Market Trends and Expectations for Advanced Therapies in 2023

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The cell and gene therapy space has undergone transformational change in the last few years, driven by the promise these modalities have demonstrated in addressing rare and intractable diseases. Achievements in the CAR-T therapy space – there are now six approved CAR-T treatments on the market – in conjunction with breakthroughs in gene therapy and viral vector drugs, have signaled a new era of innovation aimed at furthering cell and gene therapies within the greater healthcare landscape. A crucial component of this innovation centers on the cutting-edge technologies developed to support end-to-end therapeutic development, as well as the ever-evolving foundational science that continues to uncover new and novel modalities, processes, and analytical approaches.

In a recent panel discussion hosted by Precision ADVANCE, experts from across the cell and gene therapy sector convened to explore the ways their organizations have met headlong the challenges and opportunities that typify cell and gene therapy development. Panelists for the event included:

- **[Moderator] Andy Kinley**, Vice President, Innovation and Clinical Science, Precision for Medicine
- **Peter Andersen**, Chief Scientific Officer, Vita Therapeutics
- **Deborah Phippard**, Chief Scientific Officer, Precision for Medicine
- **Palani Palaniappan**, Chief Technology Officer, Pioneering Medicines, Flagship Pioneering
- **Phil Cyr**, Senior Vice President, Precision Value & Health
- **Charlie Harper**, Vice President, Project Farma

Innovative Trends and Transformational Approaches in CGT

The panelists began by offering insights into their respective organizations' technology platforms and the innovations each has leveraged to pursue new and novel therapeutics. For Peter Andersen, Vita Therapeutics' core program, which targets degenerative neuromuscular diseases such as muscular dystrophy, represents a fundamental improvement over most of the treatments currently in development. That's because while many strategies center on halting disease progression, Vita's approach, which utilizes induced pluripotent stem cells (IPSCs) in combination with genome editing technology, aims to engineer cells that can regenerate or replace affected tissue. "The cells that we're generating are muscle progenitor cells, sometimes referred to as satellite cells, which are the stem cells of the muscle and essentially where muscle biology starts," Andersen said. "The goal is to rebuild healthy muscle mass for these patients."

At Flagship Pioneering, the promise of transformational therapies is what drives its Pioneering Medicines division, which essentially serves as an "asset factory," working to bring drugs to human proof of concept as quickly and efficiently as possible across its network of 29 growth companies and multiple laboratories. "We do have a number of bio platforms that we work on, and we like to convene multiple approaches from within those ecosystems to see if there's a great opportunity to tackle a particular disease," Palani Palaniappan noted. He highlighted Flagship's recent partnership with the Cystic Fibrosis Foundation, enabling Flagship to begin intervening to address CF with some of its existing assets, such as circular RNA and gene writing approaches. "It's an opportunity to be efficient in tackling some of these diseases, which requires many minds working together," he added.

Precision Medicine Group is focused on research and clinical development, manufacturing, and commercial services to progress these therapies to market. According to Deborah Phippard, while Precision itself possesses longstanding experience as a specialized CRO, its Precision ADVANCE Group was formed to act as an integrator of its various technologies and expertise. "It became very obvious to us that we needed to pull all of these disparate disciplines and experiences together," she said. "I found myself talking to the same group of colleagues at Precision for Medicine, realizing that if we don't work together as a team, we simply can't put together an efficient trial with all of the assays we need." Phil Cyr added that, with Precision's various business units, having a central hub for convening expertise is crucial, particularly for informing better, more efficient early-phase work: "Having that multidisciplinary team has been beneficial and ultimately leads to less scurrying around."

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> – Phil Cyr,
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Charlie Harper explained that for Project Farma, the manufacturing solution provider by Precision has served to complement and advance both organizations' existing expertise. He added that Project Farma's track record – to date, it has helped shepherd nearly 100 different cures for intractable diseases to market – helps drug innovators leverage Project Farma's manufacturing expertise to enable clinical and commercial success. "We like to get involved very early with companies, engage with them in developing CMC and manufacturing strategies, build their necessary internal capabilities, and advance that to standing up CDMOs and internal capabilities, performing tech transfers, and getting them to the point where they're ready to make large capital investments and build their own facility," Harper explained. "It really comes down to time – if you can get it done quickly, you're going to get these cures to the market quickly."

