Considerations for the Clinical Development of Cell & Gene Therapies (Part 1: Cell Therapies)

PRECISION
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Part 1: Focus on Cell Therapies

The regenerative medicine category is predicted to generate $39.33 billion in revenue by 2023, with the fastest growth expected in cell therapy.[1] As another indicator of the category's rapid growth, the Alliance for Regenerative Medicine, in its progress report for the first half of 2021, noted that there are 1320 industry-sponsored trials of regenerative medicine and advanced therapies ongoing worldwide and an additional 1328 ongoing trials sponsored by non-industry groups, including academic centers and governments. Compared to industry-sponsored trials, the non–industry-sponsored trials include a lower proportion of phase 3 trials (6% versus 12%) and a higher proportion of cell therapy trials (59% versus 39%) (Figures 1 and 2).[2]

Figure 1: **Industry- and non–industry-sponsored trials by phase[2]**

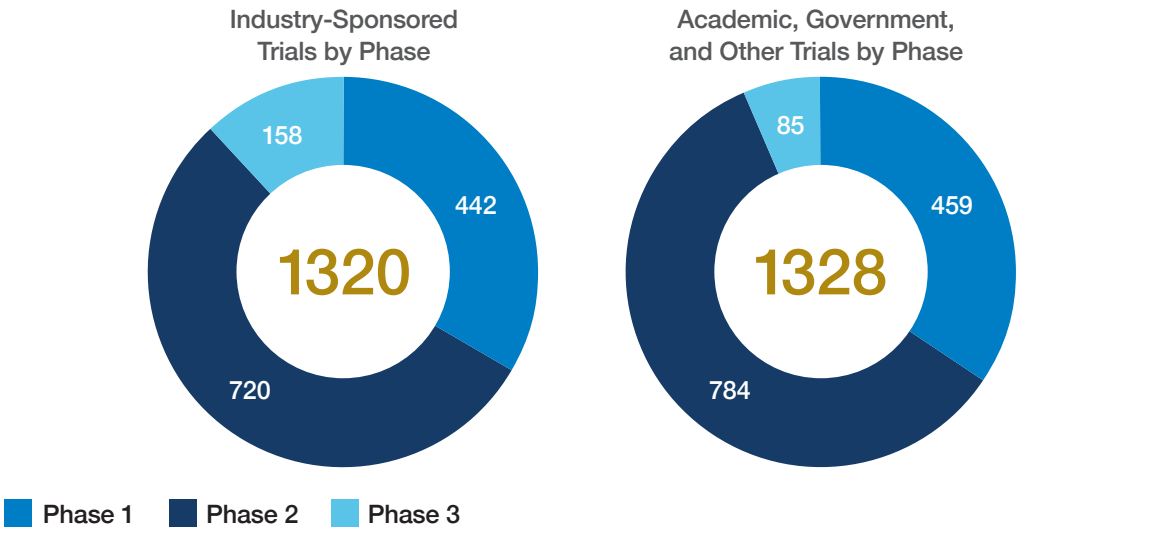
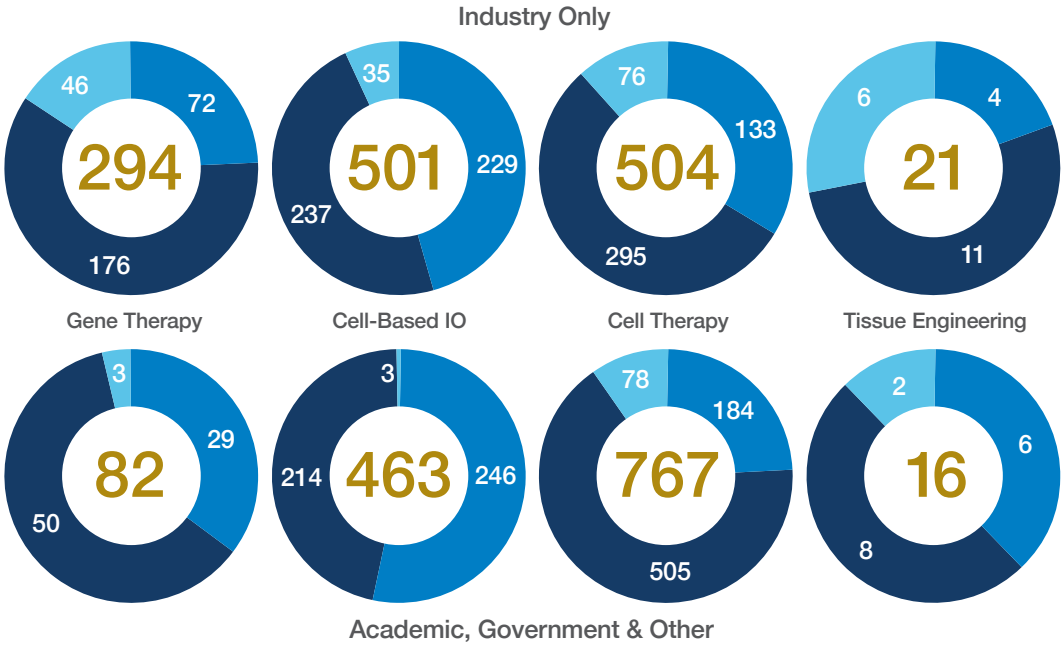


