but early on it was more about nature and wildlife."

I worked for two years on this project – and a biopharma company was interested in licensing the technology for product development. However, the whole field came to a halt because there were reports of tumors developing in patients treated with a gamma retrovirus in Europe. Many companies were scared away from gene therapy – including the company I was working with.

I continued to develop the technology on an academic basis – thanks to funding from the Telethon Foundation and other sources. Our work attracted people back to gene therapy – including big pharma. Together with the Telethon Foundation CEO we spoke with GSK executives and this led to an alliance for the development of hematopoietic stem cell gene therapy.

How did it feel when lentiviral vector therapies made it to market?
Progress doesn't happen in a single moment. Yes, early experiments can have a "eureka" moment but it takes time to bring this to humans. When you see results in patients and the disease doesn't seem to be appearing, you need to wait months before you can be sure of the results. It also then takes time to get to market. But it feels amazing!

The whole experience has been a learning curve for us as well as the industry. I feel very lucky that I've been so closely involved, from the early steps on the bench, to clinical, and then to market. I've also been able to see the challenges from both academic and industry levels.

Do we need more intense collaboration to move forward?
What we have achieved today in gene therapy is the result of academic research, charity funding (crucial), and involvement of industry – from small biotech to big pharma. Collaboration must continue – but we also need open transparency. No single treatment or tool is perfect, and there will always be advantages and drawbacks for each of them. If there is a problem with a tool, it is much better to acknowledge that upfront rather than cover it up. There is the risk of the field moving into a more protective, business and venture capital driven model. We have managed to achieve so much today because there has been data sharing and open discussion from the very beginning. Without this, we risk building a culture of suspicion. We must be open about the risks and not oversell the benefits.

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