Improving Cell and Gene Therapy Process Development

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Cell and gene therapies (CGT) represent the cutting edge of biotherapeutics, using DNA and life itself as therapeutic agents. CGTs work by replacing damaged cells or tissues to add functionality that is missing due to genetics or disease and include gene therapies delivered by a vector and cell therapies using engineered cells, such as chimeric antigen receptor (CAR) T cells developed to fight cancer.[1]

In fact, the first CGT approved in the United States was a CAR T therapy: in 2017; Kymriah® (tisagenlecleucel) was approved to treat acute lymphoblastic leukemia in children and young adults,[2] kicking off a wave of CGTs in oncology. Beyond cancer, CGTs have since been approved to treat type 1 diabetes, a rare neurological disease, and blood diseases including sickle cell and hemophilia B.[3–6] As CGT continues to advance and grow—as of January 2024 there are nearly 2,000 active CGT clinical trials[7]—innovators are leveraging their knowledge and technology to improve CGT development processes across the industry.

Starting with high-quality materials

CGT process development requires the coordination of many parts, including cells, DNA constructs, and gene delivery vectors. As a key starting material, CGT development requires a constant flow of high-accuracy, long, and complex custom DNA. Limited fidelity in DNA synthesis is one R&D and manufacturing bottleneck, often requiring costly and time-consuming cell-based cloning to address synthesis errors.

Elegen is addressing this synthesis bottleneck with its cell-free DNA synthesis process that can produce complex DNA at scales up to 7 kb linear or 15 kb plasmids with NGS-verified quality and an error rate as low as 1 error per 70 kb, meaning most synthesized products would be error-free.

According to Matthew Hill, CEO of Elegen, “The current paradigm of performing cell-based cloning to account for low-quality gene synthesis is fundamentally not a scalable solution for biopharma. Elegen has eliminated this critical bottleneck with commercial-scale cell-free DNA production that provides long, high-complexity, NGS-verified dsDNA, shaving weeks or months off the therapeutic development process.”

Streamlining R&D with physical and digital tools

CGT production involves many sensitive steps, including cell harvesting, transportation, expansion, gene transduction, and infusion into the patient, each needing to be consistent and reproducible. From personalized, autologous treatments to high-capacity manufacturing operations, Cytiva offers workflow solutions, including reagents and consumables for CGT development, to standardize processes and help move CGTs from science to industry scale.

Handling biological specimens isn’t the only area where standardization could yield process improvements. CGT development requires collaboration among multiple business units within a company and with regulators. Several companies, including Lonza with its MODA-MES platform, offer digital, regulatory-compliant data solutions. Paperless experimental and sample tracking can enhance collaboration among business units or departments by standardizing experimental protocols, making data sharing among business units more intuitive and accessible, and enhancing readiness for regulatory submissions.

Enhancing quality control with sensitive analytical methods

With the various biological inputs required for CGT development, understanding drug substance parameters, like potency and sterility, is critical for quality control (QC) from R&D to manufacturing.

“Accurately measuring potency is a key challenge, such as determining the number of empty vs. full capsids for adeno-associated virus (AAV)-based therapeutics,” explains Chelsea Pratt, BioPharma Segment Marketing Manager at Bio-Rad. “Bio-Rad is developing technologies that increase accuracy and precision that assist in QC of these complex modalities.”

Bio-Rad’s patented technology, droplet digital PCR (ddPCR), is a high-sensitivity method that provides absolute quantification of DNA, allowing for applications such as counting viral capsid copy numbers. This sensitive technique has also found use in detecting rare events such as recombination and quantifying gene copy numbers in cells, aiding in the reproducible creation of CGTs. Required regulatory measures for sterility are also addressable with ddPCR.

“ddPCR enables researchers to have the accuracy and precision needed for tests to enter a QC environment. This spans from measuring copy number variation (CNV) in gene modified cell therapies to viral titer in gene therapies using AAV, both regulatory requirements. Additionally, this technology continues to expand in the number of assays incorporated in the QC setting, with mycoplasma detection and host cell DNA quantification and sizing being increasingly adopted across biopharma,” notes Chelsea Pratt, BioPharma Segment Marketing Manager, Bio-Rad

Planning for manufacturing

Moving from preclinical and phase 1 studies to later phases and commercialization requires a robust manufacturing scale-up platform. Maintaining CGT batch-to-batch consistency and stability through scale-up presents notable challenges, to which the best solution is to plan your research so that it can be translated to commercialization.

“Process and analytical development starts with an incredible team that has a vision for what the drug looks like in commercialization,” notes Antonio F. Santidrian, Chief Scientific Officer of Calidi Biotherapeutics. "You start with strong science and talent that understands the process, can characterize it, and can make phase-appropriate changes to ensure that you achieve a quality product that is safe and efficacious in the clinic.”

Calidi Biotherapeutics is using stem cells as carriers for oncolytic virus therapy, exploiting the virus’ tropism for cancer cells and the stem cells’ abilities to protect the virus from the patient’s immune system and to amplify the viral particles. Early clinical studies with autologous stem cell carriers demonstrated several instances of tumor debulking, leading Calidi to develop an allogeneic approach for an off-the-shelf product,[8,9] which would improve its potency and reproducibility, simplify the commercial manufacturing process, and ease its use for patients who need it.

One increasing challenge faced by Calidi and others is finding talent in the CGT space, including contract development and manufacturing organization (CDMO) partners in the United States; currently, fewer than 35 CGT products are approved in the U.S.[10] Calidi also takes its role seriously in moving the industry forward by sharing its best practices as a member of the industry group NIIMBL and at scientific meetings:

“We as an organization are contributing to many scientific meetings with a focus on process development and manufacturing to share knowledge with the community. In the end, we have a common objective to make these drugs available to as many people as possible,” Santidrian explains.

Conclusion

Continued innovations in the R&D process, increased knowledge in biology and bioengineering, and more CGT approvals will continue to drive this field forward. The CGT market is predicted to grow rapidly, with some estimates predicting a $45 billion industry by 2030.[11] Aligned with the projected growth of this industry and potential supply chain issues in manufacturing, the White House in 2023 announced measures to enhance U.S. biomanufacturing.[12] With these rapid technological advances and CGT process improvements, it's exciting to think about what currently unaddressable illnesses may soon become treatable.

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