



Making cells better:

**Complex challenges drive
innovation in cell and gene
therapy manufacturing**

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Contents

Executive summary	4
Introduction	5
C>s: A new era of treatments	7
Innovation and complexity: The manufacturing challenge	9
Novel science, novel processes	11
Materials, labor, and the C> cost equation	13
The C> supply chain	16
Innovations in research, development, manufacturing, and delivery	18
Conclusion	19
Contact us	20

A close-up, shallow depth-of-field photograph of a microscope. The right side of the frame shows the metallic, cylindrical parts of the microscope's eyepiece and objective lenses, which are in sharp focus. The background is a soft, out-of-focus blue and white, suggesting a laboratory setting.

Executive summary

- Emerging cell and gene therapies (C>s) are revolutionizing medicine, offering the possibility of curing, not just treating, life-threatening illnesses.
- Because these innovative therapies represent a completely new treatment paradigm based on medical research rather than drug development, scientists face significant technical and logistical challenges in bringing treatments to market in sufficient commercial quantities.
- The processes required for C> manufacture are wholly new and extremely complex. As production and delivery of these new therapies to patients are still nascent, biopharmaceutical companies will need to harness new technological advances and innovate continuously in the manufacturing process.
- Large capital investments in the industry are likely to bring breakthroughs in the coming years that will standardize processes, simplify delivery logistics, boost efficiency, and increase competition.



Introduction

A revolution is rapidly beginning to reshape medicine, driven by advances in scientists' understanding of human biology at the genetic and cellular levels. This deeper insight is helping biopharma innovators develop a new generation of therapeutic approaches to treat life-threatening diseases and conditions.

These emerging therapies, known as cell and gene therapies (C>s), offer the promise of using the body's own cellular processes to not just treat or manage diseases but to potentially cure them. Highly personalized, these therapies often involve developing a specialized, tailor-made product for each individual patient.

The promise of the pipeline

The US Food and Drug Administration (FDA) has already approved several therapies, including one gene therapy

that may permanently halt the progression of a spinal muscular atrophy affecting infants as well as two advanced cell therapies to cure leukemia and lymphoma. Other transformative C>s are coming soon: According to a 2020 analysis of the AdisInsight database, US biopharmaceutical companies are working to develop close to 400 cell and gene therapies. The FDA has indicated that it expects to approve 10 to 20 new C>s between now and 2025, and potential treatments span a range of therapeutic areas, including oncology, central nervous system disorders, hematology, and respiratory diseases.

These emerging therapies have caught the eye of venture capitalists, who invested more than \$16 billion in global biotech during 2019 alone.¹ Fig. 1, overleaf, illustrates the number of registered studies conducted in the last 10 years, which reflects the growing investment in researching and developing these therapies.

By their nature, cell and gene therapies are a complex new breed of treatments. Most emerged from medical research,

¹ https://www.svb.com/globalassets/library/managedassets/pdfs/4q_2019_pitchbook_nvca_venture_monitor.pdf

Number of registered studies with posted results over time (as of November 24, 2019)

