Moving Clinical Development Forward in 2023

cell&gene day 2023

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In today's cell and gene therapy landscape, there are over 1,400 companies striving to move their products forward into clinic—a critical step in commercializing these groundbreaking treatments.[1] Clinical development is a complex endeavor and the path to market requires careful consideration of factors ranging from chemistry, manufacturing, and controls (CMC) and regulatory strategy to study design, CRO selection, and clinical trial diversity.

To explore this and other cell and gene therapy sector priorities, 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, on May 11, 2023. Throughout this event, over 25 successful innovators from across the advanced therapy sector shared fresh ideas and insights on overcoming critical challenges in bringing life-saving therapies to patients in need.

This white paper is based on a wide-ranging clinical development discussion moderated by **Teresa Pokladowski**, Regional Vice President of Clinical Business Solutions at Precision for Medicine, and the following panelists immersed in novel technologies:*

Kanya Rajangam, PhD, Head of Research & Development and Chief Medical Officer, Senti Biosciences
Senti Biosciences has built a synthetic biology platform that can be used to program next-generation cell and gene therapies with gene circuits. Gene circuits are created from novel and proprietary combinations of DNA sequences to reprogram cells with biological logic, allowing them to sense inputs, compute decisions, and respond to their cellular environments to impact disease.[2]

Robert Ang, MD, CEO, Vor Biopharma
Vor Biopharma is a clinical-stage company focused on developing novel treatment approaches for patients with blood cancers by engineering treatment-resistant hematopoietic stem cell (HSCs) to enable potentially curative targeted therapy opportunities post-transplant.[3]

Albert Seymour, PhD, President and CEO, Homology Medicines
Homology Medicines is leveraging its proprietary HSC-derived adeno-associated virus (AAVHSC) platform to develop gene therapy and gene editing treatments for diseases caused by variants in a single gene, as well as gene therapy to produce monoclonal antibodies.[4]

Cristina Musselli, MD, PhD, Head of Clinical Development, Abata Therapeutics
Abata Therapeutics is focused on engineering regulatory T cells (Tregs) as targeted therapies that stop immune-mediated destruction, restore homeostasis, and promoted repair in affected tissues in autoimmune and inflammatory diseases.[5]

1. Alliance for Regenerative Medicine. The Sector Snapshot: April 2023. Available at http://alliancerm.org/wp-content/uploads/2023/04/WEB_ARM_Sector-Snapshot_Report_R02_Web.pdf.
2. SentiBio. Gene Circuit Engineering: Pursuing New Classes of Cell and Gene Therapies. Available at https://www.sentibio.com/index.php/approach. Accessed June 17, 2023.
3. Vor Biopharma. Not just a better treatment — a totally novel approach. Available at https://www.vorbio.com/approach/. Accessed June 17, 2023.
4. Homology Medicines. AAVHSC Platform. Available at https://www.homologymedicines.com/technology-platform/aavhsc-platform/. Accessed June 17, 2023.
5. Abata Therapeutics. Our approach. Available at https://abatatx.com/our-approach/. Accessed June 17, 2023.

Integrating CMC and clinical development

In recent years, there has been increasing emphasis on the need to integrate CMC and clinical studies in the overall drug development continuum to drive greater efficiency and cost-effectiveness, mitigate risk, and improve patient outcomes. By bringing together the CMC and clinical teams during the early stages of the drug development process, potential issues can be identified and addressed more quickly, with the goal of successful submission. Pokladowski opened the discussion by asking the panelists to share lessons learned during the investigational new drug (IND) submission process, starting with how their respective organizations decided whether to build in-house manufacturing capabilities or outsource to a contract drug manufacturing organization (CDMO).

Dr. Musselli indicated that Abata chose to partner with a CDMO that is also an investor in the company, with representation on the board. The CDMO is located only 20 minutes away from their headquarters and this proximity enables in-person information transfer and cross-training. "It's been a very well-established and productive partnership [that has] allowed us to get from the beginning [to talking] about the pre-IND in six months, which is an amazing amount of time," she said.

Vor started with a CDMO, but built in-house manufacturing capabilities after its initial public offering (IPO). With four clean rooms in the same building as their office space, the facility is sufficient to support late-phase clinical development and possibly early commercialization. Nevertheless, Vor is maintaining its relationship with its CDMO to reduce risk and enhance capacity.

THE MOST IMPORTANT CRITERION FOR VENDORS AND CROs IS
flexibility_

For Homology, Dr. Seymour explained, "Because we were developing a novel type of approach, we made the investment to bring process development—at least the earlier part of CMC—in-house." The advantages of an in-house approach include real-time data and a team that is highly invested in the success of the development program. Following its IPO, Homology was able to build its own Good Manufacturing Practice (GMP) facility to provide all the material for its programs to move into the clinic. With both process development and GMP manufacturing as internal capabilities, the teams were able to collaborate on troubleshooting and working together with regulatory and development colleagues throughout the pre-IND and IND submission process. Interestingly, Homology recently spun out its GMP facility as a joint venture with Oxford Biomedica, enabling the company to recoup some of its investment.

