Considerations for the Clinical Development of Cell & Gene Therapies (Part 2: Gene Therapies)

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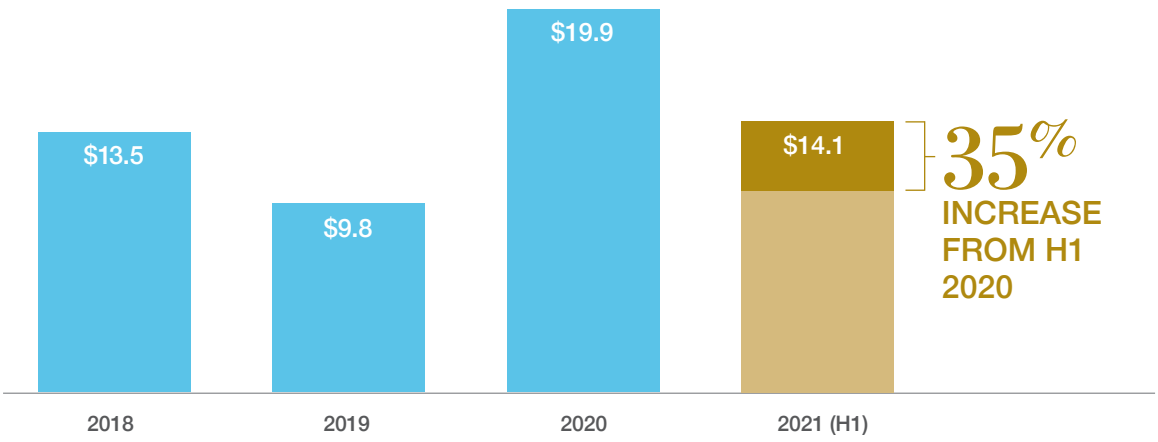
Part 2: Focus on Gene Therapies

Advances in stem cell technology, combined with the increasing prevalence of chronic diseases, are driving rapid growth in the regenerative medicine category, which is predicted to generate $39.33 billion in revenue by 2023.[1] The Alliance for Regenerative Medicine, in its latest progress report, noted that in addition to the 1320 ongoing industry-sponsored trials worldwide, as well as a similar number (1328) of ongoing trials sponsored by non-industry groups, financing for regenerative medicine and advanced therapies has reached new heights, with $14.1 billion raised in the first half of 2021—71% of what was raised in full-year 2020 (Figure 1). That surge in investment has made the first half of 2021 the strongest half-year on record, and puts the sector on pace to outperform 2020, during which nearly $20 billion was raised despite the COVID-19 pandemic.[2]

Figure 1: **Total global regenerative medicine financing (in billions of $)[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 second part of the discussion, which focused on gene therapies and included the following panelists:

- Phil Cyr, Senior Vice President, Customer Solutions, Precision Value & Health
- Tim Kelly, President of Manufacturing, AskBio
- Deborah Phippard, Global Head of Research, Precision for Medicine
- Tony Khoury, Executive Vice President, Project Farma
- Ottavio Vitolo, Chief Manufacturing Officer, Alcyone Therapeutics
- Steven Zelenkofske, Chief Manufacturing Officer, SwanBio Therapeutics

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 Gene Therapy

Adeno-Associated Virus (AAV) Vectors

AAV vectors present several challenges including scalability to clinical and commercial capabilities, limited yields, quality issues associated with adhering to Good Manufacturing Practices (GMP), and tissue tropism. However, AAV vectors can offer numerous advantages as well, including robust clinical data from more than 3,300 patients, with few adverse events; a wide range of therapeutic applications, including ophthalmic, neurologic, metabolic, and neuromuscular diseases; and capability for both localized and systemic administration. Additionally, this approach is validated by the presence of 2 US Food and Drug Administration-approved AAV-based gene therapies: Luxturna® (voretigene neparvovec-rzyl) and Zolgensma® (onasemnogene abeparvovec-xioi).

Advances in AAV vector capsid technology may enable both localized and systemic administration but pose challenges in terms of clinical impact. During the panel discussion, Kelly remarked that AskBio has built a "fairly broad dataset" for the naturally occurring serotypes that the company may be able to leverage in its clinical programs, although he also noted the need to build up a safety database as well as a therapeutic efficacy database for novel serotypes.

Ongoing preclinical studies of AAV9–based gene therapy have demonstrated proof of concept in terms of affecting the mechanism of disease in animal models of adrenomyeloneuropathy (AMN). Nevertheless, it remains challenging to validate endpoints in AMN (as well as in most neurologic diseases) and to translate biology from animal models to humans.