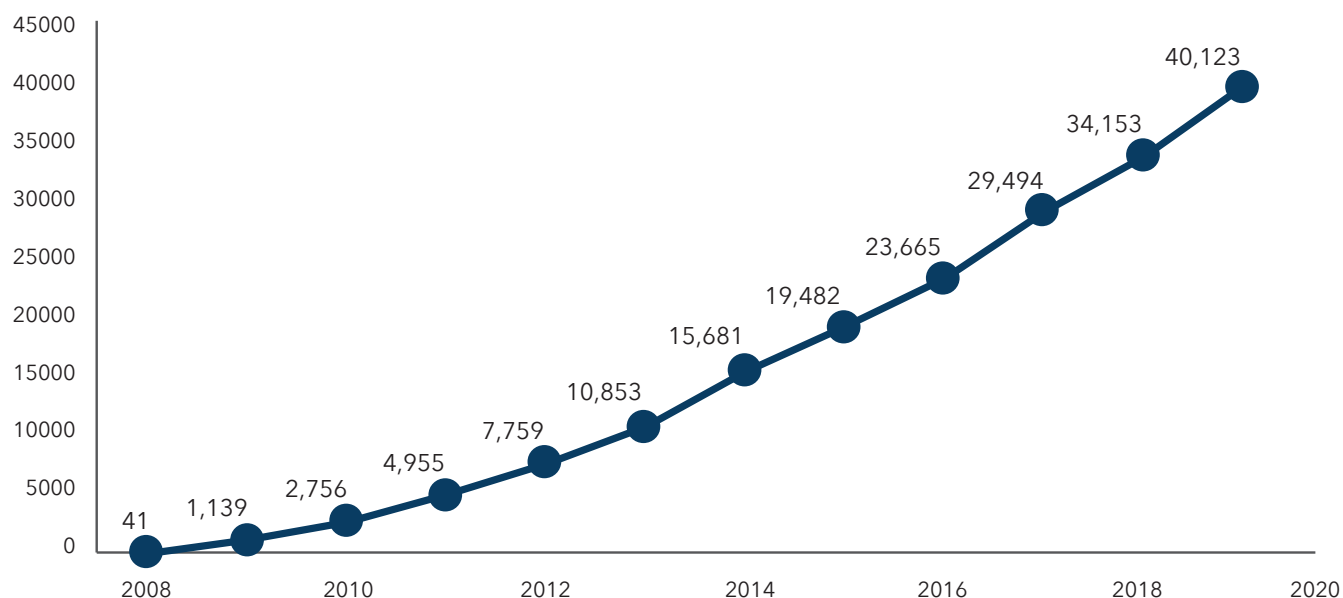


Fig. 1: C> studies are proliferating

rather than from the normal drug development process. They require precise science, first to identify pathologies at the genetic or cellular level, and then to create a process for altering the cell or gene to correct the deficiency. While scientific understanding is deepening, much mystery still surrounds the behavior of individual cells and how it might be manipulated. Researchers need more experience with clinical data to understand the long-term effects of C>s. For example, Richard Klausner, former director of the National Cancer Institute, told a scientific meeting in January, “We still don’t know enough about the cell biology of tumors.”²

The biopharmaceutical industry is partnering with scientists in academia and the National Institutes of Health to understand more about the molecular biology of diseases and which gene mutations are most likely to be important for modifying biological processes to treat patients with limited options.

Another area requiring innovation, particularly for process inventions, is the scaling of manufacturing to ensure that a specific therapy can meet the needs of an expanding commercial market. Technologies that work in clinical settings may not necessarily be adaptable for large-scale manufacturing. In hopes of getting safe and effective treatments to patients efficiently, 11 biopharmaceutical companies have set aside an estimated \$2 billion in just the

past two years to invest in gene therapy manufacture—even as clinical data for certain therapies is still being collated. As cell behavior remains enigmatic, drug makers are in some ways taking a “leap of faith,” one executive notes, making large capital investments in C>s even before a therapeutic benefit has been proven with data.³

These emerging therapies alter the paradigm for how the biopharmaceutical industry approaches previously untreatable illnesses. Many C>s are created after years of trial and error in research labs, and so far, they have proven costly to bring to commercial scale. The challenges include:

- Developing and deploying new “purpose-driven” technologies specifically designed for C> manufacturing;
- Transforming supply chains to produce the raw materials needed for C>s and deliver the finished products;
- Addressing logistical and delivery strategies; and
- Identifying new payment and coverage strategies to enable widespread access and get the right treatment to the right patient at the right time.

Manufacturers are rising to face these logistical and financial hurdles as they transition from experimentation to mass commercialization, and resolving these challenges will require thoughtful and innovative solutions.

² Wuxi Global Forum, Jan. 19, 2020

³ <https://www.reuters.com/article/us-genetherapy-novartis/pfizer-novartis-lead-2-billion-spending-spree-on-gene-therapy-production-idUSKBN1Y11DP>



C>s: A new era of treatments

Before discussing the challenges of bringing life-changing new therapies to market, it is important to understand how C>s function, how they differ from previous generations of biopharma products, and why the new treatments remain so difficult to manufacture.

Cell and gene therapies modify genes or cells to achieve a sustained outcome in a specific disease state, often treating the underlying cause of a disease.

Most conventional chemical and biological drugs temporarily modify an enzyme or receptor within the body, addressing symptoms. These drugs may be small-molecule chemicals that patients take as pills. Or they may be living viruses that are injected as vaccines or biologic medicines that are infused.

Cell and gene therapies, by contrast, are therapies that modify genes or cells to achieve a sustained outcome in a specific disease state, often treating the underlying cause of a disease.

There are many forms of cell and gene therapies, which are usually categorized as autologous or allogeneic.

Autologous vs. allogeneic therapies

Today, most C> treatments are autologous, meaning they come from a patient's own cells—the ultimate “custom-made” medicine—and are returned to that patient after being modified in a lab. These are sometimes referred to as “vein-to-vein products,” which use intricate processes to extract genes from humans, modify their structure, and

then re-inject or infuse the modified genes. The hope is to either target and kill off specific disease-causing cells, or to produce—or inhibit production of—certain proteins. Autologous therapies illustrate the very personalized nature of C>s. Such treatments upend the traditional system of drug manufacturing and delivery.

One example of such a product is Kymriah, a chimeric antigen receptor T-cell (CAR-T) therapy developed by Novartis and approved by the FDA in August 2017. As described below, this cell therapy requires the company to develop what is essentially a new product for every patient, since a patient's own immune cells are harnessed to treat his or her specific cancer.

