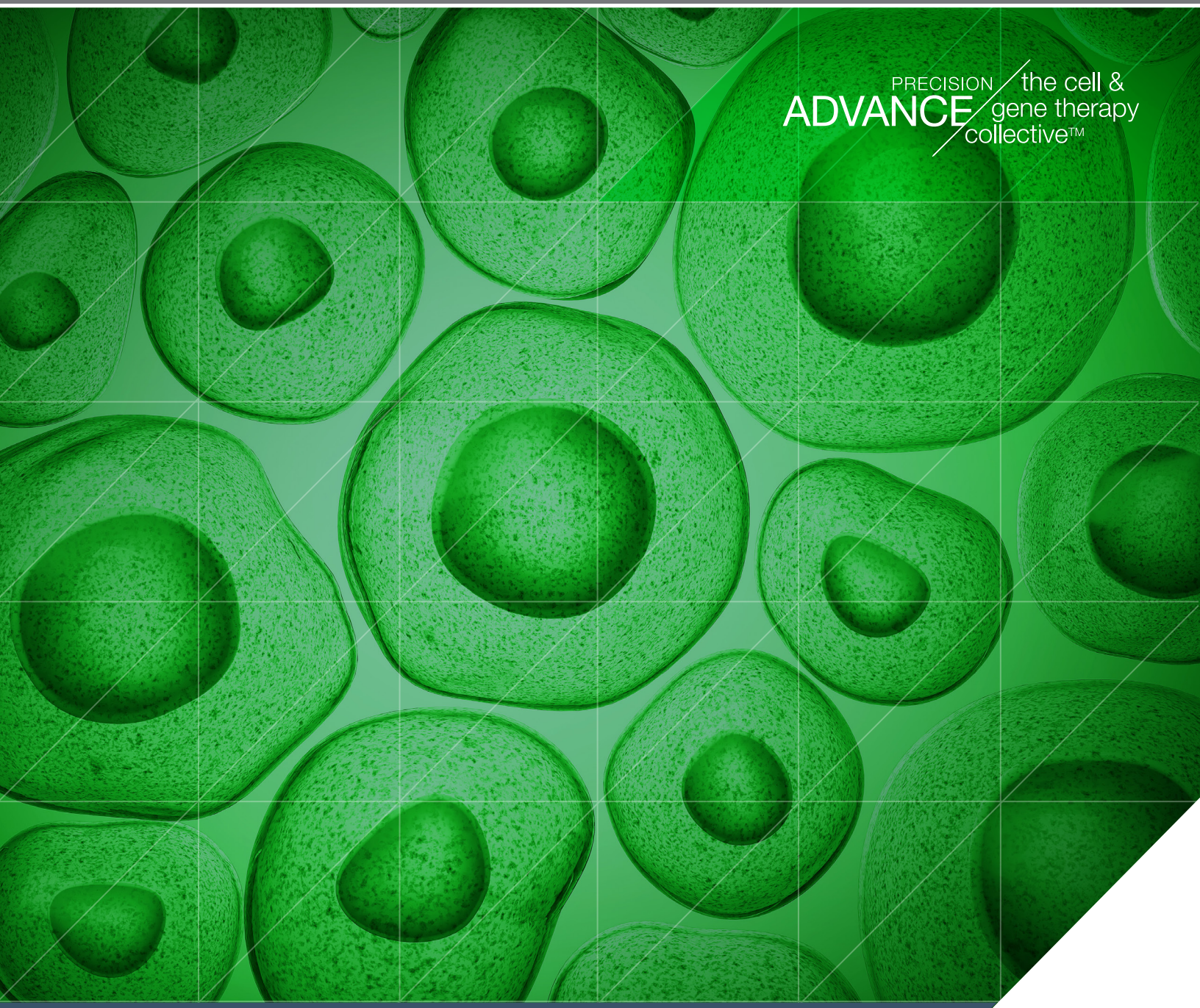

PRECISION ADVANCE the cell & gene therapy collective™

The Future is Now: Cell and Gene Therapy Innovation, Challenges, and Perspectives

cell&gene day 2023

The Future is Now: Cell and Gene Therapy Innovation, Challenges, and Perspectives

Cell and gene therapies have the potential to revolutionize treatment of a wide range of diseases. With six new therapies approved in 2022, including the first allogeneic T-cell therapy, and at least as many slated for approval this year, the sector is poised for rapid growth. This innovation comes with challenges, though, and many consider 2023 to be a seminal year for establishing a strong foothold for advanced therapies in mainstream medicine.

