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Insights

CLS Digital Magazine December 2022

Cell & Gene Therapy

Realizing the Potential

PLUS

- *Meeting manufacturing demand*
- *Solving supply chain challenges*
- *Accelerating therapies*

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Dear Reader,

It's such a pleasure to welcome you to Life Sciences Insights for our final edition of 2022.

I'm particularly excited about this edition because of the promise of cell and gene therapy (CGT). CGT is unique–and our members are using it to explore new, innovative ways to treat, prevent, or cure diseases that are currently incurable.

According to the Alliance of Regenerative Medicine, there are more than 200 CGT companies in California. Most of them are small–with fewer than 10 employees. Throughout the year, California Life Sciences (CLS) has made it a priority to engage and support this important segment of our industry.

We've hosted legislative briefings and tours with legislators at our CGT member company facilities. We've participated at several CGT conferences and selected CGT startups to receive free, expert advisory services through our FAST program. And I'm excited to announce here that next year, we're planning a CGT summit with Johnson & Johnson Innovation, where you'll enjoy panel discussions, networking, partnering sessions, and more.

In this special edition of Life Sciences Insights, you can expect to gain real understanding about the latest trends and drivers and the overall market environment. As you read these articles from our member companies, you'll learn how they're solving real challenges, like manufacturing demand, supply chain approaches, and lowering cost. You'll see investment considerations. You'll discover how they're accelerating therapies and working with the FDA on the path to commercialization.

I'm inspired by the insights, ideas, and innovations of our members.

As we head into 2023, we'll center each magazine around a theme, exploring topics and trends most relevant to our California life sciences sector. Our goal with Life Sciences Insights is to shed light on this important work; as we all work to bring solutions for healthier, longer lives for all people.

Best,

Mike Guerra
President & CEO, California Life Sciences

Meeting Cell and Gene Manufacturing Demand Requires a Blended Solution

Submitted by Dan Dernbach, Senior Vice President of Global Operations, Azzur Cleanrooms on Demand™

The cell and gene therapy market is growing rapidly and is at the forefront of innovation within the pharmaceutical industry. Pharmaceutical companies are fully leaning into a custom-tailored approach to develop critical therapies for treating and curing certain diseases. The speed and versatility of these novel therapeutic modalities have shown great promise, and the success and benefits of such custom treatments are likely to surpass some of the more traditional options.

A tremendous amount of investment is being made into cell and gene therapy development. Large and small companies alike have numerous therapies entering the clinical pipeline. The global cell and gene therapy market is expected to grow by $9.97 billion from 2022 to 2026. The industry's substantial growth rate can be attributed to two factors: an increase in ongoing cell and gene clinical trials and an increase in government funding for cancer research. The American Society of Gene and Cell Therapy reported that the pipeline is focused predominantly on anticancer indications, followed by rare diseases.

The FDA predicts that by 2025, they will approve 10-20 cell therapies annually. There are such a high number of new therapy applications that the FDA has created a "Super Office" for cell and gene therapy in an effort to increase the number and shorten approval time for these drugs. The high operational costs associated with cell and gene therapy manufacturing are expected to restrain the growth of this market to a certain extent. Additionally, speed to market will become increasingly

important as the pipeline expands. This will require new and innovative approaches to manufacturing.

Pharmaceutical companies are hamstrung by traditional manufacturing options, either working with a third party such as Contract Manufacturing Organizations (CMOs) or building their own facility. Both options have several drawbacks. Partnering with a CMO, companies give up a degree of their intellectual property, their flexibility, and ultimately may face significant schedule delays. Industry observers have acknowledged that CMOs are at capacity, waitlisting companies anywhere between 16 to 24 months. On the other hand, building your own facility enables companies to control their process completely, but doing so requires considerable time and capital. This is not a viable option for many cell and gene start-ups, which have to deal with capital constraints.

The drawbacks to the current manufacturing options will negatively affect projected cell and gene market growth if companies continue to choose only between these two options. To overcome their manufacturing challenges, companies are turning to a new manufacturing path: cleanroom licensing, a blend of the previously mentioned options.

Cleanroom licensing enables companies to customize cleanrooms to satisfy their manufacturing needs fully. In doing so, companies have complete control over the process, the space they are occupying, scheduling, quality control, and other activities.

Cleanroom licensing enables companies to customize cleanrooms to satisfy their manufacturing needs fully. In doing so, companies have complete control over the process, the space they are occupying, scheduling, quality control, and other activities. Additionally, some cleanroom licensing facilities will offer Good Manufacturing Practices (GMP) compliance advisory solutions and additional support, such as materials handling and storage. These other services are vital to some cell and gene companies that lack GMP expertise and manufacturing experience.

It is also becoming apparent that established pharmaceutical companies and even CMOs are getting involved with cleanroom licensing to have a "bridge facility" that enables them to have more support in addition to their current manufacturing facility. These facilities allow for excess capacity, contingency planning and potentially an easy way to expand their geographic footprint with lower capital output. As the cell and gene pipeline continues to run at full speed, it will be this blended manufacturing strategy that will push some companies to the finish line. ■

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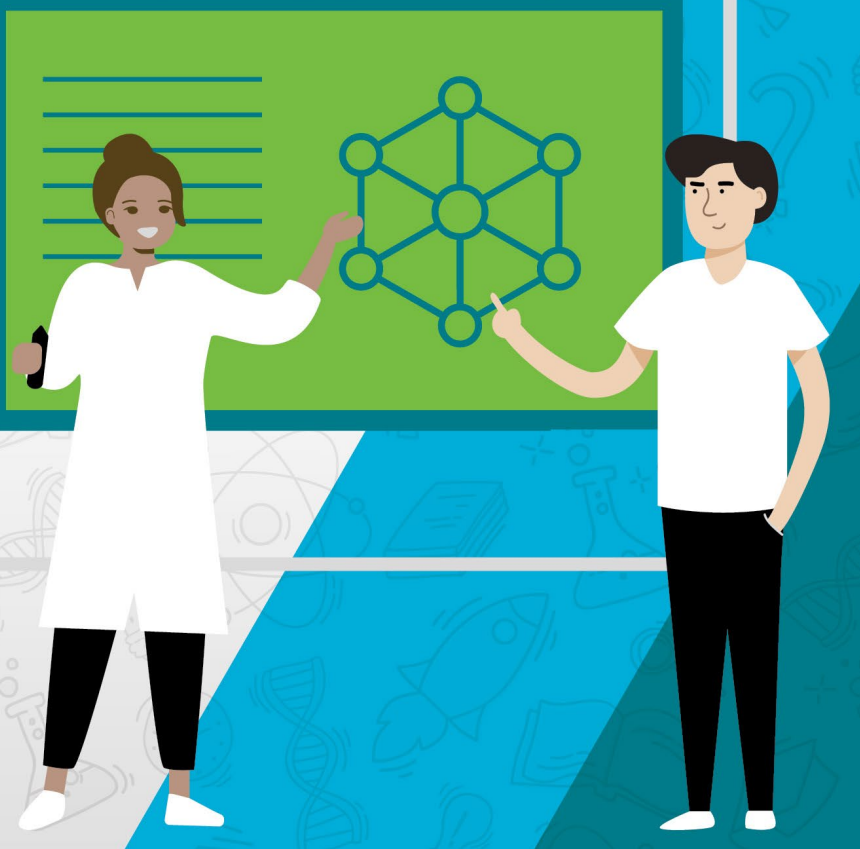


The Power of FDA Meeting Opportunities On the Path to Commercialization

Submitted by David Horowitz, Lowell Zeta, and Ted Lis, Hogan Lovells

U.S. Food and Drug Administration (FDA) approval is a critical step in the path to ensuring that regenerative medicines are available to address unmet medical needs without putting patients at risk. Sponsors of drugs and biologics undergoing expedited development have special opportunities to discuss their product strategies and goals with FDA review staff. Many cell and gene therapy products are eligible for these programs, which are designed to provide extra assistance in navigating the FDA approval process. FDA continues to expand its programs to help developers address scale-up manufacturing challenges associated with these complex therapies earlier in the FDA review cycle.

Development programs for FDA-regulated drugs and biologics intended to address unmet medical needs may be eligible for Breakthrough Therapy, Fast Track, and Regenerative Medicine Advance Therapy (RMAT) programs having accelerated clinical development timelines. Yet, marketing applications for products in these programs still need to meet FDA's exacting approval standards, including compliance with current

good manufacturing practice (CGMP) requirements. Products with accelerated clinical development activities may face challenges in aligning expedited Chemistry, Manufacturing, and Controls (CMC) development activities. Successfully expediting CMC readiness may require additional interactions with FDA during product development so that clinical benefits of earlier patient access to these products can be realized.

As a result of these accelerated review timeframes, CMC and CGMP issues are often rate-limiting factors that have resulted in Complete Response Letters and prevented FDA from approving drugs that treat serious diseases and fulfill unmet medical needs. CMC and CGMP challenges have been particularly significant for complex biological products, such as cell and gene therapies. While the Breakthrough and RMAT programs were intended to address these challenges, FDA and industry have recognized that additional interactions with, and assistance from, FDA are often necessary to accelerate resolution of CMC and CGMP issues earlier in expedited program review cycles.

Accordingly, starting in April 2023, FDA will be implementing a CMC Development and Readiness Pilot (CDRP) program to facilitate CMC readiness for selected Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER)-regulated products with accelerated clinical development timelines. For sponsors participating in the pilot, such as cell and gene therapy manufacturers, FDA will provide product-specific CMC advice during product development.

Sponsors can interact with FDA through two additional CMC-focused "Type B" meetings and a limited number of additional CMC-focused discussions based on readiness and defined CMC milestones. Although the first year of the pilot will be limited to nine applications (six designated for CBER products), FDA will continue the program for three additional years, and the number of participants for these years has not yet been disclosed.

To be eligible for the CDRP pilot program, a sponsor must have an active Investigational New Drug (IND) clinical program that has not yet reached the end of Phase 2, to allow the pilot to have sufficient time to have an impact on CMC readiness (*e.g.*, two years from anticipated marketing application submission). However, requests for exceptions may be considered, where the development programs would still benefit from the pilot.

Products with accelerated clinical development activities may face challenges in aligning expedited Chemistry, Manufacturing, and Controls (CMC) development activities. Successfully expediting CMC readiness may require additional interactions with FDA during product development so that clinical benefits of earlier patient access to these products can be realized.

In selecting INDs for the pilot program, FDA intends to consider factors such as the:

1. anticipated clinical benefits of facilitating earlier patient access to the product,
2. novelty of the product,
3. complexity of the product or its manufacturing process, including technology,
4. sponsor's overall manufacturing experience (including possible additional considerations to less experienced sponsors), and
5. sponsor's experience with the particular product type, class, or the type of manufacturing process.