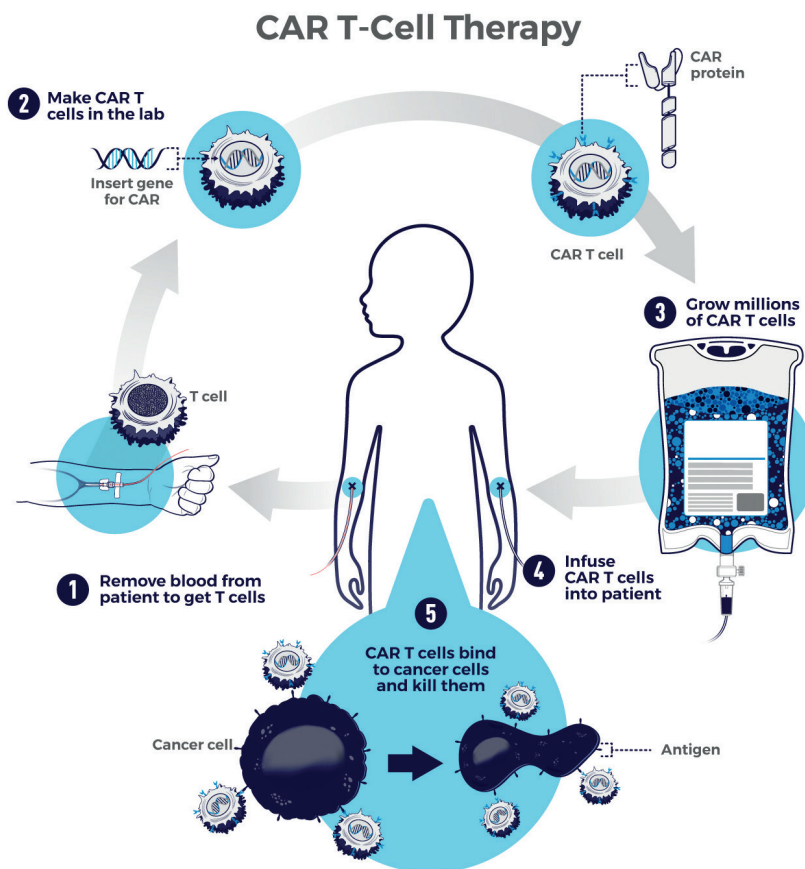


Fig. 2: How CAR-T therapies work⁴

“Each dose is developed by first drawing blood from the patient and isolating blood cells, including T cells,” explained Jennifer Brogdon, Executive Director for Exploratory Immuno-Oncology at Novartis Institutes for BioMedical Research (NIBR), at a recent conference. “We then send it to a company-designated manufacturing site where T cells are genetically encoded to recognize cancer cells and other cells expressing a specific antigen using an inactive virus.” The resulting CAR-T cells can now recognize a specific marker produced on the surface of certain cells, including certain cancer cells. Afterward,” Dr. Brogdon explained, “the CAR-T cells are multiplied, packaged, and then infused into the patient.”⁵

A newer generation of treatments—not yet fully developed—is allogeneic, or “one-to-many” treatments, meaning the cells injected into the patient come from an anonymous, healthy donor before being genetically modified. Researchers hope that if allogeneic treatments prove effective, they can be mass-produced with technologies powered by artificial intelligence, which would lower the cost of manufacturing.

“Historically, the traditional biopharma drugs were allogeneic, which means one drug could be used to treat multiple patients,” explains Dr. Andrew Bulpin, Head of the Process Solutions Business Unit within Life Sciences at Merck. “For many of these new cellular therapies it’s one drug, one patient, and effectively the modification of the cells comes from the patients themselves.”

⁴ Image from the National Cancer Institute, <https://visualsonline.cancer.gov/retrieve.cfm?imageid=12069&dpi=300&fileformat=jpg>

⁵ <http://www.koreabiomed.com/news/articleView.html?idxno=6812>

Innovation and complexity: The manufacturing challenge

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Autologous treatments are “vein-to-vein products,” illustrating the very personalized nature of a unique treatment being delivered to an individual patient.
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Since C>s fundamentally change the way patient and product interact, they are significantly more difficult to produce than small-molecule or other biological medicines. Most conventional drugs can be produced in advance, stored in inventory, and distributed when needed. Many require no extensive patient preparation or inpatient delivery. With cell and gene therapies, however, each treatment is unique and based on the raw material presented to the lab. And since there is no inventory, C>s must be developed rapidly and sent to patients immediately—usually within about two weeks.

Production time and scalability

No “one size fits all” approach exists for developing and manufacturing cell and gene therapies. In fact, suppliers, labs, and clinics need to acquire a whole range of new practices to make the treatment regimens effective. Whereas a chemical compound like a pill is mass-produced in a centralized facility with efficient, high-volume production, genetic therapies demand individualized

production. Therapeutic doses must be developed quickly, before the disease inflicts further damage; distribution must be decentralized so modified cells can be administered where the patient is being treated; and rather than being scaled up, production needs to be “scaled out,” so that individual doses, each with differing starting raw material, can be produced simultaneously for hundreds of patients.

Likewise, manufacturers must operate under the constraints of short time-to-patient intervals. For some C>s, preparing a patient to receive therapy can take up to three weeks, from collecting cells from a patient to administering the treatment; therapy may include preconditioning regimens, and insurance companies could take far longer to approve reimbursement for cell and gene therapies than for traditional medical treatments. For patients to receive timely treatment, all these factors must be well-planned and coordinated, so that the therapy is delivered to the right patient at the right time.