As part of the discussion, Zelenkofske of SwanBio commented on the difficulty of finding animals that demonstrate both genotype phenotype and molecular phenotype, although the ability to reliably count on that to go into adults or children is even harder. Whereas it is possible to detect genetic and biochemical changes in some animal models of neurologic diseases, the reliability of phenotype, in particular in the small animal models in these longer developing diseases, is much less reliable. "If you can find an animal model where you can actually exhibit a phenotype and see it change in the phenotype as well as the biochemical changes, you can have more assuredness that you're going to have a dose that should translate into an effect in adults and children," he summarized.

Intrathecal Delivery of Gene Therapies to the Central Nervous System (CNS)

The challenges associated with intrathecal delivery to the CNS—delivery efficiency, durability of effect, small patient populations—are not unique to gene therapy but are common to all therapeutics for CNS disorders, a disease area that can be difficult to understand and explore. However, what makes gene therapy unique are characteristics that are specific either to the vector or to the modality of delivery. These characteristics yield several advantages including small batch sizes, the ability to bypass or diminish the immune response (both to neutralizing antibodies and the initial dose of the therapy itself), a lower risk of liver toxicity, lower manufacturing costs, and the ability to "compartmentalize" the cerebrospinal fluid and brain.

"We can leverage what's already known about the vectors, in particular AAV9 and the tropism for specific cells and their biodistribution," said Vitolo of Alcyone during the discussion. This knowledge can be used to create "a top-of-the-line treatment approach."

Integrating Antibody Assays

One of the biggest challenges in gene therapy is choosing whether to develop a total antibody (TAb) assay or a neutralizing antibody (NAb) assay to incorporate into a gene therapy clinical development program. Whereas NAb assays are cell-based, which can make them more challenging to develop, TAb assays can be deployed to multiple laboratories and can be developed more quickly and less expensively.

"However, from an immunology point of view, there isn't clear data on whether a neutralizing antibody assay is going to be more useful than a TAb," Precision for Medicine's Phippard told the panelists. She also noted that every immunologist is going to have an opinion. Further complicating matters, the regulatory guidance is not that clear either. Consequently, Precision for Medicine is seeing some clients choose to develop both NAb and TAb assays in parallel, while others "go full on" with a NAb.

Alcyone's recently launched integrated platform combines its novel intrathecal delivery system with an advanced gene therapy platform from Nationwide Children's Hospital (NCH). The platform allows Alcyone to take advantage of NCH's experience with AAV9 vectors in spinal muscular atrophy, obviating the need to build all of these from scratch. "But notwithstanding that knowledge, certainly we are going to test for NAb," according to Vitolo. In addition to monitoring for NAbs, Alcyone is considering an immune suppression treatment that could reduce "the amount of NAbs that we have a role in," he added.

In the same vein, AskBio is researching novel capsid designs and other technologies that would allow the researcher to evade neutralizing antibody response or reduce it in a way that provides some clinical benefit.

In terms of validating assays, Phippard identified two key questions that must be addressed:

1. Will the assay be a full companion diagnostic?
2. At what stage of your clinical process do you need to start thinking about that?

Such questions underscore the importance of early planning. If an assay must be validated to Common Language Facility Codes to a companion diagnostic, validation will require GMP or GMP-like reagents. "Often they're not available," Phippard reported, "so we'll ask per vector, is that possible? Can we develop it? Do we have it?"

Another challenge in assay development is establishing a cut point for a disease in which a "dramatic" clinical effect may not appear for several months or years or when the therapy forestalls disease progression but does not reverse symptoms. According to Phippard, if the expectation is to develop a cut point using disease state samples, or at least demonstrate an effect in the disease state of interest, the cut point is not the same as that derived from normal or thermal plasma samples. Often in rare diseases it is not so simple to be able to source those samples.

Establishing a cut point can be particularly challenging in neurologic diseases in which the clinical symptoms take a very long time to develop and the ability to determine neutralization and effective, lasting transduction is quite difficult. That makes it important to identify a biomarker for transduction, according to Zelenkofske. “The difficulty in the CNS is the ability to identify that marker, to reliably know whether you have an effect and then on top of that, the ability to obtain sampling to follow that marker.”

Sample banking for assay development should therefore be a part of phase 1 planning and should be included in informed consent forms. Planning for assay development should occur at the same time as clinical protocol development, as this can avert downstream issues.

The panel agreed that early assay development is equally as important as manufacturing. Sometimes companies will forget that and wait to conduct assays for potency and other parameters, but that can complicate efforts to qualify the materials and confirm key product characteristics.

De-risking

De-risking the manufacturing strategy is a key consideration for early-stage companies seeking to scale up gene therapy manufacturing capabilities. Planning and investment for de-risking can take place as early as company infancy prior to spinning out or during early-phase seed funding. “It is a very important investment to the organization to de-risk, not just for manufacturing. It’s the business side; it’s the mobilizing of the asset,” said Khoury of Project Farma during the discussion.