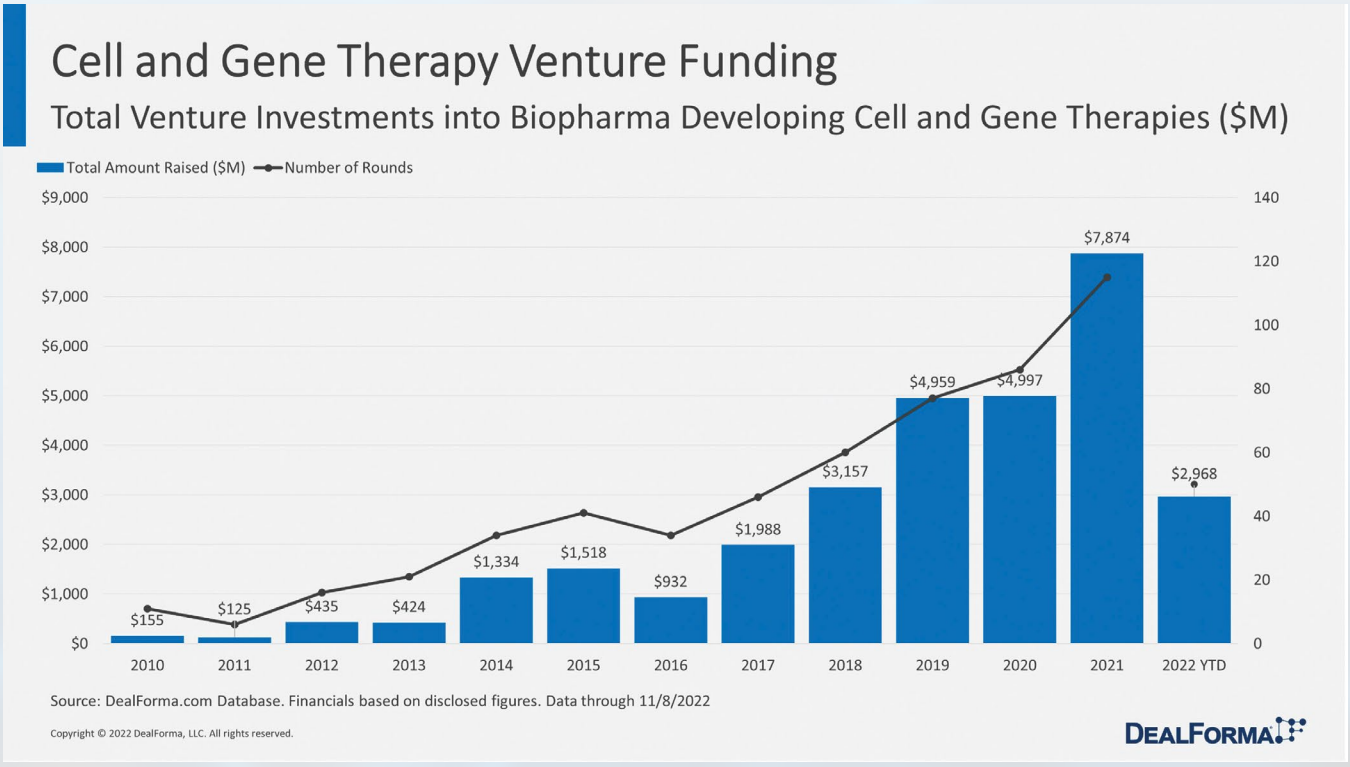
From innovative start-ups to large multinationals, Hogan Lovells works with cell and gene therapy manufacturers to engage with FDA in a meaningful way to address scale-up challenges and manufacturing readiness issues that may arise on the path to commercialization. The CDRP pilot is but one of many recent regulatory initiatives that cell and gene therapy manufacturers should consider in advancing their life-saving medicines toward FDA approval.

Investment Considerations in the Cell and Gene Therapy Market

Submitted by David H. Crean, Managing Partner, Cardiff Advisory

Cell and gene therapies (CGTs) continue to be at the very center of healthcare innovation and are the fastest-growing areas of therapeutics. We have already seen CGTs contribute to some of the most significant disruptions in the pharmaceutical industry, especially during the pandemic. CGTs represent innovative approaches to treat severe diseases, such as cancer, as well as rare diseases.

After two record-breaking years in investment for regenerative medicine and advanced therapies, the CGT sector's 2022 performance is trending back to the levels of 2018 and 2019. During the pandemic in 2020 and 2021, the biotech sector saw an unprecedented uptick in investment due to strong public attention on healthcare innovation and the low cost of capital. Reasons for this downturn in investment seen year to date include inflation, rising cost of capital, and a retrenchment in biotech financing following record levels of investment. The slowdown affects nearly all parts of the interconnected financing system, from early-stage venture capital to initial public offerings (IPOs) and the performance of publicly traded companies. Small, early-stage emerging companies like many CGT companies were particularly affected by inflationary expectations because they are furthest

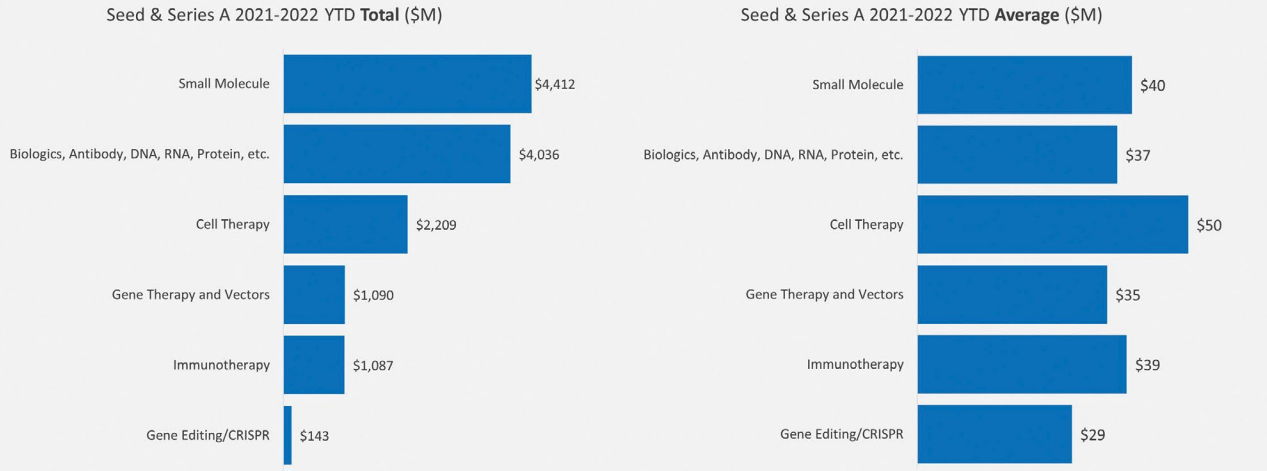


from generating profits, making their profitability projections more speculative.

According to data in the DealForma database, annual CGT venture totals have been impacted like other areas of biopharma, with only 50 rounds totaling $3 billion by mid-November, compared to 115 and $8 billion in all of 2021. Early rounds specifically into new cell therapy companies have been higher, with the average Seed and Series A rounds at $50 million 2021 and 2022-to-date.

Early Ventures into Cell and Gene Therapy vs. Other Modalities

Seed and Series A Rounds by Core Technology – 2021-2022 YTD



Source: DealForma.com Database. Financials based on disclosed figures. Data through 11/8/2022

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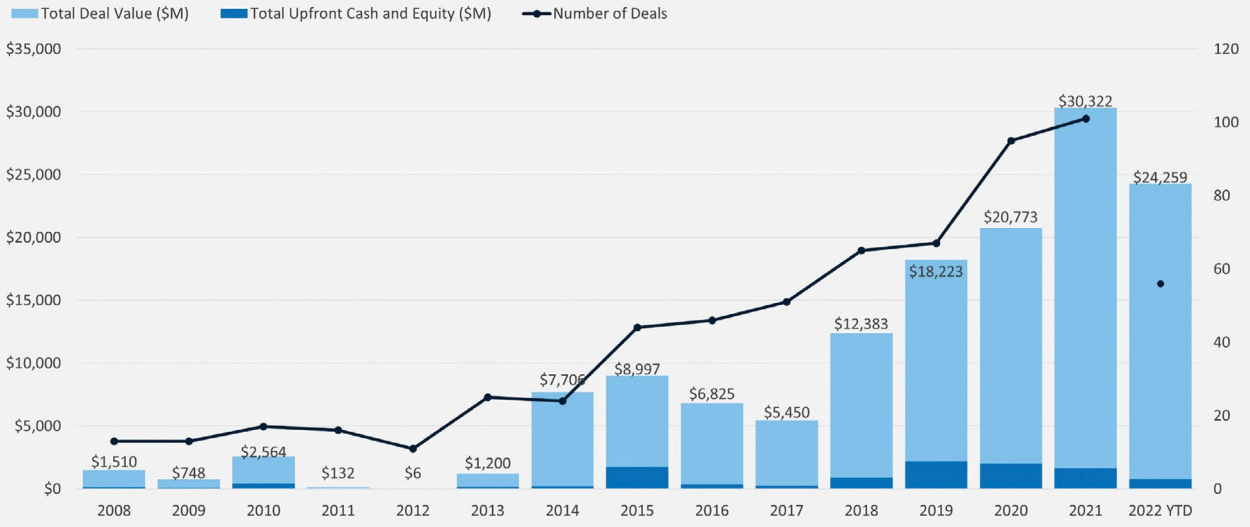
Public equity and capital markets overall have trended down in the first half of 2022. The biotechnology sector initially performed worse than general indices but more recently has outpaced the general recovery. IPO's have nearly dried up in 2022. Inflationary fears and interest rate hikes have adversely impacted the valuation of publicly traded companies that are smaller and in earlier stages of development. This includes cell and gene therapy developers, which have closely followed the trend lines of broader biotech indices but at lower valuations. Despite the retrenchment in venture capital financing for the sector, while off its 2021 peak, financing remains robust and is a clear sign of continued excitement around scientific breakthroughs and the opportunity to change the treatment paradigm across a range of rare and prevalent diseases.

Beyond the headline M&A deals, life sciences companies—from the biggest pharmaceutical companies to early stage biotechs—are collaborating through alliances to identify and develop not just CGTs but targets against which they may be effective and numerous technological components that are often needed to make these therapies work. Licensing and partnership deals have fared better than investment activities as median upfront cash, and equity payments came in at $132 million in 2022, continuing healthy increases since 2016. When equity financing from traditional investors is challenging given the current environment, companies look to alternative sources of capital through partnership deals in order to advance the pipeline and drive valuation.

Licensing Deals for Cell and Gene Therapy Programs

Number of Deals and Total Values for R&D Partnerships in CGT



Source: DealForma.com Database. Financials based on disclosed figures. Data through 11/8/2022

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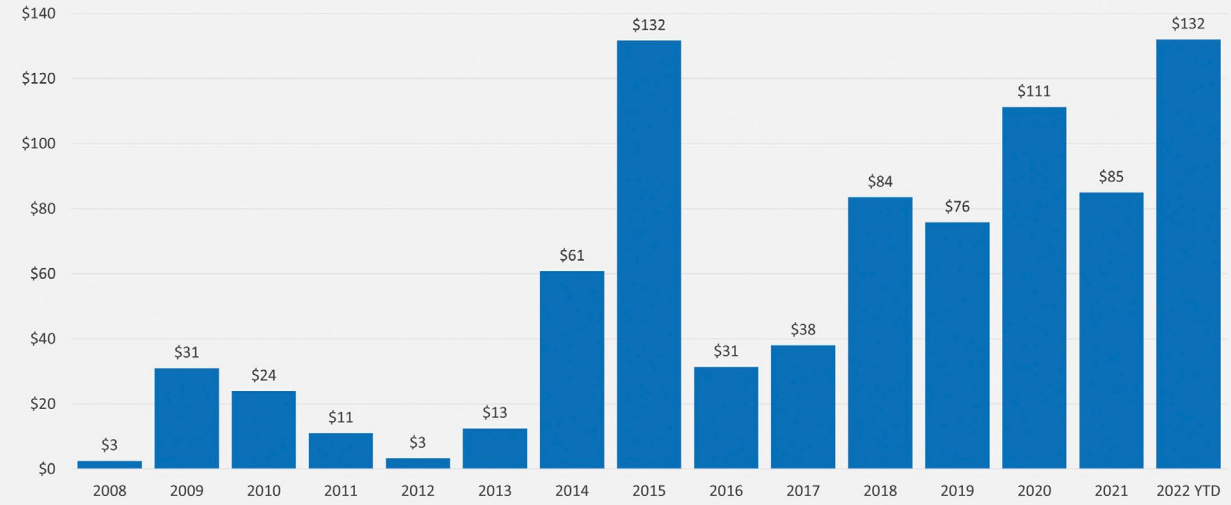
Upfront Cash and Equity from CGT Licensing Deals

Median Upfront Cash and Equity from R&D Partnerships in CGT ($M)



Source: DealForma.com Database. Financials based on disclosed figures. Data through 11/8/2022

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Deals in the remaining second half of 2022 and into 2023 could center on the need for acquirers / licensees to address operational challenges, scale and efficiencies, boosting distribution channels, strengthening their ability to source active pharmaceutical ingredients or provide manufacturing for innovative CGTs. Various drivers have motivated biopharmaceutical companies to make significant investments, or in many cases, acquire or collaborate to develop the necessary manufacturing capabilities.