“You have to get these therapies to the patient as quickly as possible, one at a time for autologous therapy,” explains Dr. Jian Irish, Senior Vice President and Global Head of Manufacturing for Kite Pharma, a Gilead company. “At Kite, we have an industry-leading median 16-day manufacturing turnaround time in the U.S. to provide treatment for eligible patients. To scale production, it requires careful planning and resource commitment. It’s like the restaurant business,” she says. “You have to serve the patients when they come in, you can’t put them in a queue. But if not enough customers show up, you don’t have a business.”

Also, whereas a restaurant can store meat and vegetables in a refrigerator until it's time to cook and serve them, the raw material needed to produce C>s—the patient's own cells—can be processed only once the laboratory receives them. And since these raw materials are highly diverse, not just from one patient to another but even in a single individual patient, it is far more difficult to standardize production and logistics. Thus, manufacturers of autologous therapies have found it challenging to achieve the scale efficiencies available to makers of small-molecule, and even biological, compounds.

The cost profile of C> development also differs from that of traditional therapies. In small-molecule and biologic treatment discovery and development, the cost of clinical trials can be burdensome. With C>s, while the costs of clinical trials remain quite high, they can be exceeded by the expense associated with perfecting the complex and intricate logistical dance that links research labs to manufacturers, manufacturers to suppliers and clinics, and the delivery mechanism to patients. The FDA—which recognizes a variety of approaches as gene-therapy products, including human gene-editing technology, patient-derived cellular gene-therapy products, gene-

edited bacterial and viral vectors, and plasmid DNA—is in the process of developing guidance to help manufacturers bring treatments to market more efficiently.

The search for standards

Researchers working on cell and gene therapies acknowledge they have not yet mastered the manufacturing piece of this puzzle. In most cases, the production processes themselves are complex, novel, require a new level sophistication, and are not yet suitable for commercial use. As the science of C> is brand new, manufacturers still depend on production processes created for older generations of drugs. Many labor-, time-, and capital-intensive techniques are still involved, and standards and templates for producing C>s efficiently don't yet exist and may face widespread challenges before being adapted across the ecosystem.

"A lot of the manufacturing processes today are still very manual," explains Dr. Kelvin Lee, Director of the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and a professor of chemical and biomolecular engineering at the University of

"The turnaround cycle time [to get therapies to patients] works against the classic efficiency and productivity you would like to achieve."

Dr. Jian Irish, Senior Vice President and Global Head of Manufacturing, Kite Pharma



Delaware. “There are people in protective clothing [bunny suits] in clean rooms doing a lot of manual manipulation” of test tubes. “That has some benefits, because you can have a worker who’s skilled, trained, and can make appropriate decisions on how to interact with the process. But at the same time, it’s a lot of labor, and one person may do things a little bit different than the next person, even with standard operating procedures.” Dr. Lee says this suggests there are opportunities to reduce the cost and accelerate the timeline of bringing medicines to market.

Adds Dr. Irish of Kite, “Right now everybody uses proprietary ingredients” in C> manufacturing. “Someday in the near future it will all be standardized.”

In addition to the vulnerabilities inherent in a highly manual production process, disruptions to the complex C> supply chain can cause production interruptions, including equipment malfunctions, facility contamination, raw materials shortages, or contamination. Any delay or mistake could result in the patients not receiving the treatment in a timely fashion, or at all. “We are used to manufacturing one batch of small- or large-molecule drugs for thousands of patients,” one biopharma executive says. “But if we are producing a CAR-T therapy, that means developing one batch for one patient. Imagine the complexity . . . logistics, quality control, process development. That is why immunotherapy products cost so much.”

“Producing a CAR-T therapy means developing one batch for one patient. Imagine the complexity... That is why immunotherapy products cost so much.”

Novel science, novel processes

Many of the complexities surrounding the development of C>s arise from a simple fact: A great deal about cell behavior remains a mystery. “Developers often don’t have a great understanding of their cells and the processes by which they grow or change,” says Nick Timmins, an expert in biopharma manufacturing and Vice President of Cell Technologies for the startup Artisan Biotechnologies. “Cells behave differently than a virus or a protein.”

However, innovation on the manufacturing side lags somewhat behind innovation in the lab. “We still don’t have very well-established methods and approaches to how to manufacture some of these medicines,” Dr. Lee says. “We are in the early stages of having technology and processes that can really fuel much more growth.”

Indeed, before final production of a potential cell therapy can take place, a series of daunting challenges must be considered and resolved. Some raw materials vital to C>s are in short supply. Academic research labs, which try to innovate therapies focused on specific targets, are often insufficiently integrated with the contract manufacturers that want to produce

In their ambition to find a curative therapy for a specific illness, academic researchers often do not prioritize how they might efficiently manufacture a therapy once it proves its efficacy, experts say. C> treatments “are incredibly expensive to manufacture,” not only because of the singular nature of each therapy, “but also because right now they don’t always work from a manufacturing standpoint,” explains Dr. Bulpin from Merck.