De-risking should consider pipeline, epidemiology, dosing (eg, localized or systemic), yields, and the company’s progression from pre-clinical to early-phase clinical to pivotal studies. The goal is to identify an approximate amount of required material (and space) per year and how that correlates to available capital in the organization. This is important because scale-up horizons are often measured in months, not years. According to Khoury, “You really have to have the space ready to go, because usually when people start looking … [they] want it now. They want to be able to get going.”

In addition to manufacturing, the de-risking exercise should encompass process development, including internal, external, and analytical development, as well as warehousing and raw materials. De-risking therefore requires examination and evaluation of the whole process across the entire company.

Securing funding is an important element of de-risking. Project Farma is working with private equity organizations on methods to deploy capital to help innovator companies avoid having to raise funds. This involves laying out scope of work, evaluating contract development and manufacturing organizations (CDMOs), and preparing capital expenditure and operating expenditure plans. That information can then be used to inform seed funding and series funding and to lay out a robust plan for the organization as early as possible.

Some companies approach de-risking by leveraging their in-house capabilities. For example, AskBio, through its CDMO business Viralgen Vector Core, seeks to leverage its proprietary technology platform and optimize its manufacturing platform for yield and product quality. The platform is

serotype-agnostic and enables rapid generation of preclinical and clinical supplies, according to Kelly, who commented that the company hopes to disrupt the “make-or-buy” or the “build-or-buy” dynamic with Viralgen Vector Core. “We’re trying to offer something unique in this space where we’re making our technology platform available, very accessible to the rest of the industry in hopes that we can help advance a lot of therapies besides our own and get those to patients as quickly as possible,” he remarked during the discussion.

Securing and Sharing Scientific Input

It is important to solicit and obtain scientific input early in the development cycle, particularly in terms of projecting commercial-scale capabilities. Every company is different, based on the talent, the position of the asset, and its trajectory. It can be advantageous to establish some process development at scale along with some analytical development to further evaluate and gauge assumptions.

It is just as important to share scientific understanding with investors. “Show that you’re mature in this space, you have that knowledge, and then you give the scientists the apparatus they need to further progress their process and fully develop it at a larger scale,” Khoury added. “And make sure it’s commensurate with the clinical development.”

Optimizing Commercialization Planning

Whereas pharmaceutical manufacturers often think of commercialization 2 years before launch, the panel’s observations here began with the notion that sooner is better and that gene therapies actually lend themselves to the necessity of thinking about this phase even sooner than 2 years out. By way of example, it was pointed out that gene therapies for rare diseases, which often involve single-arm trials, acute therapy, or 1- or 2-time treatment, are placing the onus on payers to provide upfront coverage for downstream issues.

That makes it important to understand the natural history of rare diseases, especially for payers, for whom natural history data can enhance understanding of the cost of illness, “because they’ll want to understand what’s averted,” Cyr of Precision Value & Health remarked, adding that it is important to have that type of information developed at the time of clinical trials.

Cost-effectiveness is another key consideration in commercialization planning. Health economic models for gene therapy should incorporate clinical, quality of life, and economic considerations to calculate the cost per quality-adjusted life-year. “When building those models before a launch, especially with gene therapy, there are nuances that could have been collected during clinical trials that you often don’t have,” Cyr stated as the discussion neared its close. Early creation of a health economic model encourages consideration of what will drive that assessment and what pieces of data already exist in published public literature. This also enables identification of additional data that may be needed to facilitate clinical trial sourcing.

Conclusion

Despite the inherent challenges in developing and commercializing gene therapies, this mode of therapy is highly promising and will likely continue to generate considerable industry activity as the technology continues to advance. As the panelists observed, bringing gene therapies to market requires careful consideration of issues such as antibody assay development, sample banking, de-risking manufacturing and commercialization processes, and obtaining and sharing scientific input. A common thread running through all these considerations is the importance of early planning. For aspiring developers of gene therapies, the sooner they start the planning process—and the sooner they obtain answers to the tough questions they must ask of themselves—the greater the likelihood of success.

To watch the panel discussion that informed this white paper in its entirety, click **HERE**. For a link to part 1 of the panel's discussion—Focus on Cell Therapies—click **HERE**.

References:

1. Allied Market Research. Regenerative medicine market.May 2018. https://www.alliedmarketresearch.com/regenerative-medicines-market
2. Alliance for Regenerative Medicine. Regenerative medicine in 2021: a year of firsts & records. https://alliancerm.org/sector-report/h1-2021-report/

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Precision 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.**
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