Senti built its own manufacturing facility, geographically co-located with its office. Dr. Rajangam added, "Especially for something like cell therapy, that tight collaboration and coordination between functions is so critical, whether it be doing research in clinical, translational, process development, manufacturing… all marching towards the same goal." She shared that Senti has built its team and company structure to enable rapid cycle time from bench-to-bedside and back by integrating teams and identifying target product profiles.

Supporting communication with regulatory agencies

In a sector where innovation is happening across an array of complex technologies and novel therapeutic approaches, it is a monumental challenge for regulators to familiarize themselves with all the advances that are occurring. Pokladowski shifted the conversation to how industry can support discussions with regulatory agencies.

Ang stressed the importance of transparency and having as much dialogue as possible with regulators to ensure alignment with their expectations regarding submissions and reports. He pointed out, "One of the challenges is you need to lock down your processes at [some point], certainly before you start your pivotal studies. How do you do that and how do you set those expectations both internally as well as with regulators as you're evolving that process?" Regulators recognize that clinical development is a journey and while it may not be necessary to have finalized assays before filing an IND, it is critical to have a plan to get there.

Addressing the challenges of access and diversity

Ensuring patient access and diversity in clinical trials is crucial to the development of safe, effective medications that can benefit a wide range of patients, but can be challenging—or even infeasible—with rare diseases or certain mutations. Pokladowski pointed out that lack of not just racial diversity, but also geographic and socioeconomic diversity, has led to limited data on the safety and efficacy of medications in underrepresented groups. She then asked the panelists about their approaches to alleviating access and diversity bottlenecks.

Rajangam highlighted that the underlying technology can impact access to clinical trials. "[At Senti], we've chosen NK cells as a backbone for our gene circuits. By many accounts and much of the clinical data coming out, NK-based therapy is much safer than T-cell based therapy. So, that already sets [us] up to be in a place where we can run our trials in more of a community clinic." Remote sampling and data collection can also help to increase access and diversity by limiting patient burden.

Ang elaborated on the fact that the underlying science can influence diversity. "We require HLA matching…so, unfortunately biology plays a role. There are particular races, particularly Asians and African Americans, that are more generally HLA-diverse than Caucasians…We just need to be cognizant of that as we are enrolling our trials." Further, Vor is onboarding high-volume transplant centers in the US and Canada, which are generally in large cities. Concierge services such as paying for travel and accommodations or transporting products to patients can help to overcome some access issues.

Similar to Vor, Abata requires specific major histocompatibility complex (MHC) haplotypes for its Treg therapy. Musselli referenced a previous clinical development program she had worked on where educational material was distributed to the community and where the company was invited to a church to provide information on what it means to participate in a clinical trial. "There is often a reservation [about] entering a clinical trial for historical reasons," she said. "My approach [is] looking more at the social structure and making sure that there is easier patient access for these therapeutics."

Selecting CROs and other external partners

Pokladowski expanded the discussion to collaboration not just with manufacturing, treatment centers, and regulators, but CROs and other external partners for clinical trial execution. Musselli indicated that Abata is pursuing a hybrid model where the central lab and clinical trial operations would be run by a CRO, and the biomarker assays would be run in-house.

Rajangam emphasized that the most important criterion for vendors and CROs is flexibility. Senti's intention is to keep the more strategic pieces of clinical trial execution—medical monitoring and elements of pharmacovigilance and statistics—in-house, especially for their first-in-human trial. Nevertheless, she stressed the need for an integrated, hands-on approach where internal and external resources work together as one project team.

Seymour added that, for Homology, one of the key challenges in outsourcing was identifying the skillsets needed for its unique technology. Often, that meant going to academia, which has a different culture than industry. "We did it…with a mix of internal expertise that understood the data that was coming in…and vendors that [had]…the technologies and equipment that we just didn't feel necessary to invest in," he said.

Ang indicated that Vor had hired certain functions that might typically be outsourced to a CRO, including site coordination, sample management, and registry relations. He continued by saying, "In terms of service providers…the biggest criteria is not just capability—which is a given—but we want you to commit your blood, sweat, and tears to what we're doing as well."

Sharing lessons learned

Pokladowski concluded the conversation by asking the panelists to share any advice they would give to colleagues in cell and gene therapy development. Musselli stressed the importance of communication. Seymour cautioned to never underestimate manufacturing and how quickly a mistake in that can affect a program overall. Rajangam expressed excitement about new technologies that are enabling smarter cells that do different things based on signals they receive from the body.

Ang shared, "It is a privilege to be in this space, but also it is very complex. We need the right compassion and empathy in play, not just working with patients, but with clinicians and with vendors of all kinds to make this happen. We need to have that sense of urgency combined with a sense of creativity because we are all pioneers."

**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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