Furthermore, because experience with producing C> is quite recent, expected “learning curve” effects have yet to kick in. The US FDA approved the first CAR-T treatment in 2017, and many advanced therapy manufacturing facilities “have to invent their way forward,” says Peter Walters, Lead Process Engineer at CRB USA, which builds such facilities. “Nothing is templated. Everything is novel.”⁶

As a result, efforts to simplify or scale production are in their infancy, Dr. Bulpin notes. “In most cases, manufacturing is being done on equipment that wasn’t designed for that purpose,” he says. “We’re using other equipment to get it done. It’s homemade, it’s done in your garage, so one of the variables is that it’s not fit for purpose and hasn’t been optimized or completely developed as a templated process.”

These manufacturing challenges hamper the development of a sustainable industry, Dr. Bulpin adds. “In order to be able to make a reliable business model—which at the end of the day will mean that people will continue to invest in it because they can actually make some money out of it—there needs to be a reliable process so that stakeholders know what the outcome will be in terms of yield and reproducibility. Then, you can build a suitable approach.”

Some bottlenecks may be resolved in the near future as our understanding of cell behavior improves and as innovation in the manufacturing and delivery advances. Importantly, as technology and manufacturing innovations begin to solve the various challenges, the cost of these novel treatments may fall. “Product innovators and contract development and manufacturing organizations [that collaborate with research labs] will help industrialize the manufacture of new therapy classes,” Bulpin says.

“In most cases, manufacturing is being done on equipment that wasn’t designed for that purpose. . . it’s homemade, it’s done in your garage. It hasn’t been optimized or completely developed as a templated process.”

Andrew Bulpin, Head of Process Solutions, Merck

⁶ https://www.contractpharma.com/contents/view_features/2019-11-20/transitioning-from-clinical-production-to-commercial-manufacturing/



Materials, labor, and the C> cost equation

Production of C>s requires the use of viral vectors engineered to deliver corrected cells to the proper nuclei in the patient's body. Producing those cells is time-intensive and requires tremendous human expertise, as well as specialty materials like serums, reagents, culture media, and growth factors, all of which are very expensive. However, because the few gene therapies approved for use target very rare diseases, high-volume production challenges have yet to be addressed, experts say.

Vectors: complex to produce and scarce

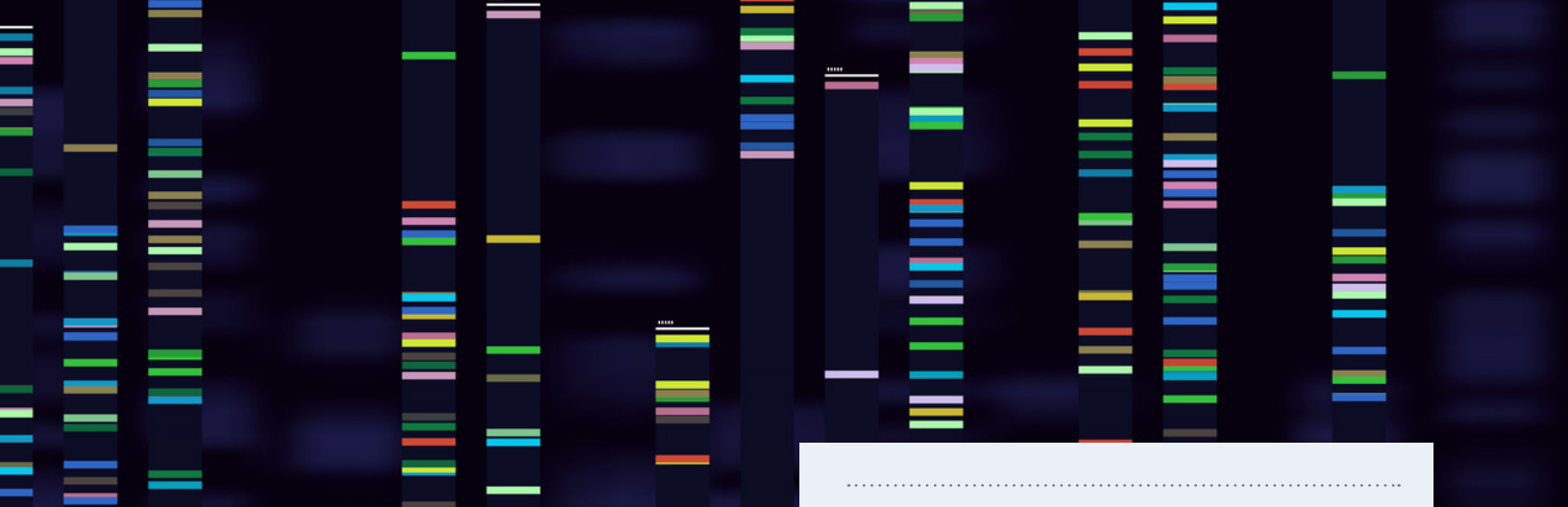
Still another challenge facing those hoping to produce advanced therapies is the immense shortage of raw materials needed to make cell therapies. Genes that have been modified to knock out diseases are generally delivered to patients through a modified virus—usually a disabled version of an adenovirus or a lentivirus—that

enters the bloodstream. Without adequate supplies of the disabled viruses, there can be no treatment. But manufacturing these viral vectors is costly and, to date, maddeningly inefficient. “We still have not achieved enough maturity in viral vector technology,” Dr. Irish of Kite says, “which is why there is a significant opportunity to improve productivity.”

