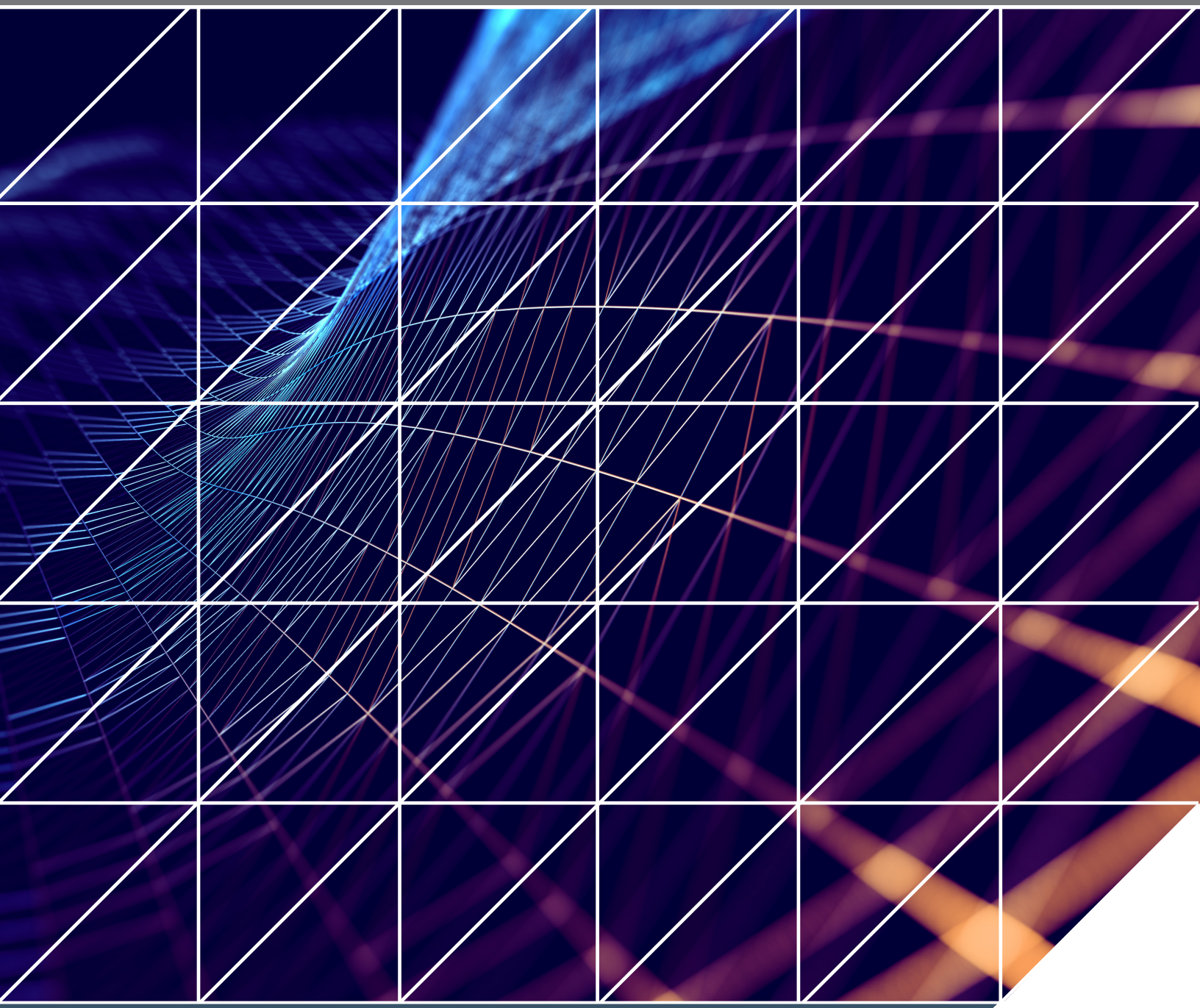

What's Next for Cell and Gene Therapies in 2023 and Beyond

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What's Next for Cell and Gene Therapies?

The cell and gene therapy (CGTx) sector has flourished in recent years due to continued investor confidence. However, the present downturn in public markets has negatively affected that confidence, raising questions about the sector's prospects for 2023 and beyond.