Figure 2: **Industry- and non–industry-sponsored trials by type[2]**



These trends provided the impetus for ***Considerations for the Clinical Development of Cell & Gene Therapies***, a two-part panel discussion featuring C-suite leaders from advanced therapy companies at the American Society of Gene & Cell Therapy (ASGCT) 24th Annual Meeting on May 11, 2021. The discussion, convened by Precision ADVANCE, the cell & gene therapy collective™, was moderated by David Parker, senior vice president of diagnostics solutions at Precision for Medicine. This white paper summarizes the first part of the discussion, which focused on cell therapies and included the following panelists:

- Adrienne Farid, Chief Operating Officer, Century Therapeutics
- Joachim Fruebis, Chief Development Officer, BlueRock Therapeutics
- Alex Grosvenor, Senior Vice President, PRECISIONadvisors, Precision Value & Health
- Sadik Kassim, Chief Technology Officer, Vor Biopharma
- John Khoury, Executive Vice President, Project Farma
- Megan Liles, Vice President, Operational Strategy, Precision for Medicine

Precision ADVANCE is a suite of interconnected services and complementary teams focused on the complexities of gene therapies and the resources needed to bring these advanced therapeutics to market.

Promising Investigational Approaches in Cell Therapy

Induced Pluripotent Stem Cells (IPSCs)

IPSCs, as a class, have been described as the "Holy Grail" because they can be grown indefinitely and differentiated at large scale. That makes IPSCs potentially conducive to "off-the-shelf" therapy,[2] which may allow patients to be treated upon presentation, and their single-therapy status may grant lifelong benefit to patients.

Chimeric antigen receptor (CAR)-targeted IPSC–derived natural killer (NK) cell therapies are considered a particularly promising subclass because of their potential to overcome major pathways mediating immune response and allorejection via specific gene editing. Additional advantages include knockout of NK cells and human leukocyte antigens (HLA) 1 and 2; knocking in the decoy receptor HLA-E; and dual targeting of tumor-associated antigens to address tumor heterogeneity and antigen loss, both of which are barriers to some current therapies.

CAR–targeted IPSC–derived NK cell therapies also offer the ability to leverage the specific biology, trafficking, persistence, and cytokine release profile of each cell type, as well as the potential for repeat dosing, due to enhanced cell fitness and persistence, possibly optimizing anti-tumor response and enabling more durable responses. Additionally, these therapies' unlimited replication and expansion capacity can enable editing of the IPSC–derived cell product, as well as manufacture from a single clonal matter cell bank, resulting in a more consistent, well-characterized product that can be expanded for clinical and commercial development.