Moreover, the surge of interest from researchers looking to develop advanced therapies has put new pressure on the suppliers of viral vectors. Experts recognize the need to make more viruses, and make them more efficiently, but progress has not been as rapid as hoped. “If gene therapy is ever going to be a common modality, we have to have better viral vectors,” says Ben Deverman, Director of the Vector Engineering Research Group at the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard. “Right now, we’re just scratching the surface.”⁷

Dr. Timmins of Artisan Bio notes that many of these delivery viruses “are horribly expensive to make.” He is hopeful that new manufacturing approaches, like the use of suspension cultures and stable producer cell lines, will improve output.

⁷ <https://reports.statnews.com/products/stat-guide-to-viral-vectors-the-linchpin-of-gene-therapy/>



These upstream challenges are paralleled by equally challenging issues downstream. There is no single vector suitable for all C>s, and because different vectors have different molecular properties, they also have different purification challenges. Once a virus has been produced in vitro using cultured cells, the resulting batch must be purified, concentrated, tested, and put into a form that can be stored, transported, and ultimately injected into patients. Each of these processes adds cost, and in some cases, are very inefficient.

Viral gene delivery is not the only option, however, Dr. Timmins notes. Non-viral technologies that enable precision engineering of genes using comparatively simple reagents may emerge as particularly promising technologies for producing cell-based drugs manufactured in vitro. For in vivo gene therapy applications, substantial challenges related to delivery and targeting have yet to be addressed for these non-viral approaches. The delivery issues are not as significant a concern for viral vector applications, however, since that is what the vectors have evolved to do: infect host cells in an organism.

“Regardless of the viral system used, the gene-therapy approach is still relatively immature, and manufacturers are still in the process of exploring safety measures and long-term implications,” says Dr. Juan A. Hernandez Bort, Head of Gene Therapy Technologies for Takeda Pharmaceutical Company. “Manufacturing processes for viral vectors are more complex compared to recombinant proteins, and substantial process development is needed to improve process robustness, scalability, and productivity.” Due to the complexity of viral vectors, Dr. Hernandez Bort adds, “new methods need to be developed to fully characterize gene-therapy products and process impurities,” such as cell debris and components used in production that are not intended as part of the therapy.⁸

“Lack of productivity is the most important bottleneck.”

Dr. Kelvin Lee, Director, NIIMBL

Dr. Lee of NIIMBL notes that “lack of productivity is the most important bottleneck” when it comes to viral vector production. He says it is important that the industry design “whole new, purpose-designed equipment” to facilitate viral vector production.

Facilities shortages

Yet another challenge is that adequate facilities to produce new C>s are in short supply. Several companies are dramatically expanding their manufacturing footprint to accommodate the rising interest in innovative C> facilities, but they are expensive to build and take months to come online. Dr. Timmins notes that there is a “literal capacity crunch” when it comes to finding suitable manufacturing facilities to produce advanced C> products. As the number of investigational clinical trials ramps up, demand for gene-therapy manufacturing services is likely to increase as well.

To meet this demand, some biopharma companies are acquiring gene-therapy manufacturing technologies, capacity, expertise, and intellectual property. For example, Thermo Fisher Scientific has acquired Brammer Bio to build its capacity in producing viral vectors; Catalent acquired Paragon Bioservices to gain more ability to produce adeno-associated virus (AAV) vectors, which, along with lentiviruses, are the most commonly used vector to deliver DNA to cells; and Danaher Corporation acquired GE Biopharma to build out its life sciences

⁸ <https://www.americanpharmaceuticalreview.com/Featured-Articles/362178-Challenges-in-the-Downstream-Process-of-Gene-Therapy-Products/>

“Developing and keeping a workforce is still a serious problem.”

Dr. Kelvin Lee, Director, NIIMBL

portfolio. Dr. Timmins says more investment needs to flow into manufacturing and analytical technologies, not just to new C> treatments.

Some notable innovations are already taking place in this arena. For example, MilliporeSigma, a division of Merck, recently announced the acquisition of a technology that uses sound waves to filter out sediments from cellular materials. The FloDesign Sonics technology can be used “upfront, to harvest and to purify” viral material to make sure the right amount of T cells has been modified, “and it can be used downstream at the back end to purify” therapies before they are reinjected into a patient, Dr. Bulpin of Merck explains.

Commercial challenges

While much activity is focused on therapeutic inventions in cell treatments, manufacturing challenges also affect the potential for gene therapies to gain real commercial viability. “There isn’t a gene therapy manufacturing playbook—yet—to guide the development of gene therapies,” notes Diane Blumenthal, Head of Technical Operations at Spark Therapeutics, developer of Luxturna, which treats patients with a rare form of inherited vision loss. “At least for now, every gene therapy is different.” Each relies on a different delivery mechanism, or vector, to transport functional copies of a gene into the patient, and each therapy will require different dosing and modes of administration.⁹

Faced with the scarcity of raw materials and the technological challenges of production, many companies that have developed innovative new therapies are also producing their own viral vectors. For example, Kite, which produces the CAR-T therapy Yescarta, announced in July 2019 it would build a 67,000-square-foot facility at its Oceanside, California, biologics site just for developing

viral vectors, with commercial manufacturing to start in the second half of 2021.