This white paper is based on a panel discussion at the Cell & Gene Meeting on the Mesa (October 11, 2022), sponsored by Precision ADVANCE, focusing on the future of advanced therapies. Moderated by Anshul Mangal, president of Project Farma and Precision ADVANCE, the panel included insights from the following industry leaders:

- **Stewart Abbot**, Chief Scientific Officer, Turnstone Biologics
- **Laura Lande-Diner**, Chief Business Officer, Satellite Bio
- **Robert Peters**, Chief Scientific Officer, Ensoma
- **Deborah Phippard**, Chief Scientific Officer, Precision For Medicine

Restoring investor confidence

The assembled experts started the discussion by considering measures CGTx developers might take to restore investor confidence. Foremost among such measures is setting realistic expectations for the category. From a chemistry, manufacturing, and controls (CMC) perspective, recalibrating expectations is largely a matter of providing robust analyses based on well-characterized manufacturing processes and products. That should result in fewer issues, fewer clinical holds, and more "wins," followed by increased funding and improved investor sentiment.

Lande-Diner observed that platform companies often get distracted and attempt to "do more than one thing or more than what's critical." They can avoid that trap by pursuing synergistic partnerships in which both parties offer complementary technologies and capabilities. CGTx developers should focus on the fundamentals: establishing a strong scientific foundation, applying that foundation in a way that brings value to patients, and conveying that value to key stakeholders. For companies maintaining that focus, "Good science will end up doing well for itself," Peters commented, adding that recently approved curative therapies will rekindle interest in the industry.

"Good clinical data solves all," echoed Abbot, who commented that CGTxs offer tremendous hope for treating complex diseases but face the same challenges as small molecules. He advised sponsors to start as many clinical studies as possible, as efficiently as possible, and with the best possible design to increase chances for success.

> "Good science will end up doing well for itself."
>
> – Robert Peters, Chief Scientific Officer, Satellite Bio

Overcoming regulatory roadblocks

Many CGTx product candidates have encountered regulatory obstacles due to disappointing study results and/or safety concerns. More than half of investigational new drug (IND) applications over the last 12 months have been placed on hold. According to Abbot, the situation largely reflects multifaceted problems at the US Food and Drug Administration (FDA). Those problems started with COVID-19, which has strained agency resources, and have been exacerbated by significant turnover within the agency, where numerous experts in CGTx have been replaced by relatively inexperienced and less knowledgeable personnel. At the same time, a series of successful clinical trials—including several involving adeno-associated viral (AAV) vectors—have generated a voluminous database that regulatory agencies are struggling to keep up with. Nevertheless, the FDA is assimilating that information and asking "quite relevant" questions of sponsors, while issuing more informed guidances.

The demanding regulatory environment largely results from high expectations at FDA, but those expectations are not new. That is "a good thing for the field, but it costs more money, takes more planning, takes more time," commented Phippard. Fortunately, the growing CGTx clinical database is facilitating a true dialogue between sponsors and the FDA. Lande-Diner cited the FDA's Initial Targeted Engagement for Regulatory Advice on CBER ProducTs (INTERACT) meetings as opportunities to "ask the right questions" about manufacturing, population targets, and product characteristics. Sponsors that plan early, keep up with changing regulatory guidance, and meet agency expectations will benefit from actionable feedback, and will ultimately be more successful.

Pricing pressures

The panel remarked upon the difficulty of balancing drug costs with the healthcare system's 1-year budget timelines, which does not allow a comparison of the long-term, transformative benefits of a curative therapy against short-term, symptom-focused treatment. They agreed that it is not helpful to tell biopharma companies to "just charge less," as that will impact quality and "ripple through" to patients.

New technologies

Several new technologies that have made waves in 2022 are poised for growth in 2023. Complex computational systems represent a potentially disruptive technology, in that they can enable carefully designed studies with good translational and investigational endpoints, according to Abbot. Although artificial intelligence (AI) "has been around for years," researchers are starting to use machine learning technologies to interrogate the vast amount of data emerging from clinical studies, a development that may "back-translate" into better drug design. He called upon sponsors to share more of their "pre-competitive" data, noting that publications increasingly provide "mine-able" supplemental data that the entire industry can learn from.

Disruption of the advanced therapy field may not result from a single technology, but from numerous translational technologies. Peters remarked upon the pace of advances in ex vivo therapy, noting that "more and more companies [are] now looking to translate that into in vivo." That may help extend the curative benefits of advanced therapies to larger patient populations.

Lande-Diner foresees a greater role for tissue engineering in enabling the therapeutic use of other cells, especially for complex, elusive diseases. She also expressed excitement over more nuanced use of patient data for product certification, noting that many promising drugs fail to succeed because of poor study design or poor patient selection. “Today we are in a position to develop really amazing drugs and at the same time really understand patients” to enable more efficient matching of drug to patient, she commented.