On May 11, 2023, Precision ADVANCE, the Center for Breakthrough Medicines, and the Alliance for Regenerative Medicine co-sponsored the second annual Cell & Gene Day, hosted by Endpoints News. Throughout this event, over 25 successful innovators from across the advanced therapy sector presented fresh insights on overcoming critical challenges in bringing life-saving therapies to patients in need.

This white paper is based on a discussion moderated by **Anshul Mangal**, President of Precision ADVANCE and Project Farma, and the following panelists:

James M. Wilson, MD, PhD, Professor of Medicine and Pediatrics and Director of the Gene Therapy Program, University of Pennsylvania

Bruce L. Levine, PhD, Barbara and Edward Netter Professor in Cancer Gene Therapy and Founding Director of the Clinical Cell and Vaccine Production Facility, University of Pennsylvania

Deb Phippard, PhD, Chief Scientific Officer, Precision for Medicine

Kiran Reddy, MD, Senior Managing Director, Blackstone

Driving the cell and gene therapy sector forward

As cell and gene therapy research advances, there is a critical need to find the resolve, resources, and commitment of stakeholders to move programs not just from proof of concept to clinic, but also through registration and into the commercial realm. To open the discussion, Mangal asked how the panelists plan to drive the sector forward in 2023, and they shared the following priorities:*

- Overcoming hurdles to getting advanced therapies to more patients around the world
- Expanding CAR-T cell therapies beyond the approvals in hematologic malignancies
- Bringing together labs, regulatory, manufacturing, and clinical trial operations to develop advanced plans for streamlining and accelerating the transition into the clinic
- Investing in technologies that will take cell and gene therapy programs to the next phase of maturation where these technologies become medicines that can be used at scale globally

Disruptive technologies

New technologies are continuously being developed and refined in this sector, enabling more precise and effective targeting of specific cells and genes and bringing personalized medicine to greater numbers of patients. There is great excitement about the potential of gene editing, where the rate of change in technology development has been staggering. The potential approval of the first CRISPR-based technology is a milestone, especially as the treatment is indicated for sickle cell disease, an underserved population. For ex vivo applications, researchers—including Dr. Levine—are studying viral vector-free methods for delivering gene editing enzymes. Meanwhile, Dr. Wilson spoke about his and other's early efforts to expand in vivo gene editing strategies to not only interrupt or knock down a gene, but also introduce a new functional gene, initially targeting the liver due to relative ease of delivery.

Neoantigen discovery and technology are also emerging areas for the cell and gene therapy sector. In May 2023, researchers from Memorial Sloan Kettering—in collaboration with BioNTech and Genentech—published the results on a Phase 1 trial demonstrating that individualized mRNA neoantigen vaccines synthesized from surgically resected tumors stimulated T cells in patients with pancreatic ductal adenocarcinoma. There have also been reports on researchers isolating neoantigens and generating T cell receptors directed against them.

From the pragmatic perspective of commercialization and access, progress is also needed in technologies that improve scalability, decrease the cost of goods, enhance overall safety, or increase durability. With such progress, it may be possible for cell and gene therapies to fit in existing commercial models where repeated treatments can be given over time.

Challenges of gene editing

While gene editing creates opportunities, it also introduces challenges. For ex vivo approaches involving multiplex gene editing, there are concerns about translocations and other genotoxicity issues. In vivo delivery introduces other levels of complexity. According to Dr. Levine, "the delivery challenges… with an AAV (adeno-associated virus) payload for gene replacement are just as daunting—if not more daunting—for editing, especially as the editing technology and payloads exceed the capacity of what an AAV can deliver." There is also room for improvement with gene insertion efficiency.

In vivo delivery is further complicated by the fact that the overwhelming majority of payloads are foreign proteins. Consequently, there is the potential to elicit an adverse immune reaction not only to the payload, but also to the vector or the editing payload. Thus, what may ultimately be needed for in vivo editing to be broadly useful is a novel approach to delivery in which the delivery is transient. mRNA-containing lipid nanoparticles may be a strategy for that approach, at least in the liver where there is no barrier from the blood to the target cell. For other organs, such as the brain, heart, and muscle, current innovation in gene editing outstrips the delivery technology available. However, there is substantial interest in this area as genetic diseases of these organs are associated with significant morbidity and mortality.

Immunogenicity is also a concern. Dr. Phippard emphasized that, "year by year the regulatory agencies are getting more cautious about immunogenicity [even with] AAV gene therapy…it's an order of magnitude higher to think about in vivo CRISPR and how you would deal with potential immune system effects."

