



VIRAL VECTORS: ARE WE THERE YET?



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Viral Vectors: Are We There Yet?

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Looking at the current state of cell and gene therapies (CGTs), it is clear they have brought major changes to the biopharmaceutical landscape. Record levels of money and interest are pouring into CGT research, as well as technologies to develop and manufacture them, both with the intent to help realize the full potential of these gene delivery vehicles. Current statistics show these efforts are driving significant growth in this area, with nearly 1,000 ongoing clinical trials for CGTs registered with ClinicalTrials.gov and 22 CGTs approved by the FDA.¹

However, since the first gene therapy was administered in 1990, the field has experienced several setbacks, with the death of a patient in 1999 serving as one of the most notable.² Critical developments have since catapulted CGTs back into the spotlight, moving the needle from hype to hope, but there is still a long way to go when it comes to addressing the uncertainties challenging their long-term success. So, what must we do as an industry to continue this momentum and ensure these revolutionary treatments become a reality for patients who need them?

To Look Forward, We Must First Look Back

According to Peter L. Saltonstall, President and CEO of the National Organization for Rare Disorders, there are over 7,000 rare diseases affecting 30 million Americans.³ Yet, over 90% do not have an FDA-approved treatment available.⁴ Gene engineering offers a promising path toward

addressing this overwhelming medical need, but those walking that path have faced an uphill climb for decades.

As far back as the 1970s, it was predicted that gene therapy would be applied to humans within a decade, as scientists discovered the concept of viral vectors as a viable approach for gene delivery.⁵ It wasn't until 1990, though, that a disabled virus was used in the first gene therapy success story. Ashanthi de Silva, a 4-year-old girl born with severe combined immunodeficiency (SCID) due to a lack of enzyme adenosine deaminase (ADA), received injections of a healthy ADA gene into her blood cells, later kicking off a series of trials for the same form of SCID.² Unfortunately, these efforts hit a wall when 5 of the 20 children who were administered the treatment and reported as "cured" later developed leukemia when the viral vector that delivered the gene to their T cells also activated an oncogene, causing the cancer. Shortly after, Jesse Gelsinger died when a viral vector in another gene therapy caused a fatal immune response.² These setbacks led to the end of gene therapy at that time and a retreat by scientists who were left with the task of finding a safer way for viral vectors to deliver genes to a target cell.

Fast forward to today, when advancements in science and technology have transformed the field, and viruses have evolved to become highly efficient at nucleic acid delivery to specific cell types while avoiding immunosurveillance by an infected host. As a result,

they are now popular gene delivery vehicles, and several treatments have since been approved, with some notable achievements just over the last year, such as Biomarin's Roctavian™, the first gene therapy for adults with severe hemophilia A; PTC Therapeutics' Upstaza™, the first gene therapy to be administered directly into the brain; and bluebird bio's Zynteglo®, the first U.S. approval for a lentiviral vector gene therapy, as well as Skysona® (also by bluebird bio), which is the first FDA-approved therapy for early, active cerebral adrenoleukodystrophy.

The rapidly emerging CGT field seems to be on its way to fulfilling the prediction made by the FDA only a short time ago when the agency stated the growing pipeline of these products would eventually lead to 10 to 20 gene therapy approvals a year by 2025.⁶ Their continued commercialization, though, relies on a consistent supply of viral vectors to meet demand, which ultimately requires efficient large-scale manufacturing methods that offer satisfactory yield and purity and a lower cost of goods. Some solution providers have already begun to answer the call with products and processes designed specifically for viral vectors, but writing the next chapter of their history means an industry-wide effort to address those challenges that remain.

The State Of Viral Vector Manufacturing Today

This history of the viral vector market shares many similarities with that of monoclonal antibodies (mAbs): a remarkable discovery

set to revolutionize patient care that was initially blighted by side effects and overall development and manufacturing costs. However, efforts across the industry helped overcome these challenges through advancements in science and technology. Today, mAbs make up over 50% of biologic drugs on the market.⁷

Looking at the viral vector market, over 70% of gene therapy clinical trials worldwide rely on this critical component, yet their development requires specialized skillsets and manufacturing strategies.⁸ In addition, recent reports estimate the cost of goods/manufacturing for a gene therapy can be anywhere between \$500,000 and \$1 million, a number that does not take into account other factors, such as R&D, clinical trials, and building commercial infrastructure to support commercial access once a drug is approved.⁸

Nevertheless, despite the increased complexity of these viruses compared to a protein like a mAb, the bioprocessing community has forged ahead, adapting templates from mAb manufacturing for use in viral vector production. But capturing the possibilities of viral vectors – and the therapies they enable – means streamlining the viral vector workflow through standardized methods and purpose-built products that fit their unique development and manufacturing needs. This could help resolve the remaining challenges with viral vectors, allowing companies to get to commercialization faster, thus taking their piece of the proverbial CGT pie.

The challenges with viral vectors that manufacturers still face today can be categorized into three separate areas: unique, urgent, and uncertain.