Wanted: Refined expertise

In addition to the lack of adequate facilities and raw materials, pharma executives and academic experts say a shortage of highly trained workers with STEM skills also contributes to the manufacturing bottlenecks. “Developing and keeping a workforce is still a serious problem,” says Dr. Lee of NIIMBL. “There are many more jobs available than people who have the skills or interest to fill them.” The problem is especially acute in C> manufacturing operations, whose infrastructure requires highly educated, trained, and skilled workers to perform complex tasks. It is hoped that machines someday will carry out many of these tasks.

Adequate facilities to produce new C>s are in short supply. There is a ‘literal capacity crunch’ when it comes to finding suitable manufacturing facilities to produce advanced C> products.

Dr. Nick Timmins, Vice President of Cell Technologies, Artisan Bio

⁹ <https://www.statnews.com/2019/12/18/manufacturing-the-next-breakthrough-in-gene-therapy>

The C> supply chain



Biotechnology companies producing autologous gene-therapy products also must develop and manage a new and complex supply chain to get a patient's cells from a certified hospital or site to a processing facility and back, vein-to-vein.

We have already noted that time is of the essence in developing a specialized treatment, and a great deal can go wrong along this journey. Cells must be kept extremely cold between the time they are extracted from a patient and the moment they are re-infused, as they quickly break down outside the body and can become toxic. Timing and accuracy are everything. If the process is not completed quickly enough, or if the patient accidentally receives someone else's modified cells, the therapy may be ineffective or worse.

As a novel concept grows into a commercially marketable product, the supply chain must adapt to a host of logistical intricacies, including storage, labeling, traceability, packaging, and shipping and release requirements. Autologous therapies are especially challenging as they require a make to order supply chain and the need to manage the chain of identity and chain of custody as the cells travel from a patient to

the manufacturer and then return to the patient. Once a therapy is administered, biospecimens must be collected regularly to monitor the treatment's safety and efficacy, and biopharma firms must develop strict protocols on how to collect, transport, and store each specimen, and how best to assay its potency.

It's one thing to "muscle your way through" and produce a few hundred batches of personalized treatments, Dr. Irish notes. "But once you get over, say, 1,000, the complexity rises to a completely different threshold," because resource management, data management, and logistical issues grow exponentially more complicated. Advances in Big Data analytics are likely to help in the development of more agile manufacturing solutions, as sensors and other adaptive technologies can recognize and adjust for variations in the manufacturing process for specific C>s. These technologies might discover relationships and correlations—and flag potential problems more quickly than the human mind can.

An important consideration for manufacturers relates to patient location and the task of physically delivering a custom-made therapy at a specific time and temperature. According to PwC, there are over 200 accredited cell therapy organizations, but only five zip codes in the US can offer all four products that are currently approved. As a consequence, manufacturers must account for differing



risk evaluation and mitigation strategies for how and where they deliver these therapies.¹⁰

New technologies—especially artificial intelligence and machine learning for autologous drug production—can help integrate information formerly siloed at different points along the supply chain. Individualized treatments generate enormous flows of data, both in early-stage clinical development and in treatment situations where patient outcomes often help determine reimbursements. In addition, Big Data offers the potential for better pattern recognition among a diverse set of patients.

Some C> companies use their own platforms to integrate IT systems, track shipments, and keep logs of a product's temperature. Although production facilities are bound by strict Good Manufacturing Practice requirements, treatment centers currently are not. Each hospital or treatment center can operate differently. So far, the FDA has not issued guidelines dictating who should pack the cells for initial shipment, how many clinical investigators should assess them, or how they should be handled in the clinic where patients receive the infusion. More clarity may be needed to set standards related to raw materials, product quality, and supply chain logistics. Meanwhile, the FDA has recognized the need to add staff with expertise on C> and has created a regenerative medicine pathway.

To sum up, the challenges facing autologous C> manufacturing and supply chains are significant:

- Customized therapies mean no product inventory and highly variable raw materials;
- Manufacturing processes can scale out, but generally cannot be scaled up based on current technologies;
- A manufacturing error or contamination can destroy a whole batch of products—processes are not yet fault-tolerant;
- Production of viral vectors and other critical supply-chain elements is costly;
- Analytical assays to measure potency and ensure quality control have yet to be automated;
- Dedicated equipment is required for each patient's batch of treatments, which limits efficiency; and
- Facilities are expensive to build and take years to get up and running, resulting in a squeeze on manufacturing sites.