Final Thoughts

Few technologies in the life sciences sector hold as much promise as CGT. Rather than just treating a disease and its symptoms, this technology can target the underlying cause, with long-term benefits and curative potential. Significant investment and deal energies are being put forth to drive the sector. The key point for consideration is that the companies are anticipated to be well placed for the next wave of innovation. Now is a great time to invest in the future.

The Role of Institutional Biosafety Committee in Gene and Cell Therapy Research

Submitted by Raffaella Hart, Senior Vice President, IRB, IBC, & QA, Biomedical Research Alliance of New York (BRANY)

It's an exciting time to be a researcher in gene and cell therapy. Advances and innovation in this area of research have led to exciting breakthroughs across disease states in cardiology, immunology, oncology, and other fields. It has led to the realization of the long-sought holy grail of personalized medicine.

Promising research in cell and gene therapy has accelerated over the last decade, bringing patients new hope for the treatment of cancer as well as rare diseases. Collaborations have led to unprecedented speed of the development of the COVID-19 vaccine, for example.

During this time of advancement for gene and cell therapy research, it is also important to remain cognizant of the federal guidelines and regulatory requirements associated with this type of research.

Get to Know the IBC Requirements

NIH guidelines require Institutional Biosafety Committee (IBC) review when NIH is funding research involving recombinant or synthetic nucleic acid molecules, or such research is conducted by an institution that receives NIH-funding. The IBC is responsible for ensuring that the research will be conducted in compliance with the provisions of the *NIH Guidelines.*

An IBC is responsible for assessing the biosafety containment level for research involving recombinant or synthetic nucleic acid molecules or human gene

transfer, as well as hazardous biologics. The IBC reviews and confirms that potential biological hazards have been identified and that appropriate controls are in place.

The guidelines may also pertain to the sponsor in some cases when NIH-funding is involved. There are several public-private partnerships, such as NCATS and the Bespoke Gene Therapy Consortium, that brings together NIH, FDA, multiple pharmaceutical and life sciences companies, nonprofit and other organizations with a goal to speed the development and delivery of customized or "bespoke" gene therapies to millions of patients affected by rare diseases.

California's life sciences sector received $5 billion in funding from the NIH in 2021, according to the annual report by California Life Sciences.

Biosafety guidelines set policies, rules, and procedures necessary for personnel working in various facilities that handle biological agents.

According to a report by the American Society of Gene and Cell Therapy, there are more than 3,500 therapies in development from preclinical through preregistration. According to a report[1] from the Alliance for Regenerative Medicine, the cell and gene therapy sector raised $17.6 billion in investment in 2021, a 53 percent increase in investments from the previous year.

BRANY is a national organization providing a continuum of compliance support services to investigators, hospitals, universities, academic medical centers, biotech, pharmaceutical and medical device companies.

The FDA continues to seek ways to partner with industry to accelerate the development of these therapies. They plan to launch a new pilot program in April 2023 that addresses chemistry, manufacturing, and controls (CMC) readiness. This has been an ongoing challenge in the industry. The pilot program seeks to increase and improve communication between FDA and sponsors.

Safety concerns continue, however, and regulatory agencies continue to actively monitor the issue. Just this month, the FDA released guidelines[2] regarding *Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial.*

According to the guidance, "Although multiple versions of a product can be studied together in a single clinical trial, each version of the product is distinct and is generally submitted to FDA in a separate investigational new drug application (IND). The objective of these early-phase clinical studies is to guide which version(s) of the product to pursue for further development in later-phase studies."

Cell and gene therapy has been shown to have an enormous impact when effective, and the potential to develop future cell and gene therapy products seems limitless. It is paramount that these products be developed and tested while keeping people, and communities safe. ■

1 https://alliancerm.org/sector-report/2021-annual-report/
2 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/studying-multiple-versions-cellular-or-gene-therapy-product-early-phase-clinical-trial

Advancing Cell and Gene Therapies Through Closed Aseptic Processes

Submitted by FUJIFILM Diosynth Biotechnologies

Time is of the Essence

The U.S. Food and Drug Administration has approved 25 cell and gene therapies (CGTs) since 2017 but predicts that by 2025 it will license as many 20 new treatments per year. That prediction may be an under-estimate, as CGTs become "industrialized" through the application of allogeneic cells and platform processes and through the expansion of treatable disease states. With more than 800 cell or gene therapies at the IND development stage, pipelines are now at full capacity, but sponsors still rely on outdated production methodology borrowed from therapeutic protein processes.

No one anticipated the speed at which CGTs would capture our collective interest. To support this rapid growth, best-in-class CDMOs are investing in development and manufacturing technologies to meet the needs of rapidly-emerging development programs.

FUJIFILM Diosynth Biotechnologies is a global CDMO focused on advancing tomorrow's medicines through leading-edge technologies, trusted partnerships, globally integrated facilities, and contributing to building and nurturing a skilled STEM workforce.

The industrialization of CGTs will require deep appreciation of the biological roles of key components, including advanced viral vector production technologies and adoption of allogeneic cell therapies to achieve scalability.

Viral Vectors

FUJIFILM Diosynth Biotechnologies (FDB) stays ahead of the manufacturing technology curve by collaborating with innovators on novel unit operations and by providing clients with flexible, modular manufacturing located near clinical development sites.

Viral vector production, which supports all gene therapies—including many development-stage vaccines—and most cell-based treatments, was until recently a "black box" capability based on a limited number of production platforms with poor scalability.

FDB employs a flexible, streamlined, scalable, highly-productive "triple-transfection" approach to viral vector product manufacturing that saves both time and cost, with appropriate concern for the scarcity and value of cell-based components (e.g., harvested cells). Typical projects take weeks from sequence to preclinical-grade material and several months for cGMP production.

Advanced Aseptic Processing

Lessons learned from therapeutic protein manufacturing, particularly for cell culture-based processes (which routinely achieve zero in-process bioburden), have enabled FDB to apply single-use strategies to most CGT processes and production steps. Single-use technology avoids process bottlenecks associated with clean-in-place sterilization, while eliminating cross-contamination of infectious or patient-related materials.

As a global CDMO, FUJIFILM Diosynth Biotechnologies currently operates at seven locations in the US, UK and Denmark, including a well-established, 90,000-square-foot cell therapy facility in Thousand Oaks, California, acquired in 2022. Through these facilities we engage with clients and technology innovators to bring the promise of C&GTs to patients worldwide.

But perhaps the most significant success for our company has been early adoption of closed, aseptic processing for cell-based processes at our global CGT facilities located in College Station, Texas; Darlington, United Kingdom; Watertown, Massachusetts; and Thousand Oaks, California.

Recognizing the unique sterility requirements of cell-based therapies and their susceptibility to degradation, the FDA encourages companies to utilize closed manufacturing for these products. Unlike small molecule drugs, biologics and especially CGTs cannot withstand terminal heat- or chemical-based sterilization.

Closed, aseptic processing assures sterility throughout the process but involves additional investments in process development, engineering, automation and equipment standards. In return, benefits include greater process scalability, robustness, flexibility, and consistency with fewer batch failures. Long term, these advantages lead to lower capital and operational costs, and ultimately, greatly expanded access to critical therapies for patients. ■

Acceleration of Cellular Therapy at Janssen

Submitted by Johnson & Johnson Innovation

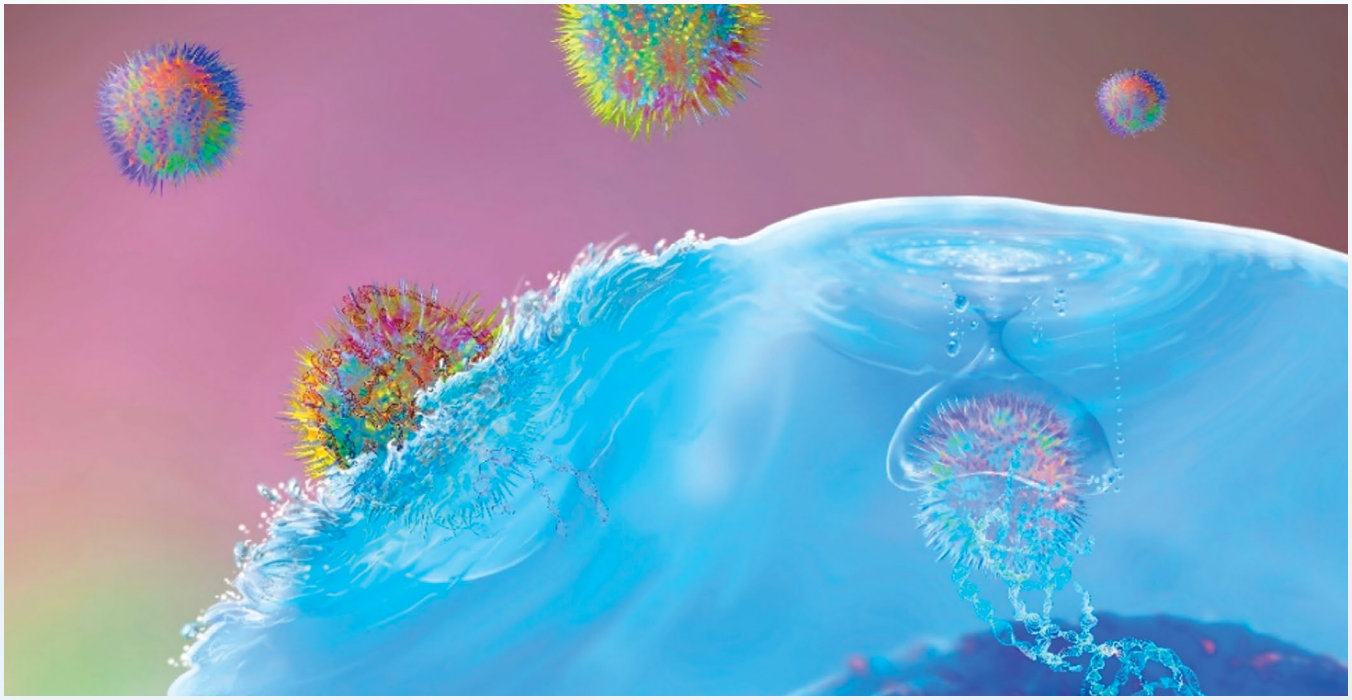


Illustration: CART-T cell immunotherapy

The year 2017 marked a key achievement in cancer immunotherapy with the FDA approval of Kymriah for the treatment of Acute Lymphoblastic Leukemia. Since then, five more autologous chimeric antigen receptor (CAR)-T cell therapies have been approved. Autologous cell therapy genetically engineers one's own immune cells, weaponizing these cells with a CAR, and like a trained assassin, these cells target and kill cancer cells with precision. The high-curative potential of cellular therapy has given patients with hematologic cancers renewed hope and a real possibility for longer remission and survival.