New Technologies to Further New Discoveries

The gene therapy space has seen an uptick in recent regulatory approvals. Other related modalities, such as approved CAR-T therapies to treat large B cell lymphoma, as well as potential approvals for non-viral delivery methods for genetic material and advances in vivo gene editing, have begun paving the way for another big year for cell and gene therapies, according to Kinley. "There's the potential there to see a [tumor-infiltrating lymphocyte] therapy and a T-cell receptor therapy approved in 2023," Kinley said. Patel, who stressed the importance of expediting delivery to patients and making the experience "as positive as possible for the patient."

For innovations that represent an alternative to incumbent approaches, such as non-viral delivery, Phippard notes that viral and non-viral delivery methods each have their pros and cons, and the demonstrated efficacy of viral vectors is likely to result in their continued exploration, even as non-viral methods continue to receive attention. "I think about it more in terms of, am I trying to get into a tissue where I know an existing AAV or other type of viral vector isn't going to work? Then I think about re-dosing – we're seeing a lot of efficacy studies now. For hemophilia trials, we've got three-plus years of data, and it's looking good," she explained. "We still don't know if we have to re-dose, so you may have an initial therapy with a viral vector, and then maybe you want to dose with some other therapy."

These diseases, and the biology underlying them, are complex. There is a wealth of new data coming out of the allogeneic therapy space, for example, signaling the therapies' potential even as challenges persist for their overall development. While a handful of autologous cell therapies – which, in contrast to allogeneic therapies, use a patient's own cells to generate a dose of a therapy – have been approved in the U.S., the advancements that have been made for allogeneic therapies have been possible, in part, due to the foundational research that exists for autologous therapies. "Autologous therapies are here to stay, and we will learn more about allogeneic therapies and get more products approved," Palaniappan said. Addressing issues such as immune rejection and grafting in order to further allogeneic approvals will necessitate building upon the insights gained bringing autologous therapies to market. For Cyr, it isn't a question of allogeneic vs. autologous, but rather what disease states and patient populations can be better served by building an arsenal of allogeneic therapies. "I don't think it really should be an auto versus allo conversation. Similarly, I don't think it should be an AAV versus lenti versus non-viral conversation," Cyr noted. "I think you have to pick the right thing for what you're looking at."

> "**Autologous therapies** are here to stay"
>
> – Palani Palaniappan, Chief Technology Officer, Flagship Pioneering

Ultimately, the cell and gene therapy space is poised for disruption, with technologies like in vivo gene therapy delivery shifting the paradigm around patient treatment entirely. "That could be something that may revolutionize how we think about diseases," Palaniappan explained. "In an ex vivo setting, patients come into a trial and may wait almost six months to get a drug infusion. It's their cells, but it comes back to them after laboratory insertion of a gene, quality control, etc. That kind of waiting period for some diseases is unacceptable." From Phippard's view, pursuing both sides of the equation – addressing the safety signals and regulatory hurdles that hamper in vivo, as well as trying to shorten the development and manufacturing timelines for ex vivo – is key to furthering the field.

Manufacturing Outlook: Challenges and Opportunities

One of the major bottlenecks in the cell and gene therapy space relates to manufacturing capacity. "You don't have to look any further than the recent CAR-T approvals for multiple myeloma, where we see long lists of patients waiting for therapy, and where these centers are often given one slot a month," Kinley said. Two of the major hurdles, according to Andersen, are linked to product or process understanding and to manufacturing capacity and control. With regard to process understanding, one of the biggest considerations centers on automation, particularly what can be automated and when.

"It's also not an easy decision to choose the platform right for your process," he added. "You need to spend time and really understand your process before you choose a system to implement, and ensure you're implementing it at the right time." Likewise, supply chain constraints, as well as those manufacturing considerations such as when to outsource or insource, can further complicate a company's overall paradigm, he said. "For a smaller biotech like Vita, partnering with a CDMO is obviously favored to preserve capital in the short term and extend the burn rate," Andersen said. "That said, it's important to keep thinking about building a sustainable biotech."