Among the challenges with this approach is the need to optimize the modality (ie, binders and CARs) preclinically and to develop the therapeutic index (eg, dose ranging, dose expansion) early in development. There is also uncertainty regarding pharmacokinetics/pharmacodynamics and long-term safety, given the industry's limited experience with IPSC–derived platforms.

The US Food and Drug Administration (FDA) recently granted Fast Track designation to DA01, BlueRock Therapeutics' investigational IPSC–derived dopaminergic neuron therapy for the treatment of advanced Parkinson's disease.[3] In its discussions with BlueRock, the agency raised concerns about tumorigenicity and proliferation, even though "we never saw a tumor in our tumorigenicity studies, and it took us a long time to convince them that we should stop talking about tumorigenicity because there is no data," Fruebis noted during the panel discussion. The FDA also sought to determine a healthy background proliferative index in the putamen of the brain "because, guess what, it's not zero," Fruebis added. By contrast, discussions with Health Canada, which earlier this year granted BlueRock permission to initiate a phase 1 safety and tolerability study of DA01,[4] focused more on "the pragmatic aspect of how the procedure is done" because DA01 is a combination product (device and drug product) handled by separate arms of the agency and because there are no devices that are currently approved for the delivery of cells into the putamen.

Engineered Hematopoietic Stem Cells (eHSCs)

The rationale for using eHSCs is that they are "invisible" to targeted therapies after transplant. That helps avoid the toxic effects of concomitant therapy, particularly for acute myeloid leukemia (AML). The eHSC approach uses CRISPR gene editing to selectively knock out the antigen that is expressed on the leukemic cell as well as on the HSC graft. In so doing, eHSCs create a bone marrow environment that selectively protects the graft while making the leukemic cell vulnerable to follow-up therapy, which may include CAR T-cell therapy, CAR-NK cell therapy, or antibody drug conjugates. However, eHSCs must improve upon the efficacy of the current standard of care, allogeneic stem cell transplant.

Despite the promise of eHSCs, there are several unanswered questions about this approach, including:

- How to target more complex tumors that express multiple targets
- Whether there any genes with a similar redundancy to CD33
- Whether multiplex gene-edited cells engraft like a wild-type cell

Common Challenges in Cell Therapy

The primary challenge to conducting cell therapy trials is finding sites with the requisite infrastructure and capacity, which may explain why a handful of top centers, such as Memorial Sloan Kettering, MD Anderson, and City of Hope, account for the majority of cell therapy trials. That challenge is compounded by the COVID-19 pandemic, which has impacted several sites through staff attrition, layoffs, or shortage of providers. Another challenge for trial sponsors is that many larger academic institutions are developing their own therapies and prioritizing them over industry-sponsored trials.

Additionally, sites need to be adept and watchful in monitoring for safety signals with newer therapeutics. That may be especially challenging for secondary and tertiary sites, which generally have less experience and fewer resources to accommodate cell therapy trials. For example, many early autologous cell therapy sites lacked familiarity with manufacturing logistics, supply chain, apheresis, and infusion. Similarly, many companies lack experience with specific cell types, even when they have therapeutic area experience.

That makes it important to assemble product engineering teams specializing in formulation and delivery. "We don't just infuse cells into blood; we basically provide a frozen vial that can be readily, almost without training, be prepared for injection into the brain," Fruebis remarked as the discussion continued. It also helps to limit investigators' focus to specific indications in order to build and strengthen the translational platform, as well as product characterization and design, added Farid, who commented upon the importance of having a "close link to understand what our product is in depth and partner with investigators who will be working with us for some period of time."

Key Considerations for Early-Stage Cell Therapies

The "make-versus-buy" question is "a node where pretty much everything comes together on the manufacturing critical pathway," Precision for Medicine's Parker commented. Choosing one or the other is key to securing a roadmap for manufacturing and funding. Innovator companies must therefore balance short- and long-term plans with pipeline risk and demonstrate "proof of manufacturing" along with proof of concept.