However, autologous CAR-T cell therapy is not without its challenges. This therapy is complex to manufacture. CAR-T is a "living drug" with a patient's immune cells extracted from the blood, re-engineered with a CAR, and then infused back to the patient. The vein-to-vein time often takes several weeks. This process can only be done in specialized manufacturing locations, with an individualized approach on each patient's immune cells to create a personalized therapy taking time, thus, sometimes limiting patient accessibility and leading to an increase in treatment cost. Additionally, current approved therapies only treat hematologic cancers, and none exist for solid tumors. Companies, like Janssen, understand these challenges and strive to make cell therapy accessible, affordable, effective, and safe in a variety of cancer types.

Accelerating Janssen's Leadership in Cellular Therapy through External Innovation

In efforts to advance Janssen's cell therapy portfolio, Janssen is investing in next generation, "off-the-shelf" cell therapy approaches. In 2020, Janssen entered a strategic collaboration with Fate Therapeutics, a California-based company, to develop CAR products that avoid the manufacturing complexity of autologous cell therapy. Rather than repeat the manufacturing process for each patient, Fate Therapeutics' technology enables a one-time re-engineering of a master cell line known as induced pluripotent stem cells (iPSCs), which can be used to generate immune cells, including T-cells and Natural Killer (NK) cells. This collaboration synergizes Janssen's proprietary antigen binders with Fate's iPSC platform to develop CAR-T and CAR-NK products, which can potentially be expanded indefinitely and provide unlimited product supply. This is an example of how external strategic partnerships have allowed Janssen to leap-frog into next generation cell therapy. Janssen is also advancing antigen targets for cellular therapy in solid tumors. In November 2022, Johnson & Johnson Innovation – JLABS in Toronto, in coordination with Janssen, partnered with Centre for Commercialization of Regenerative Medicine in hosting a symposium to explore recent approaches to hematologic malignancies, and innovations in the solid tumor space, as well as effective industry-academic collaborations to accelerate innovation, investment, commercialization, and capacity-building for manufacturing the next generation of innovative medicines.

While the collaboration with Fate Therapeutics focuses on the immune cell type (i.e., T-cells, NK-cells) for the CAR product, Janssen's recent collaboration with Serotiny, another California-based company located at the Johnson & Johnson Innovation – JLABS in South San Francisco, focuses on the CAR design itself– making the best "weapon" for the immune cell to be an efficient tumor killer. A CAR designed for a T-cell is unlikely to work with the same effectiveness in an NK-cell. Therefore, a CAR needs to be tailored for the immune cell and possibly the tumor type. A CAR is a very complex protein with multiple components and a capability is needed to screen tens of thousands of CAR configurations in immune cell environments. Janssen will leverage Serotiny's high-through screening platform to identify the novel CAR designs at scale to optimize tumor targeting and killing. This collaboration with Serotiny illustrates another example of how Janssen's strategic partnerships with external innovators continue to push the boundaries of next-generation cellular therapies with the goal of saving the lives of cancer patients.

Working in partnership with Johnson & Johnson Innovation, Janssen will continue to accelerate innovation through strategic collaborations that synergize with internal expertise and capabilities and maintain its position at the leading edge of next generation cellular therapy.

As cellular therapy gains momentum, Janssen has constructed a portfolio balancing staged, external collaborations to complement and synergize with its internal R&D efforts. This balance between internal and external innovation has positioned Janssen as a leader in cell therapy with an approved cell therapy product in less than 10 years. Working in partnership with Johnson & Johnson Innovation, Janssen will continue to accelerate innovation through strategic collaborations that synergize with internal expertise and capabilities and maintain its position at the leading edge of next generation cellular therapy. Johnson & Johnson Innovation will continue to explore how the life science ecosystem can collectively drive the development of cell and gene therapies and bring potential innovations to patients more efficiently, in furtherance of Janssen's commitment to strive toward the elimination of cancer. Cellular therapies will play an important role in that future vision.

Challenges to Reimbursement for Cell and Gene Therapies for Payers Like Medicare

Submitted by Arnold & Porter

Cell and gene therapies (CGTs) represent tremendous scientific advancements for serious conditions and have upended how many diseases are treated and, in some cases, cured. Often indicated for small patient populations, CGTs can be incredibly expensive, costing hundreds of thousands of dollars for a single treatment, and resource intensive. Accordingly, by their very nature, CGTs present unique reimbursement challenges, particularly for payers like Medicare.

Significantly, the Centers for Medicare & Medicaid Services (CMS) lacks the flexibility of other payers in that it is constrained by the Medicare statute, which structures the program based on benefit categories, settings of care, and associated payment systems, making it difficult for Medicare to keep pace with improvements in medical care and innovative therapies such as CGT. Recent treatments, such as chimeric antigen receptor (CAR) T cells, serve as an instructive example of how payers like Medicare have approached reimbursement, and in some cases, adapted its policies to address CGTs while working within the confines of its authorities.

To date, the hospital has been the primary setting where gene therapies such as CAR T have been provided under Medicare. The applicable setting (inpatient vs. outpatient) is often driven by factors such as the severity of potential adverse events and required length of observation stay, which in turn, impact Medicare payment. Similarly, depending on the payment methodology, the type of administration procedure can affect whether Medicare pays separately or packages the payment into a procedure. Initial CGTs required inpatient monitoring, making the inpatient hospital setting the operative payment system for CMS to first tackle reimbursement.

Generally, the Medicare hospital inpatient payment system is not well designed to reflect high cost, low volume technologies, because Medicare makes one comprehensive, prospectively determined payment per stay (inclusive of therapies and drugs) based on a patient's diagnosis and assignment to a Diagnosis Related Group (DRG). The system is not intended to cover any given hospital's costs; rather, it is designed to

incentivize hospitals to operate efficiently in furnishing quality care and minimize unnecessary costs. This presents challenges for new therapies like CGTs existing DRGs are based on existing therapies and thus may not be reflective of new high cost items. Indeed, the initial DRG assignment for CAR T therapy had a payment amount far lower than the high price tag for the treatment. After collecting sufficient cost data, CMS eventually established a new Medicare Severity-DRG (MS-DRG 018) specific to CAR T and "other immunotherapies" (*i.e.*, to capture other cell therapies under CMS' pre-major diagnostic category grouping logic) and significantly, used a different methodology to develop the relative weight in a way that was significantly higher than usual, ensuring greater reimbursement.

...Medicare makes one comprehensive, prospectively determined payment per stay (inclusive of therapies and drugs) based on a patient's diagnosis and assignment to a Diagnosis Related Group (DRG).

Medicare's inpatient hospital system does build in other adjustments for added payment, as applicable, including outlier payments to help cover extremely costly cases and new technology add-on payments, the latter of which is based on the satisfaction of certain criteria regarding newness, cost, and substantial clinical improvement. Even when available, however, such adjustments may not make hospitals whole and for new technology add-on payments, are temporary.

As more high-cost CGT innovations come to market and potentially apply to larger patient populations and shift to other sites of care like outpatient hospital settings, payers like Medicare will continue to navigate reimbursement. Changes in reimbursement are likely to lag behind therapeutic innovations, and CGT companies may want to better understand current payment systems to identify ways to prepare those systems to accommodate new technologies. ■

How *In Vivo* Genetic Medicines have the Potential to Expand Patient Treatment Options

Submitted by Abintus Bio, Inc.

For genetic medicines to have maximal patient impact, they should be designed to engineer cells directly from within a patient's body.

Many of the advances in genetic medicine have focused on taking cells outside the human body (*ex vivo*), manipulating them, and subsequently putting these now therapeutic cells into a patient. While some genetic medicines, such as *ex vivo* CAR-T, are curative in some patients, they are cost prohibitive, inconsistent, and may cause debilitating toxicities. When cells are removed from their normal environment and then subject to extensive processing, they can lose important functions including their intended therapeutic effect. Furthermore, *ex vivo* immunotherapies, like CAR-T, require depletion of patient's own immune cells prior to treatment, which can result in significant side effects including the risk of life-threatening infections. Given the complexities of *ex vivo* procedures, patient access is mostly limited to leading academic hospitals that can support the administration and management of these complex therapies. In addition, the cumulative price tag for using these therapies can be over one million dollars, and the patient's share of those costs can be prohibitive. In contrast, genetic medicines that are available as an off-the-shelf, product-in-a-vial administered with a simple injection, have the potential to meet the needs of patients, caregivers, and other key stakeholders. These "*in vivo*" genetic medicines are poised to address the current challenges associated with *ex vivo* therapies and have the potential to expand treatment options for patients (Figure 1). There are three key criteria for successful *in vivo* genetic medicine:

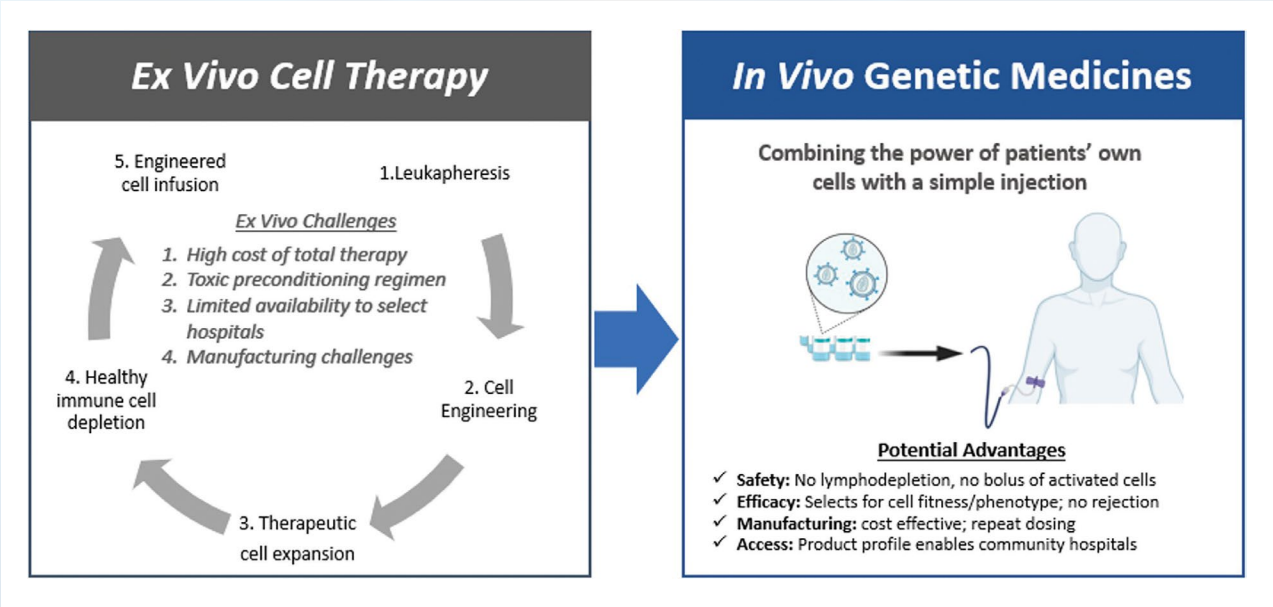


Figure 1. Comparison of current *ex vivo* cell therapies versus the potential of *in vivo* genetic medicines. *Ex vivo* therapies require harvesting of cells from patients or healthy donors (1. Leukapheresis) and then processing outside the body under synthetic conditions that may reduce the fitness of the engineered cells (2. Cell engineering). Engineered cells are then artificially expanded to achieve the required dosing (3. Cell expansion). This step further reduces cell fitness and cell can lose effectiveness. Before therapeutic cells can be injected, patients must undergo chemotherapeutic depletion of their healthy immune cells (4. Cell depletion). Only after these steps can the engineered cells then be injected into the patients (5. Cell infusion). Conversely, *in vivo* genetic medicines involve delivery vehicle injection and subsequent engineering of patient cells directly within their body to make cells with therapeutic activity. This approach has the potential to improve safety, efficacy, manufacturing, and increase patient access relative to *ex vivo* approaches.