Vector technology for gene therapies

As with other areas of cell and gene therapy research, there has been a great deal of innovation in vector technology, including non-viral delivery methods. Much is already known about the advantages and limitations of in vivo viral vectors, though questions about durability and ability to retreat with the same or a different vector remain unanswered. Given the existing body of knowledge, the panelists emphasized the importance of being smarter about how the technology is applied. Dr. Wilson challenged sponsors and stakeholders in the viral gene therapy space to "start out with an evaluation of the applications of the technology…in which there is a high probability of success," rather than starting with market sizing and reimbursement strategies and trying to back into the technology.

Dr. Wilson also referenced work his lab has been doing on non-viral delivery for gene editing in which the expression needs are transient. For now, this is the best application for non-viral vectors. In situations where the expression needs are prolonged or durable, it is likely an integration event would be required for non-viral delivery as there are no easy ways to achieve durability outside the context of a viral vector.

Expanding beyond rare diseases for gene therapy

For gene therapy, monogenic diseases currently represent the highest probability of success, but as Dr. Phippard pointed out, many companies are contemplating more prevalent conditions where the commercial opportunity is greater. The challenge of rare gene therapy programs is sustainable revenue. While companies may see a short high revenue period post-approval related to treatment of the prevalence population, the ongoing incidence population will be low and unpredictable. Thus, continuous innovation in bringing the next product forward is essential, according to Dr. Reddy.

Investing in non-monogenic applications may be highly risky and further evolution of the science may be needed before looking at more common diseases. Dr. Wilson suggested that a potential strategy for mitigating risk and expanding beyond rare diseases might be to start with a rare monogenic disease, such as Barth syndrome, a lipid metabolism disorder that is characterized by dilated cardiomyopathy. If a gene therapy is successfully developed for Barth syndrome, it may be possible to leverage that into more common forms of congestive heart failure.

The role for allogeneic cell therapies in the treatment landscape

Allogeneic cell therapies have been given a great deal of attention over the past few years. As Mangal moved the discussion toward this topic, the panel collectively agreed that there is room for both autologous and allogeneic therapies in the current treatment landscape. In large part, allogeneic therapies are still being given in the context of stem cell transplant and these therapies have not yet been proven to be either as potent or more efficient than autologous ones.

The need for both autologous and allogeneic options is underscored by the reality that there are patients from whom a sufficient number of potent cells cannot be obtained or generated. For patients who have received multiple rounds of treatment—especially chemotherapy—the quality and function of their T-cells and other immune effector cells deteriorates. As advanced therapies are approved for earlier lines of therapy, though, there may be a reduction in failures to generate autologous therapies.

As Dr. Reddy opined, "There will probably be circumstance- and indication-specific use cases for both autologous and allogeneic in the near term…I think the dream is that allogeneic will in fact be able to overcome and supersede everything in the next five years."

Perspectives on the public markets

While investment in the cell and gene therapy sector peaked in 2021, it has returned to pre-pandemic levels, with $12.6 billion invested in 2022. Dr. Reddy commented that, at $3-4 billion per quarter, investment on the pure private capital side is still significant. He also pointed out a "barbell-like effect of where the capital is going…to later stage projects where perhaps there is strong validation…[and to] highly innovative next generation editing technologies, viral vector technologies, [and] non-viral vector technologies." The companies who may be struggling are those seeking financing to get to first proof concept or to move preclinical technologies to the clinic.

To some extent, consolidation of the ecosystem may have been inevitable. At some point, there were 150 AAV gene therapy companies, each with multiple programs, but none with all the resources necessary to develop and commercialize products with any efficiency, opined Dr. Wilson. Today, there is an incredible opportunity to reconfigure this ecosystem to leverage the power of platforms that target similar diseases or utilize the same capsid, route, or manufacturing. By consolidating diseases developed in a similar way, platforms increase the probability of success—and cost-effectiveness—of follow-on applications and allow companies to stitch together markets that make commercial sense in the aggregate.

Most exciting developments in the pipeline

The full potential of cell and gene therapies is yet to be realized. Mr. Mangal closed out the discussion by asking each of the panelists to share what they are most excited about in the sector for the upcoming year. Their responses included using AAVs to target tissues other than the liver, streamlining CAR-T cell manufacturing from 10 days to three days, optimizing technology to deliver medicines that have a clinical benefit to patients around the world, and increasing collaboration to maximize access, all of which would bring more life-saving therapies to those in need.

**The views and opinions expressed in the context of this discussion are those of the panelists and do not necessarily reflect those of the official policy or position of their respective companies.*

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