Kassim, of Vor Biopharma, noted that deciding whether to make the drug product by itself, or also to internalize the critical raw material manufacturing, adds "another level of complexity that's somewhat unique to the cell and gene therapy space," particularly for companies using a viral vector, which "is a complex starting material." That makes it vital to develop a deep understanding of the cells, processes, assays, and critical materials in the early stage and to have hands-on analytical expertise to inform development and scale-up of robust processes and enter a reliable supply chain.

Another key question revolves around internal versus external manufacturing. "Internal gives you more flexibility as your pipeline matures, but it comes at a higher cost and a longer lead time to start your production," Project Farma's Khoury noted. He went on to observe that external manufacturing is more expensive per batch or per patient but has the advantage of being faster. He advised cell therapy developers to devise a cost per square foot to "discipline ourselves to different funding gates to eventually manufacture, whether it be the early clinical or the commercial lot."

Continuing the conversation, it was pointed out that early-stage efforts should focus on the development side, understanding the science, and being able to react quickly to findings and continue to run tests. It is not unusual for many companies to "straddle that line." As a company's pipeline matures, internal manufacturing may make more sense as a means to control costs.

Pricing and Market Access

Pricing and market access are widely regarded as the third key pillar for commercial success (ie, in addition to clinical development and manufacturing). This consideration is informed by three factors that differentiate cell therapies from conventional medicines:

1. **Potential for cure:** Although cell therapies are potentially curative, "the value proposition at launch may not fully reflect the true potential value based on the longer-term outcomes," Grosvenor of PRECISIONadvisors noted. From a payer perspective, it can be challenging to assess these treatments' value. That underscores the importance of phase 1 data for a curative therapy. It was also pointed out that at the time of approval, long-term data is not necessarily available, but the first patients in a phase 1 trial who are started on a potentially efficacious dose are those who will ultimately make the longest and biggest contribution to safety as well as efficacy.

2. **Very high cost of goods and price expectations:** Both of these factors fuel concerns about affordability and funding. Companies must therefore think very carefully about the pricing strategy and structuring the payment model or pricing agreement they strike with payers, which may need to accommodate some of these affordability concerns. For example, a static payment model could incorporate an outcomes-based component to factor in and address some of the uncertainties about long-term outcomes.

3. **Complex, multi-step administration, often in highly specialized treatment centers:** The distribution model and technology implementation strategy for a cell therapy have important implications for launch and the downstream commercial strategy.

In wrapping up this phase of the discussion, it was noted that manufacturers must very carefully consider not just the clinical development planning and targeting, but also regulatory considerations, study designs, the source of endpoints, and other data that would be meaningful to payer decision makers, including non-clinical and real-world evidence.

Conclusion

The ongoing evolution of the cell therapy field is intensifying pressure on regulators, payers, and other stakeholders to keep up with the rapid pace of technologic and therapeutic advances. For many cell therapy companies, questions regarding "make-versus-buy" or internal versus external manufacturing are arising sooner than they may have planned for, potentially elevating the importance of issues such as study design, site identification and monitoring, pricing, and market access. While addressing these issues can be quite challenging, the promise of cell therapy, as conveyed by the panelists, makes this a potentially rewarding pursuit and an exciting field to watch.

To watch the panel discussion that informed this whitepaper in its entirety, click **HERE**. For a link to part 2 of the panel's discussion—Focus on Gene Therapies—click **HERE**.

References:

1. Allied Market Research. Regenerative medicine market. May 2018. https://www.alliedmarketresearch.com/regenerative-medicines-market
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4. BlueRock Therapeutic. BlueRock Therapeutics receives permission from Health Canada for DA01 trial in Parkinson's Disease. April 7, 2021. https://bluerocktx.com/bluerock-therapeutics-receives-permission-from-health-canada-for-da01-trial-in-parkinsons-disease/

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