1. The ability to deliver the therapeutic gene or genes to patient cells of interest directly inside the patient. There are many approaches to engineer therapeutic cells, but few approaches have actually been evaluated directly in humans or have demonstrated successful gene delivery directly *in vivo*.
2. The delivery system must be safe and well tolerated and enable repeat intravenous administration. Companies must overcome significant challenges to be able to inject their products directly into patients, including requirements of high product purity, avoiding strong immune reactions, low toxicity, and long-term safety.
3. For intravenous delivery, the gene therapy product must be consistently manufactured at concentrated dose, high purity, high stability, and at commercial scale with a low cost to meet the needs of patients globally. This requires development of a manufacturing process that, to date, has only been accomplished by a few highly specialized groups and remains a significant barrier to many others.

Several companies are currently pursing *in vivo* genetic medicines using varying delivery vehicles, routes of delivery, and mechanism of therapeutic action. For all approaches, the three key criteria outlined above will be important and challenging milestones to achieve. Abintus Bio is pioneering the advancement of a next generation delivery vehicle that leverages important lessons and setbacks from more than 20 years of prior technology advancement, nine clinical trials involving direct injection including intravenous administration, and commercial-scale manufacturing processes. Key insights from these prior experiences include safety, tolerability, gene delivery, clinical trial operations, biomarker studies, manufacturing, and regulatory. Importantly, successful *in vivo* engineering of immune cells was observed in patients following intravenous injection of a delivery vehicle similar to Abintus'.

Abintus Bio is pioneering the advancement of a next generation delivery vehicle that leverages important lessons and setbacks from more than 20 years of prior technology advancement, nine clinical trials involving direct injection including intravenous administration, and commercial-scale manufacturing processes.

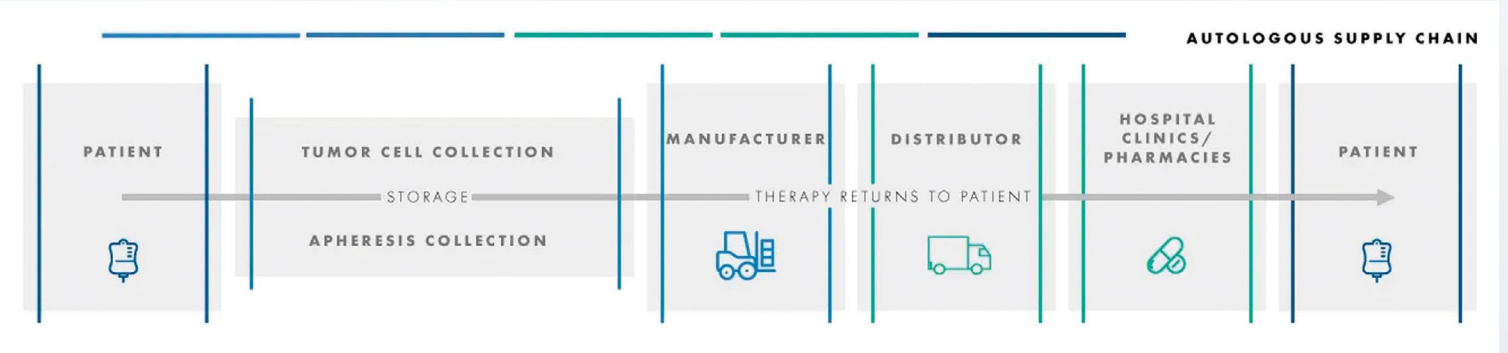
While Abintus' clinically-proven delivery vehicle and related technologies meet the three key criteria for successful *in vivo* applications, key challenges remain, including understanding therapeutic thresholds related to the number of cells engineered *in vivo*, the type of cell(s) engineered *in vivo*, and the therapeutic payloads delivered. *In vivo* genetic medicines, such as those being advanced by Abintus, represent an exciting new therapeutic modality that offers new hope to meet the needs of patients, including those in underserved communities. ■

Simplify The Supply Chain for Your Cell Therapy Products

Submitted by Susan Shockey, Principal Quality Systems Consultant, Clarkston Consulting

The field of personalized medicine has grown significantly in the past seven years. In fact, personalized medicine now accounts for more than 25% of drugs the FDA has approved since 2015.

One subset of this group is autologous cell therapy products, which use the person's own cells to generate their therapy. This process involves a complex and time-sensitive supply chain to obtain the cells from the patient, transport the cells to the manufacturing facility, modify the cells, transport the cells back to the patient, and reintroduce the cells into the patient's body. However, complexity is reduced when the cells are cryopreserved during storage and transport.



Cell Therapy Products

Clarkston Consulting received three recent cell therapy product submissions, and the FDA's response to differences in approaches to supply chain were notable.

Utilization of refrigerated cold-chain storage requires that every step is highly time- and temperature-sensitive. The FDA's concerns for use in these refrigerated conditions (2-8°C) centers around cell stability during shipments of varying duration and temperature. Any delays or changes to the plan could cause a loss of product viability.

Notably, the FDA had *far fewer* pre-approval questions for products that are cryopreserved. The use of cryopreservation provides increased product stability and viability of cells, which makes the supply chain more adaptable to unforeseen circumstances.

Shipment tracking with temperature monitoring is standard in all cases, but the shipment timing is critical for unique cell therapy products due to the need to coordinate the many activities of the complex supply chain. A robust courier management process is critical to control transport requirements. Any breakdown in the cold-chain process, such as temperature monitoring or shipment duration, needs to be monitored and responded to due to a ripple effect in the remainder of the treatment process.

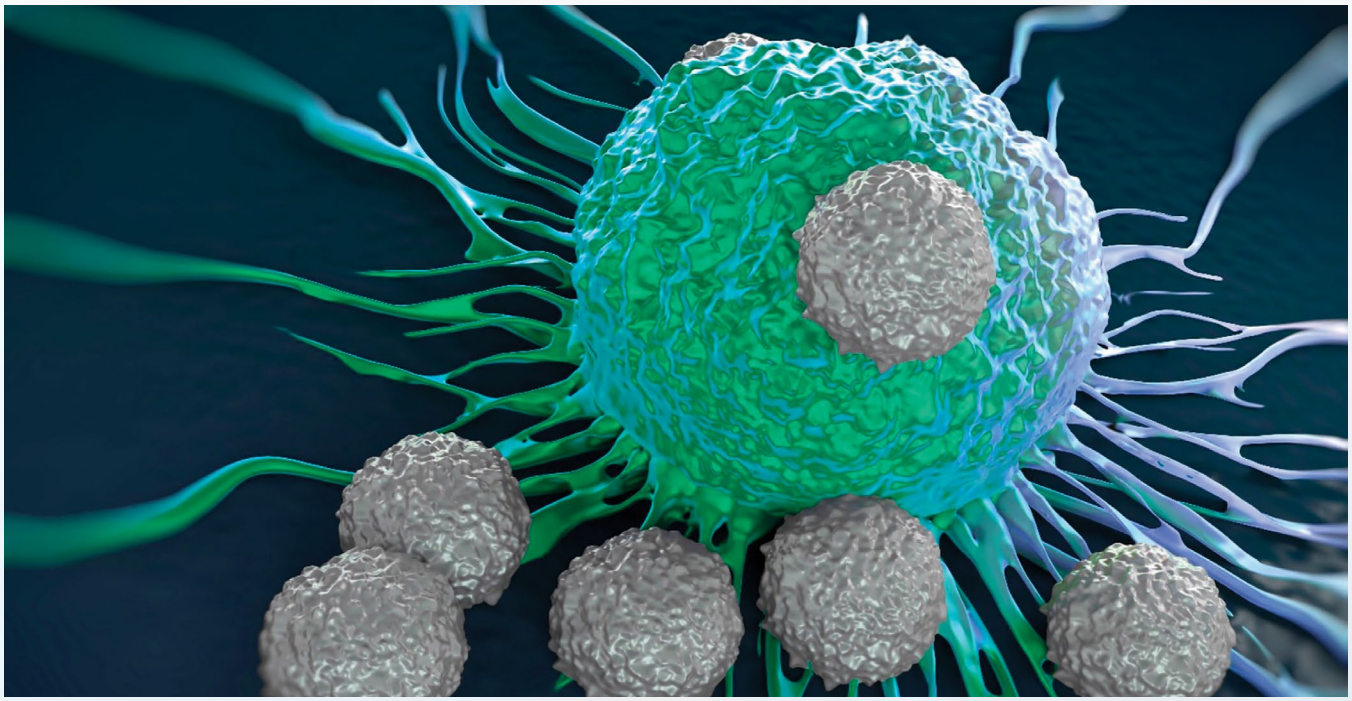
Implementing Technology Solutions

The cell therapy landscape is complex and fast-moving. Companies need to implement strategies, processes, and technologies that can enable them to effectively manage their cell therapy products supply chain in an integrated way – from monitoring and tracking couriers for cold-chain tracking, to managing event timing, to coordinating production and product management.

Clarkston Consulting's Cell Therapy Orchestration Platform (CTOP) was designed to meet this need and built on the SAP S/4HANA platform. CTOP provides a multitude of benefits beyond the control of the supply chain and aims to simplify the processes associated with cell therapy supply chains and provide a single platform to manage integrated and collaborative communication with stakeholders. ■

Synthetic Biology Can Enable the Development of Next-Generation Cell and Gene Therapies

Submitted by Emily Leproust, Ph.D., CEO & Co-Founder, Twist Bioscience



When envisioning revolutionary solutions needed to advance cell and gene therapies through to commercialization, the full discovery, optimization, and development process needs to be examined, evaluating when and where solutions can be put into place. Offering a wide range of tools and services, and relevant to both COVID-19 vaccines and therapeutics, synthetic biology and next generation sequencing (NGS) applications can be used during the discovery phase to enable candidates to overcome hurdles faced by cell and gene therapies further down the road in the development and commercialization process.