Phippard lauded CRISPR technology for its flexibility, while acknowledging the need to work through safety challenges. She also remarked upon the potential of new vector technologies to enable tissue specificity, though questions remain regarding immunogenicity and duration of effects. “If you treat neonates, what happens?” she asked. “Do you keep expression levels as those patients move into adulthood? How do you think about re-treating?”

> “The field needs a better understanding of the effects of allogeneic therapies on the body.”
>
> – Stewart Abbot, Chief Scientific Officer, Turnstone Biologics

There was considerable discussion about allogeneic versus autologous cell therapies. Each modality has its own set of opportunities and challenges, according to Abbot. The complex immunology of allogeneic cells is “not yet fully solved,” particularly in immuno-oncology, though several groups are making great strides in that direction. He said the field needs a better understanding of the effects of allogeneic therapies on the body and vice versa. As for autologous therapies, developers need to solve the complex manufacturing challenges they present. Abbot also noted that the market will tolerate the high cost of autologous cell therapies if they provide durable, curative outcomes.

Manufacturing

Mangal introduced the discussion of CGTx manufacturing by asking if the paradigm has shifted away from scaling up internally. The panel replied that it has not changed, as external manufacturers offer abundant capacity but not a lot of competent capacity. Peters noted that Ensoma is scaling up manufacturing internally, despite the perceived difficulty for a small startup. This approach facilitates internal research manufacturing as well as process development, as a prerequisite for partnering with contract development and manufacturing organizations (CDMOs) that “work hand in hand with our platform.” He added that Ensoma is building analytical tools internally to enhance understanding of the company’s products and to facilitate characterization assays for all products.

Phippard observed that analytical assays are often overlooked early in the manufacturing process. Early development of analytical reagents, in parallel with drug product, eliminates the need for “massive batches,” and enables a level of quality to satisfy regulators of an assay’s robustness.

Abbot remarked that the long lead time for implementing manufacturing technologies internally often requires investing in those technologies before clinical data are available. Mangal described this conundrum as a “chicken-and-egg” problem: “You need good clinical data to raise the capital [but] you need internal manufacturing to have the drug product data.”

Reasons for optimism

When asked what he was most excited about for 2023, Peters replied that he was pleased with the progress of the Ensoma platform, which bodes well for future progress. As for industry-wide developments, he expressed excitement about recent drug approvals in the US and Europe for both ex vivo and in vivo therapies for hemophilia, as well as new CAR-T cell therapies.

Phippard enthused about new second- and third-stage vector designs, such as those that carry a payload for truncated proteins "so you can pack more into an AAV." She said the industry would also benefit from off-the-shelf neutralizing antibody assays that could be used for multiple products/therapies, given that building assays is time-consuming and expensive, though many therapies use modified AAVs. She added that increased exploration of preexisting immunity and its implications for efficacy will help us move therapies forward and improve utility of the vectors we have.

For Lande-Diner, the use of cells as therapies is a trend to watch. She noted that Satellite Bio has expanded beyond immune cells, and "more and more" companies are developing induced pluripotent stem cells (iPSCs) or primary approaches for using other cells. Meanwhile, synergistic partnerships are creating complementarity that "can be extremely valuable for patients." Mangal added that more partnerships should result in greater consolidation and better portfolio construction, which will be good for the industry.

> "Synergistic partnerships are creating complementarity that **'can be extremely valuable for patients.'**"
>
> – Laura Lande-Diner, Chief Business Officer, Satellite Bio

According to Abbot, 2023-2024 will yield more insights into how to use gene therapy for polygenetic disease (ie, not just monogenetic). As for Turnstone's prospects, the company's first tumor-infiltrating lymphocyte data readout will make 2023 a "transformational" year. He also voiced optimism about the continued evolution of Turnstone's virotherapy "clinical picture," saying the company's large nonclinical pipeline will transition to the clinic within the next 2 years.

Conclusion

2022 has been a challenging, up-and-down year, as Mangal noted, but therapeutic advances have generated "a lot of hope for patients." Overcoming the market-based, regulatory, and manufacturing challenges of developing CGTxs will allow sponsors to sustain and justify that hope.

In the meantime, we encourage you to contact us to discuss potential opportunities, and to **click here** to access a recording of the full panel discussion.

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