Unique

Unlike mAbs, there are no standardized templates for viral vectors with respect to process development and manufacturing. Furthermore, process requirements

can vary greatly depending on the patient population, target organ, and in some cases, serotype. This means that two processes using the same core viral vector might look almost nothing alike. For example, in AAV-based therapies, ocular indications require somewhere around 10^{11} viral genomes per kilogram, whereas a muscular indication, such as Duchenne muscular dystrophy, would require about 10,000x higher viral load. Manufacturing therapeutics for these indications would likely require different process volumes and, therefore, have varying footprint needs. Adding to the list of challenges is the use of different serotypes of AAV for tissue tropism, which would mean that the chromatography and cell culture media products used in these manufacturing flows will be different, and the analytics strategy may not be the same. Dynamics such as this make it difficult to compare one process to another, ultimately making it harder to find broadly applicable solutions for the industry. Without industry standards to rely on or the benefit of hindsight from looking to past mistakes and learnings, viral vector manufacturers could make critical mistakes early that threaten their success later.

Urgent

When targeting rare disease, manufacturers typically face shorter commercial license pathways than those for other products, due to a demand that currently has limited to no supply. This makes the race to market even faster, not only in asset development but also tech transfer and manufacturing. In addition, every year that a therapy remains in the clinic is another year when some people who previously qualified for it have passed the eligibility phase. This puts considerable pressure on developers who want to see these therapies make it to the patients who need them but are also relying on research-based manufacturing practices that have scaled beyond their practicality, leading to a

reduction in process efficiency and, thus, increased costs and, ultimately, treatments that can become cost prohibitive.

Uncertain

As demand drives manufacturers to scale up processes faster than standards can be developed, it is much more difficult to learn from those who have gone before you. The result is a highly ambiguous space with incredible pressure to move as quickly as possible. Compounding this is the uncertainty surrounding clinical outcomes and regulatory expectations, especially when trying to move from the research stage to a GMP environment. Additionally, as more emerging companies turn to CDMOs to fill gaps in knowledge and experience, there is significant strain on available capacity, with lead times for viral vector manufacturing up to 18 months. Without access to reliable, sustainable, and cost-effective processing capabilities that can keep pace with demand as it changes over time, manufacturers are left with potentially viable treatments they are unable to deliver, preventing the realization of viral vectors and cell and gene therapies.

As we look ahead to the future of viral vectors, there are certainly many obstacles that stand in the way. Non-viral delivery systems offer an alternative but also come with their own bottlenecks and risks, and a comparison of each system's trajectory in the biopharmaceutical space shows an advantage to viral vectors, firmly establishing them as the most effective method for delivering genetic material.

Forging A New Pathway For The Future Of Viral Vectors

Addressing the three areas above could yield a wide range of positive outcomes, particularly that of accessibility to the general population, in terms of both availability and price. And while

process efficiency will always be a critical component of improving success in the CGT space, addressing the higher-level needs of manufacturers — i.e., access to capacity and expertise, simplified pathway to GMP manufacturing, shortening process development timelines, and reducing the exorbitant fixed costs associated with facility development — will help identify new ways to truly disrupt the CGT manufacturing space. Fit-for-purpose products geared toward the reality of scalable viral vector manufacturing, as mentioned previously, are incredibly important in this effort; however, adopting a holistic and integrated approach to viral vector manufacturing rather than just looking at improving one unit operation at a time is the key to moving the field forward by leaps and bounds as opposed to incremental steps.

As experts in the industry continue to explore the possibilities with viral vectors, it is important for solution providers to dig deeper into some of the pressing questions in viral vector manufacturing today, such as: Can closed processing be leveraged to reimagine how viral vectors are manufactured? How can automation be used to reduce the need for operator expertise? Can we use systems engineering to deliver viral vector process expertise directly to manufacturers in such a way that drastically reduces process development needs and facility requirements? These answers and more would create an entirely new pathway into the clinic and, ultimately, to market.

A Comprehensive Approach To Support Viral Vector Bioprocessing

At MilliporeSigma, we are a product, testing, and manufacturing services provider focused on developing solutions catered to viral vector bioprocessing that offer our customers a comprehensive approach to addressing the

challenges they face in this complex and increasingly competitive market.

Our VirusExpress® upstream platforms for both Lentivirus and AAV are designed to simplify process development and decrease process variability from one gene of interest to another. We are also heavily invested in scalable single-use technologies and closed processing to reduce the burden of capital expenditures and lower the barrier to GMP manufacturing.

In addition to a broad spectrum of solutions, capabilities, and experience in viral vector manufacturing at our Carlsbad, CA, location, our team is able to leverage more than 30 years of history in the development and manufacture of biologics. This includes characterization and analytical testing as well as platform testing methods, which offers our customers alternatives to time-consuming methods for release. MilliporeSigma also has internal R&D labs dedicated to bioprocessing of novel modalities and state-of-the-art M Lab™ Collaboration Centers where pharmaceutical and biopharmaceutical manufacturers can explore ideas, learn innovative techniques, and work side by side with our scientists and engineers to solve critical process development and production challenges.

From Hype To Hope

Thanks to the advancements in viral vector technology, the bioprocessing community has come a long way in realizing the revolutionary impact of these therapies and, as a result, has taken great strides in its quest to cure rare diseases. As we learn more about these gene delivery vehicles, the expectation is that this area of the market will continue to mature and advance much-needed treatments. And while remaining challenges continue to serve as a reality check that the journey is far from over, successes thus far have proven that the early hype of viral vectors has already translated into hope for patients around the world.

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