Lack of ideal cell models is a hurdle faced by developers working in cell and gene therapies. Induced pluripotent stem cells (iPSCs), which can be turned into any human cell, have the potential to overcome the bottlenecks of primary cells or tumor-derived cell line models. In theory, they could be an unlimited source of cells for different mature cell types as ideal cell models for cell and gene therapies. However, the process of differentiating iPSCs into desired cell types relies on the addition of growth

factors as extrinsic signals in a petri dish, which limits the scalability. With synthetic biology, a new process has been developed to incorporate transcription factor genes into iPSCs. The over-expression of the transcription factor inside the cells as intrinsic signals provides direction for the iPSCs to develop into desired cell types with high scalability, purity, and consistency. Twist manufactures synthetic DNA at scale by "writing" DNA on a silicon chip that allows for the production of one million oligonucleotides (oligos) at a time, compared to other approaches that use a 96-well plate and produce 96 oligos at once. This enables Twist to produce thousands of genes at a time, compared to a handful. With the scale and speed of gene production, Twist can make transcription factor genes readily available to researchers, enabling rapid development of cell models for gene therapies.

Manufacturing oligos at scale can also help to further research. Pools of oligos can be used to create single guide RNA (sgRNA) and dual guide libraries at scale. One of the ways that researchers use sgRNA libraries is by loading sgRNA into Cas9 proteins to conduct CRISPR screens that alter the sequence or expression of genes. This accelerates the discovery and validation of novel disease targets for drug development. To unlock new drug targets through successful screenings, it is essential to have sgRNA libraries with low error rates and high uniformity. Libraries can be skewed by non-uniform synthesis of oligos and by multiple cycles of PCR amplification. Oligo pools manufactured in the same batch have high uniformity, which is maintained during PCR amplification and can be used to create high quality sgRNA libraries.

When developing cell and gene therapies for patients, it is important not only to find disease-related targets, but also to find targets relevant to a patient's specific form of cancer. Tools for next-generation sequencing (NGS) can be used to sequence a tumor and identify targets relevant to that patient's cancer. These targets can be used to determine the best therapeutic approach for the patient.

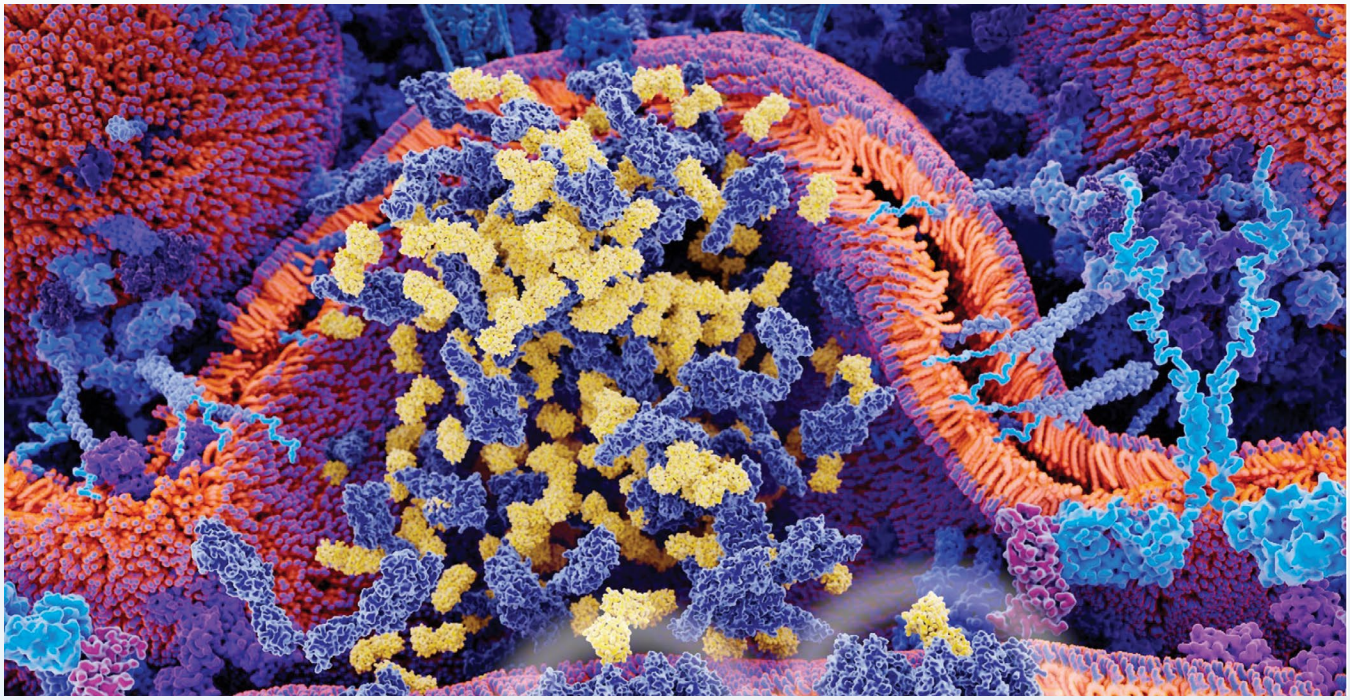
Even with the right targets, cell and gene therapy approaches can face challenges with off target effects. A way to overcome this is by selecting candidates that are highly specific. With unlimited synthetic DNA, Twist can create specific antibody libraries containing up to 10 billion antibodies. These libraries can be used to discover antibodies against specified targets for various therapeutic approaches. Custom TCR and CAR-T libraries can also be created using synthetic DNA. TCR gene parts (plus antibody parts for CAR-T) made up of sequences that occur naturally in the human body can be synthetically manufactured and shuffled to create novel constructs for cell and gene therapy candidates. These highly specific libraries enable drug developers to select and advance the best candidates, which are more likely to overcome challenges faced by less specific antibodies.

With unlimited synthetic DNA, Twist can create specific antibody libraries containing up to 10 billion antibodies. These libraries can be used to discover antibodies against specified targets for various therapeutic approaches.

Access to unlimited DNA enables researchers to identify relevant targets and create libraries specific to those targets that can be screened for precision candidates. This allows them to treat a specific cancer using a precision medicine approach and to repeat the process for new forms of cancer. Oligos manufactured at scale can be used to support research by relieving bottlenecks such as reprogramming iPSCs and creating sgRNA libraries, freeing up scientists to focus on advancing research for next-generation cell and gene therapy approaches. ■

Looking to the Future of Cell Therapy

Submitted by Bristol Myers Squibb



One of the greatest scientific breakthroughs of the last decade has been researchers' ability to harness the power of the immune system to treat cancer, resulting in the discovery and development of new modalities of medicines—from immune checkpoint inhibitors to cell therapies—that have transformed patients' lives.

In the five years since the first treatment was approved, cell therapy has upended the way some cancers can be treated, providing hope to patients and medical professionals around the world. While the first cell therapies were approved to treat specific patient populations with certain blood cancers, it is critical for industry leaders to continue to push the boundaries of what is possible with cell therapy.

As the only company with two approved chimeric antigen receptor T-cell therapies (CAR T) with two distinct targets to address separate blood cancers, Bristol Myers Squibb is drawing upon its transformative work and unparalleled experience in hematology and immuno-oncology. The company is pursuing opportunities to bring cell therapies—currently available on three continents—to more patients across disease states who may benefit while advancing early, cutting-edge research approaches in cell therapy.

One researcher leading the charge on next generation cell therapy approaches is Kristen Hege, M.D., senior vice president, Hematology, Oncology and Cell Therapy Early Clinical Development at Bristol Myers Squibb. Based in the San Francisco Bay Area, Hege and her team of physicians—many of whom are still practicing clinicians at the University of California San Francisco—along with clinical scientists, use translational insights

to shape clinical trials, guide biomarker strategies, and inform asset development.

The complexities of delivering autologous CAR T therapies are unlike any other traditional biologic or medicine due to the highly sophisticated and personalized manufacturing process in which a patients' own T cells are modified to recognize and bind to proteins found on the surface of cancer cells, while sparing healthy cells. The company continues to explore novel ways to make autologous CAR T cell therapies more efficient, scalable, and accessible through approaches such as allogeneic, or off-the-shelf, CAR T cell therapy.

Additionally, with its strategic partners, Bristol Myers Squibb is advancing early, cutting-edge research approaches in cell therapy that include dual antigen targeting CAR T approaches to help mitigate antigen heterogeneity or loss; CAR T cells armed with tunable, or custom, payloads aimed to overcome tumor microenvironment resistance; the use of sophisticated platforms to identify novel engineered T cell receptors (eTCRs) recognizing antigens found on the inside of cells that can be used to develop eTCR T cell therapies; and gene editing technology applications to enhance eTCR and CAR T cell selectivity, persistence, potency and "off the shelf" manufacturing platforms to increase access of CAR T to more people living with these cancers.

These future innovations may have the potential to bring the benefits of cell therapy to people with solid tumors or even other disease states.

"We are actively investigating how to bring cell therapy into the solid tumor space through our deep understanding of tumor biology, the immune system and by looking at a number of targets and approaches to optimize tumor trafficking and overcome the suppressive tumor microenvironment," Hege said.

Real-time insights are critical to developing next-generation cell therapies, and development and

manufacturing teams work closely together to use technology and automation to continually improve the process, assessing which new approaches can be translated from the lab to the manufacturing floor.

"It's critical to be able to analyze clinical data quickly and leverage impactful findings, as cell therapy is a fast-paced field," said Ashley Koegel, M.D., medical director of Early Clinical Development at Bristol Myers Squibb.

"It's critical to be able to analyze clinical data quickly and leverage impactful findings, as cell therapy is a fast-paced field," said Ashley Koegel, M.D., medical director of Early Clinical Development at Bristol Myers Squibb. "In my role as a clinical trial physician, I work to translate the scientific learnings of our clinical trials to our pipeline to improve the next generation of cell therapies that we bring into the clinic. Currently, we are working across teams to bring CAR T cell therapies to patients faster, more efficaciously, safer, and in a broader variety of disease indications."

Koegel and her team operate at the intersection between discovery, translational science and clinical drug development and collaborate with several of Bristol Myers Squibb's broader thematic research centers (TRCs), predictive sciences, and biosample operations.

Partnering across the ecosystem is essential to delivering truly life-changing medicines to patients. By continuing to focus on the innovation and discovery required to unlock the full potential of cell therapy, the scientific community can work to broaden access to care for patients everywhere.

Realizing the Potential of Cell and Gene Therapy

Submitted by Toby Blackburn, Head of Business Development and Strategy, Emerald Cloud Lab

Cell and gene therapies have exploded over the past decade, with 25 products approved by the FDA and more coming down the pipeline. However, there is still much to do before these therapies reach the mainstream due to multiple factors, including price, widespread lack of accessibility to these therapies, and the increasing gap between supply and demand of industry experts needed for development.

The vision of widespread commercial success is within reach. But fully realizing that vision, cell and gene therapies will require a dramatic overhaul of traditional research methods.

Addressing the Elephant in the Room

On average, cell and gene therapies can cost upwards of $3 million for a single treatment course. A significant portion of that cost is attributed to the extraordinary price tag of manufacturing and research and development (R&D) that happens behind the scenes. Drug development is an expensive process in general, with a median estimate of $1.1 billion to bring a drug to market. Cell and gene therapies are an entirely different, more specialized playing field given their custom-tailored approach to medicine. The average cost to bring a gene therapy to market skyrockets to a whopping $5 billion, as clinical and commercial manufacturing requires expensive raw materials and advanced equipment.

Another critical factor in the high cost of cell and gene therapy development is the shortage of skilled talent in multiple areas, from bioengineers to regulatory experts. This issue is further exacerbated by the burnout that researchers regularly experience in biotech–especially as scientists in a traditional lab spend 80% of their time at the lab bench and only 20% on new experiment development and data analysis.