Another across-the-board challenge for organizations is resourcing – attracting and retaining the necessary talent to build and operate these manufacturing facilities has been particularly challenging in recent years, according to Harper. "The growth in the industry has really pulled talent in a lot of directions," he explained. "It's sort of grown faster than the ability for talent to mature within the space." There has been a commensurate contraction in certain parts of the space, he added, creating new potential for a more available talent pool. "You need a good understanding of what talent you need to drive key activities. Sometimes it's looking beyond general industry experience and asking: how do these individuals form relationships? Are they able to influence people to get work done?"

CGT in 2023: Innovation, Evolution, and Challenges

Ultimately, cell and gene therapy is an incredibly complex field, with teams and sponsors developing therapies for broad therapeutic areas and disparate, difficult rare diseases. This year is likely to yield a number of key advancements for the space, owing to the continued collaboration of players across a wide range of scientific and medical disciplines and teams. Kinley pointed to a number of promising modalities and research focuses, including tumor-infiltrating lymphocytes, armored CAR-Ts, and emerging data on cell therapies treating solid tumors, as some of the key areas he plans to watch in the near future. "How things like [T cell receptors] get commercialized will be really interesting to watch in the coming year," he said.

One arena that Phippard is particularly excited about is the study of immunogenicity and biomarkers: "I think we're starting to get more and more data on whether immunogenicity and preexisting immunity to AAV vectors, etc., is an issue," she said. "I think that's going to be evolving for a number of years." For Palaniappan, the potential for more proven therapies such as viral vectors to continue to gain in efficacy and yield is particularly promising. "I worked on antibodies in the 1990s, and I remember at the time that CHO cells produced maybe a gram per liter of antibodies. Today, those same CHO cells produce 15 or 20 grams a liter. I believe we're going to see the same kind of trend, maybe on an even faster timescale, with viral vectors."

Harper agreed, adding that the slew of companies currently working on platform-based technologies aimed at achieving greater manufacturing consistency for these modalities will serve to shorten development timelines and bolster new innovation. But he noted that innovation can create its own pitfalls – for example, the emergence of single-use technologies, which have paved the way for simplified validation processes, have likewise, in recent years, created new complications for strained supply chains. “There’s going to have to be a bit of a resetting there,” he noted. On the discovery side, Andersen pointed to innovations surrounding IPSCs, allogeneic therapies, and in vivo delivery methods as arenas he intends to watch in 2023, adding that he was particularly interested in seeing Sarepta Therapeutics’ gene therapy for Duchenne muscular dystrophy navigate an accelerated regulatory path in the coming year. “It would be the first gene therapy approved for any muscular dystrophy, so that’s very exciting.”

For Cyr, shifts in pricing and reimbursement will be some of the most interesting elements to watch as the space progresses. “I think we’re beginning to see a shift from cost-effectiveness to affordability,” he explained. “The price of gene therapy, for the public, is shocking, though from a value standpoint there is shown to be cost-effectiveness. But you will start to hear rumblings from payers as they look at the pipeline – they see 2,000 trials, they see 17 potential approvals in 2023, and they say, ‘is this affordable?’” As more gene therapies move toward treating more prevalent diseases, Cyr said he believes the affordability question will drive more of the conversation moving forward, noting that some payers have already begun establishing carve-outs for cell and gene therapies, something that hadn’t existed a decade ago. “People are really starting to think about affordability, whereas in the beginning, they weren’t.”

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ADVANCE, a collection of interconnected services and complementary teams, uniquely focuses on the complexities of clinical, regulatory, manufacturing, and commercial needs to successfully bring cell or gene therapies to market.

Connect with one of our experts. Contact us at **precisionadvance@precisionmedicinegrp.com**.
To learn more about Precision ADVANCE, visit **precisionmedicinegrp.com/advance**.

2 Bethesda Metro Center
Suite 850
Bethesda, MD 20814

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