¹⁰ <https://www.pwc.com/us/en/industries/health-industries/assets/pwc-health-research-institute-beyond-the-hype-gene-therapy-report.pdf>

Innovations in research, development, manufacturing, and delivery

The few cell and gene therapies approved for use today target diseases that result from unusual genetic defects and affect very few patients. Their rarity means the viral vectors for delivering corrected cells to the proper nuclei are highly specialized. For now, producing the required serums, reagents, culture media, and growth factors is very expensive.

However, many biopharma experts believe innovations on the horizon will help drive down the costs of research and manufacturing. Great hopes surround the prospect of developing effective allogeneic therapies, where, many believe, automation could reduce production costs over the next three to five years. Automation would also make the end-to-end journey of a gene culture more predictable and reliable. Once they can be proven in the lab, “allogeneic therapies may become a faster route” to large-scale manufacturing, says Dr. Lee of NIIMBL. For the moment, however, “autologous approaches can have a tremendous impact,” he says, “even if the production runway is not yet mature.”

Executives at firms like Novartis and Gilead are strengthening their manufacturing processes, often buying or building new production facilities to shorten

the time needed to develop bespoke CAR-T products. And development of non-viral technologies could improve the safety profile and lower the cost of specific C> therapies. Meanwhile, blockchain and other new inventory management technologies may help in the tracking and delivery of individualized treatments. Biopharma firms also recognize that expertise developed in other industries like freight forwarding might help in solving the logistical issues involved in C> production and distribution.

The recent history of pharmaceutical innovation suggests that manufacturing process improvements and lab innovations will likely lead to steady cost reductions for clinical treatments. For example, Dr. Patrick Yang, former Executive Vice President of Technical Operations for Juno Therapeutics, believes the development of monoclonal antibodies (mAbs)—now used to fight diseases like leukemia and cancer—hints at the future path for C> treatments. While at first the cost of producing mAbs was extraordinarily high, process improvements have brought more treatments to the marketplace. Over the past 30 years, for example, the output of mAb titers (i.e., the measurement of how much antibody has been produced in a process) has improved by a factor of 20, according to process engineers at Wuxi AppTec, a leading contract development and manufacturing organization.

Dr. Yang says firms will also need to take steps to push down manufacturing costs. A number of approaches could help achieve that goal:

- ***Efficiently translate basic research into a commercially scalable product.*** More effective technology transfer between research houses and manufacturers will be required. Too many labs, experts say, focus on developing treatments for specific diseases without considering the degree to which their results can be reproduced, and how the treatment can be manufactured.

“The smart factory of the future will have to include a great deal of data integration in automation and resource planning.”

Dr. Jian Irish, Senior Vice President and Global Head of Manufacturing, Kite Pharma

- **Develop accessible platform technologies.** Accepted, purpose-driven platforms—systems built specifically to enhance the production of advanced therapies—need to be developed to speed C> manufacture. Industry-wide collaborations like NIIMBL will help develop opportunities to share information and develop common standards.
- **Innovate not just in the science, but in the manufacturing and supply chain.** Investment in basic research must be accompanied by a vigorous acceleration in capabilities by contract development and manufacturing operations. The last 18 months have seen consolidations and major investments as these operations build capacity. Undoubtedly, more capacity will come on line as more C> products gain regulatory approval.

Dr. Irish of Kite believes Big Data will simplify C> manufacturing. “The smart factory of the future will have to include a great deal of data integration in automation

and resource planning,” she says. If a company produces thousands of batches of tailor-made C>s using discrete processing equipment, data integration is vital to allow rapid product release and distribution to the right patient. Sophisticated use of data in manufacturing and testing may also allow producers to develop reliable “manage to the exception” processes—that is, systems that flag only meaningful deviations from the norm—so that the final release of any treatments that fall within an acceptable, predetermined range can be vastly simplified.

Equally significant, automation of allogeneic processes may not be too far away. “There is a strong movement in the T-cell manufacturing world to move toward the use of fully automated systems,” says Dr. Paul Lammers, President and CEO of Triumvira Immunologics. Under such a structure, a cartridge-like system would process the patient’s weakened cells into finished CAR-T therapies in 10–14 days, then a new cartridge would be installed for the next patient.¹¹

¹¹ <https://www.cellandgene.com/doc/a-strategy-to-drive-down-therapy-costs-manufacturing-improvements-0001>

Conclusion

The development process for monoclonal antibodies—another medical breakthrough therapy, now used to treat cancers and other severe illnesses—took about seven years to move from bleeding edge to commercial viability. Many experts in C>s believe a similar maturity curve, albeit somewhat faster, will also transform cell and gene manufacturing.

“Cell and gene therapies have just started,” Dr. Irish of Kite says, “but I think similar lessons can apply.” Over time, standards, templates, and knowledge-sharing could allow a common manufacturing standard to emerge.

Likewise, advances in gene-editing technologies and viral vector production can be expected to increase the supply of raw materials and perhaps automate parts of the production system.

“Firms will need to cooperate and compete at the same time,” Dr. Yang says. Continuous learning will lead to breakthroughs that will make the new generation of C> treatments more effective and affordable. Biopharmaceutical manufacturers have the resources and expertise to drive process innovations in manufacturing to realize the promise of C>s.

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