While there are other complicated regulatory and economical components that tie into the hefty price tag of cell and gene therapies—for example, insurance coverage—addressing manufacturing and staffing will dramatically impact its overall trajectory. Ultimately, for cell and gene therapies to become more accessible to the public, more of the process needs to become automated, which will streamline production and lower costs.

The Future is in Automation

Though cell and gene therapy (CGT) development is significantly more specialized than development of small molecules or biologics, there is still ample opportunity to accelerate key components of CGT manufacturing through automation.

That is the vision of cloud-based laboratory providers—highly-automated, secure, and centralized research labs that allow scientists to run daily experimentation by a computer from anywhere in the world. Though cloud labs already contain hundreds of instruments needed to run most experiments, the next frontier to improve CGT access should be dedicated to automating cell culture. Examples include incubators, robotic multi-parallel bioreactors for smaller experiments, and large bioreactors to assist in manufacturing therapies at scale.

That is the vision of cloud-based laboratory providers—highly-automated, secure, and centralized research labs that allow scientists to run daily experimentation by a computer from anywhere in the world.

Not only does automating key components of CGT development help streamline the manufacturing process, but it can also serve as a perk for skilled researchers currently experiencing burnout. With the power to automate experiments, researchers can save precious time focused on scientific breakthroughs and less time on experiment execution and replication.

Making the Future a Reality

Right now, the process of developing cell and gene therapies is complex, timely, and incredibly expensive. The writing is on the wall—manufacturers are beginning to implement automated processes at earlier stages of development of cell and gene therapies, which will accelerate timelines, lower costs, and get treatments into the hands of more patients who need them most. And one day, through the power of cloud labs, researchers will be able to develop these therapies from anywhere in the world and at any time. ■

Embracing Challenges Spurs Innovation

Submitted by David Sheehan, Founder, President & CEO, Nucleus Biologics, LLC, Stoic Bio, Inc.

We operate during a transformational inflection point for human health. The biologics market now makes up a full 40% of the pharma development pipeline. The era of pharmacies dispensing medications will be converted to autologous or allogeneic cell and gene therapies that can be delivered in a hospital or clinic. These treatments leverage the ingenuity of cells to reprogram them to kill cancer or accept healthy genes that will cure disease. As we endeavor to push these biologic-based cures out, we must accept a few things:

Embracing Entropy

With tens of thousands of known diseases and a myriad of pathways and cell and gene attributes to manipulate, the industry will explore an expanding number of solutions to solve disease. Each approach will be manufactured in a unique ecosystem. The idea of standardization is anathema to innovation. This is a healthy and evolutionary process. We should all embrace that the pace of innovation will increase, and the breadth of enabling technologies will also. Given all these variables, you need to closely control everything in your ecosystem that is affecting cell growth. At Nucleus Biologics, we developed NB-AIR to allow scientists to leverage its AI engine to scrub Pub Med and create an optimized media formulation based on a meta-analysis of peer-reviewed literature.

Being Transparent

The business models of the prior generation were focused on gaining advantage or control over customers by withholding data or creating proprietary solutions. That was acceptable when the customer was growing cells in a dish or plate in a lab for research. It is ill-suited to the needs of pharma and biotech when they are trying to culture biologics that will be injected into humans. We should almost think about transparency as a fourth dimension. To truly understand what is going on with your cells, you must be able to know everything in your ecosystem, including cell culture

media, and have visibility throughout the supply chain for that product. Growing biologics is complicated, so that visibility is critical. Nucleus created NB-Lux which allows users to order custom cell culture media and get a real-time specifications sheet that includes a list of components, their grades, purities, and concentrations.

We Are Racing a Clock

All of the 2,000 clinical candidates making their way through the cell and gene therapy pipeline will want to get a readout as soon as possible. Many will never make their way into the market. But there will be valuable lessons learned from all the failures. The key for therapy developers is to get to that first clinical readout fast. As a media supplier to the industry, Nucleus is at the bottom of an inverted pyramid where the patient is at the top—and the clock is running out for them. They sit above the physician who is dependent on the therapy developer who is dependent on their suppliers. Moving fast is ill advised in a regulated industry, therefore it's critical to learn how to be more efficient in getting quality solutions to the patient, because their lives depend on it. We have learned to LEAN even more of our manufacturing and quality processes than we thought possible this year, as we sought certification and underwent numerous facilities audits.

Consistency and Resilience is as Important as Cost

The solutions we develop must thread the needle on cost, consistency, and resiliency. The COVID-19 vaccine moonshot was a great example of what an entire industry can do with focus. But it also pointed out the weaknesses of our supply chain. Many customers were left stranded because industry capacity was required to support vaccines. With many cell therapies costing $300 thousand or more, and gene therapies in the millions of dollars per patient, we need to create simpler or LEANer workflows. We need to have solutions that allow customers to own more of their supply chain and have technology solutions that allow them to be delivered quickly. This year, Nucleus Biologics and its sister company, Stoic Bio, launched Krakatoa™, the first point of use media manufacturing system in the world. Now customers can store formulas in powdered form in pods that can be stored and shipped at room temperature. This eliminates the major costs of shipping and storing liquid, as well as the obvious shelf-life limitations.

We need to have solutions that allow customers to own more of their supply chain and have technology solutions that allow them to be delivered quickly.

We Can't Forget the Environment

The pharma industry has a bigger carbon emission footprint than the auto industry. That we have the intelligence and creativity to modify human biology to heal itself is incredibly powerful and profound. But we cannot lose sight that generational extension of life cannot be to the detriment of future generations. Every major pharma company has an ESG initiative with clear goals. Our solutions must help pharma achieve those environmental goals. At Nucleus and Stoic Bio, we take this mandate very seriously and are working closely with organizations like My Green Labs and others to get more environmentally sustainable solutions into the market.

We can and will speed the time from discovery to cure. The best is ahead.

How One Startup is Using Innovative Cell Therapy Manufacturing Methods to Lower Costs

Submitted by CellFiber Co., Ltd.

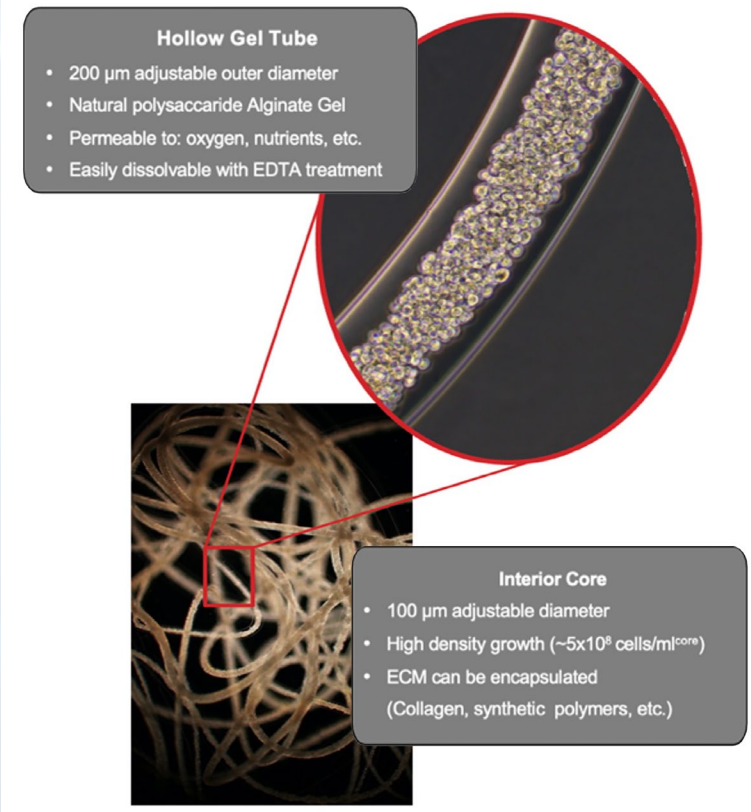
Cells as medicine is rapidly becoming a reality. Soon, these methods could lead to a new solution to cure cancer, heart failure, liver failure, respiratory failure, and many other unmet medical needs. Unfortunately, there is a significant obstacle to widespread cell therapy--the cost. Without game-changing technology, these new solutions may possibly remain unaffordable therapy to patients for another 5 to 10 years. CellFiber Co. Ltd. aims to reduce manufacturing costs for cell therapy to make it an affordable option for drug development and, ultimately, affordable medication for patients.

Why exactly are cell therapy products so pricey? As cells are very sensitive material, it is not easy to scale up. Unlike small molecule medicines, a slight change in manufacturing methods has negative effects on cell comparability. Since developing scaled-up manufacturing methods and maintaining cell comparability at the same time is technically challenging, when added to the overall financial burden, many pharmaceutical companies have no choice but to choose small-scale manufacturing methods for mass production. This has resulted in millions of dollars in additional cell therapy development costs.

What is the CellFiber Technology?

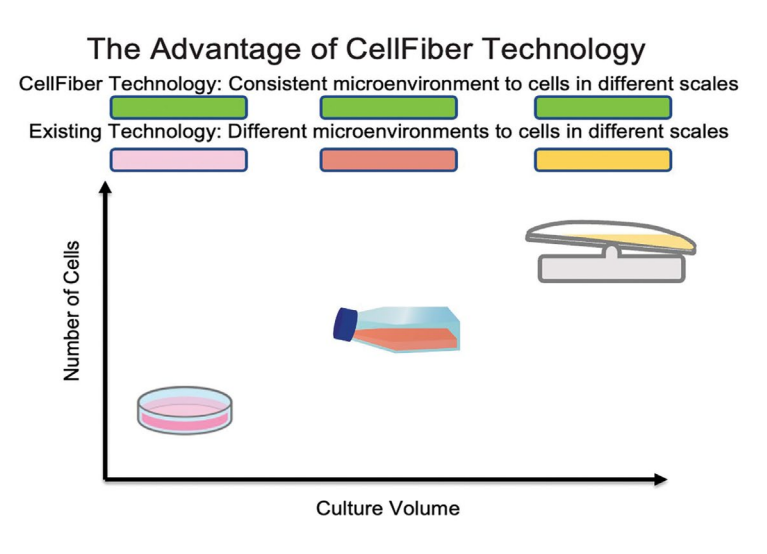
CellFiber's technology consists of a porous, hollow, and uniform gel tube that encapsulates the cells.

Hollow Gel Tube Technology for Extraordinary Cell Growth



The tube or the fiber is just hundreds of micrometers in diameter. Cells are encapsulated in the fiber and then cultured in a standard bioreactor, such as a rocking bioreactor, to achieve high rates of cell expansion. The

microenvironment for cells inside the fiber is maintained stable regardless of the outside environment. This means, even with the change in manufacturing methods, the influence on the actual cells is kept to a minimum. With CellFiber's proprietary technology, pharmaceutical companies can develop culture methods in flasks and scale up with ease without sacrificing cell comparability.



"I believe our technology can be a solution to difficulties that all cell therapy product developers face," said Yu Yanagisawa, Ph.D., CEO of CellFiber. "During the past year, we have been proving to clients that CellFiber technology works for a variety of cell types such as iPSCs, T cells, NK cells, MSC, etc.. CellFiber's process is applicable to both floating and adherent cells. I believe our technology has the potential to be a platform technology in the market. And now, we are finalizing the specification of our first machine for GMP production. The machine enables you to culture up to 1011/batch. I am sure that the CellFiber approach will contribute to reducing the cost of cell therapy products which will be reflected in the price to patients.

The Benefit of the GMP Machine

Once the GMP machine is made available commercially, it will bring huge benefits to cell therapy products manufacturers and development labs worldwide. The CellFiber GMP machine is an automated and closed system. While the conventional culture method typically requires eight operators spending hours of manual operation to culture one 1011/batch, the CellFiber GMP machine will require only two operators. Additionally, the CellFiber GMP machine can reduce the required machinery footprint dramatically (see Fig. B).

Medical grade CellFiber machine
(cell encapsulation machine)

The Real-World Potential of the CellFiber Technology

The technological advantage is provided by CiRA Foundation, which is directed by Nobel-Prize winner Professor Shinya Yamanaka, M.D., Ph.D.. Currently, one scientist from CellFiber resides professionally in the CiRA Foundation working closely to develop an advanced mass culturing process of iPSCs.

The application of CellFiber technology is not limited to cell expansion. It can be used to make homogeneous aggregated cells whose size is about 100 micrometers and can be easily harvested by removing fiber by solution. The technology also works for viral vector production as well as exosome production. Moreover, CellFiber looks for applications beyond cell therapy such as cultured meat.

CellFiber is one of the selected life sciences start-ups to participate in the 2022 California Life Sciences (CLS) FAST International Program. Their innovative platform provides a significant advance in cell therapy technologies and represents the focus of innovation championed by CLS FAST. ■

Gene Medicine: Renova's Quest and its Journey for the Treatment of Debilitating Diseases

Submitted by Vijay Mahant, Ph.D., CEO, Renova Therapeutics

Renova Therapeutics was co-founded in 2009 by Dr. Kirk Hammond in San Diego, California. Hammond is a Professor of Medicine at the University of California San Diego and a cardiologist at the VA San Diego Healthcare System.

Renova Therapeutics is creating transformational gene therapies for treatment of chronic and debilitating diseases to restore health and longevity. While most pharmacological drugs treat symptoms, gene therapy targets the cause of the disease by replacing or editing a defective gene. Renova has a pipeline of candidate products using gene transfer for hard-to-treat or incurable and high prevalence chronic and debilitating diseases, including heart failure and diabetes mellitus.

Renova's lead product, RT-100, completed Phase 2 clinical trial[1], and it recently achieved a pivotal regulatory milestone, an IP award from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK for the treatment of heart failure with reduced ejection fraction (HFrEF).

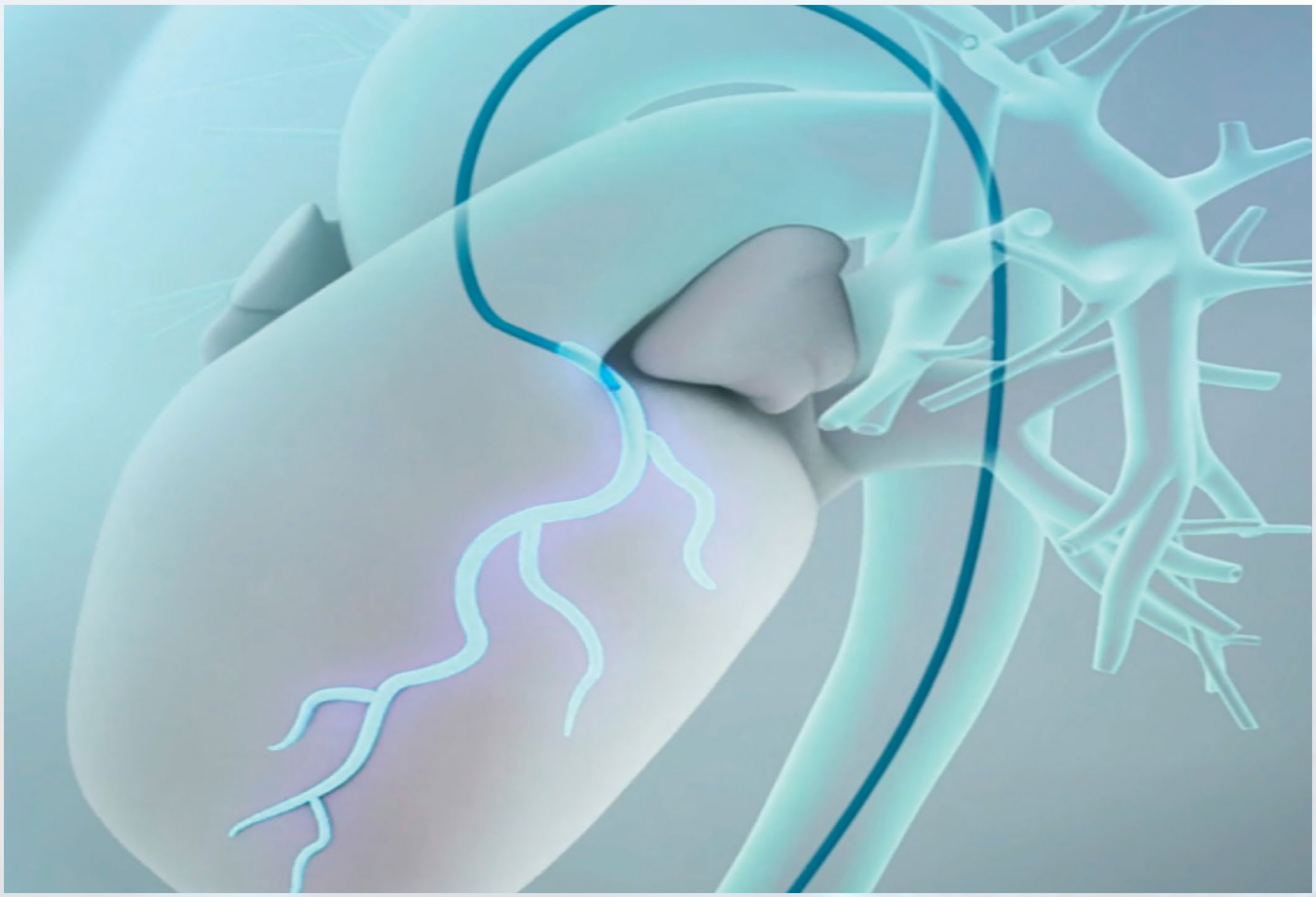


Diagram illustrating a one-time intracoronary AC6 Gene Transfer Therapy (RT-100) Intervention

Heart failure affects 64 million people worldwide, and this, along with other cardiovascular diseases, is the leading cause of death in the United States.

The second candidate product (RT-200) under development is the therapy for long term resolution of insulin resistance in diabetic patients. Diabetes affects 537 million people globally[2]. The prevalence of diabetes, including cardiovascular diseases, is expected to increase due to the COVID-19 pandemic. Preliminary evidence suggests that some patients are at high risk of developing diabetes due to an acute COVID-19 infection, because the SARS-CoV-2 can impair the insulin-producing pancreatic β cells[3].

Based on pre-clinical studies, RT-200 has the potential, in a one-time intravenous injection, to normalize glucose homeostasis and reduce the devastating effects of diabetes. The pre-clinical studies, performed in 5 models of diabetes via a one-time intravenous

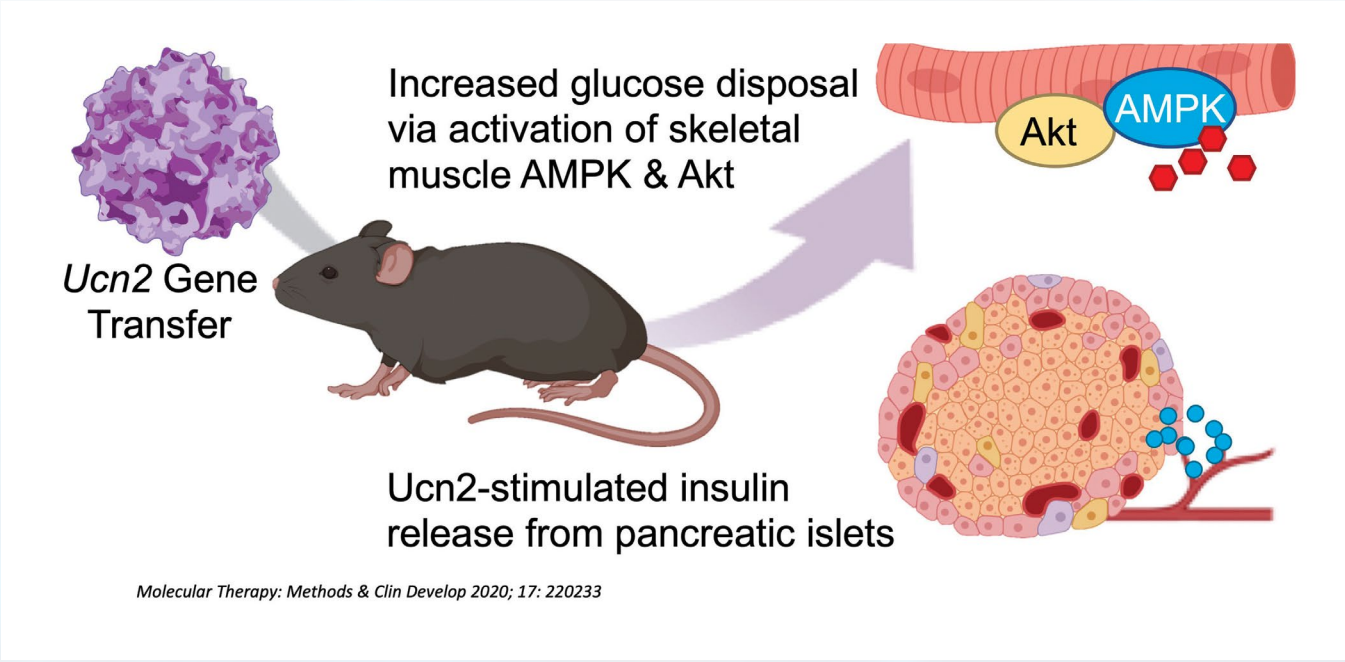


Illustration of the mechanism of action of RT-200 for type 2 diabetes mellitus

injection of a vector encoding urocortin 2, increased insulin sensitivity and glucose disposal, providing long-lasting resolution of abnormal glucose homeostasis, and fatty infiltration of the liver[4].

These evidence-based findings offer promising approaches for treating diabetes and unlock the potential for better outcomes for such patients, including reduced cardiovascular and metabolic diseases.

Gene therapy is an emerging field, and despite the advances, it faces both technical and non-technical challenges. Some of the technical challenges include the potential risks, such as immunotoxicity associated with the use of virus vectors, duration of expression, and potential immune response. These challenges are being addressed, and progress is being made on several fronts. Non-technical challenges, on the other hand, for most young gene therapy companies include funding, regulatory process, intellectual property, in house manufacturing versus outsourcing, and unique reimbursement models in the wake of the costly single treatment modality.

Because gene medicine treats the underlying cause of a disease, it is thus able to complement, supplement, and/ or bridge the gap between traditional pharmacological interventions and invasive procedures. Leveraging artificial intelligence (AI) will play an integral role in managing patient care and cutting development costs. In addition, precision gene therapy combined with AI and data refinement by refineries in diagnosis, prognosis, research and development,

clinical trials, durability, and manufacturing, including pharmacovigilance, is a potential game changer in realizing gene medicine for treating debilitating or incurable diseases.

The recent advances in gene medicine have resulted in an increasing pipeline of new products, a surge in the number of clinical trials, and recent regulatory approvals of gene therapy products. Interest in this sector has further accelerated the momentum in funding and recent acquisitions of several gene therapy companies including Spark Therapeutics by Roche, Akouos by Eli Lilly and NightStar Therapeutics by Biogen. ■

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