GEN INTERVIEW

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The Importance of CDMO Flexibility in AAV Manufacturing

GEN: ***Would Biovian, a contract development and manufacturing organization (CDMO) since 2003,tell us why manufacturing is a critical bottleneck in the development of adeno-associated virus (AAV) vector–based therapies?***

Dr. Gustafsson: The bottleneck links back to the unprecedented global increase in demand. Multiple companies are performing more clinical trials. Another reason is the transition from local administration to systemic delivery, which requires higher doses. Also, patient populations are getting larger as gene therapy applications are no longer only targeting rare diseases.

Magnus Gustafsson, PhD

As an example, an AAV-based product (Luxturna) targeting a rare eye disease is administered via local injection of 1.5E11 vg per eye. On the other hand, Roctavian for hemophilia A is delivered systemically using 6E13 vg per kilogram. With an average weight of 90 kg, one will need 5.4E15 vg per patient. This is 18,000 times the need for Luxturna per patient. The hemophilia A patient population size is estimated to be ~30,000 patients, which is at least 15 times higher than Luxturna's <2,000 patients. The dose demand for Roctavian is, therefore, 270,000 times greater! What can be done at a 1-L scale when Luxturna needs 270,000 L for Roctavian?

Dr. Padzik: Quality is even more relevant than capacity because it reduces both the effective dosage and enormous production requirements. New disruptive manufacturing technologies can help. For example, shift from fast but ineffective triple transfection to the use of transduction or stable cell lines that retain scalability. The ways to improve AAV efficiency without increasing the dose include the cell selectivity by serotype, GOI promoter selection, and induced gene switching with recombinases.

GEN: ***What kinds of concerns do small and mid-sized gene therapy companies (SMEs) have when they come to you?***

Dr. Gustafsson: Typically, SMEs have programs to start, but they struggle to get production slots. SMEs are at the heart of innovation but often find themselves overrun by more prominent clients when requesting CDMO resources. SMEs are not looking for massive bioreactors. They need small batches fast for early-phase trials because they need that data to support future funding. We often help them in a step-wise approach.

Clients may also need help with some basic things such as the selection of manufacturing platform, culture type, or sourcing of GMP-grade raw materials, which we routinely provide as part of our services. They may have questions about the technologies that can support scale-up scenarios or concerns about how to implement guidelines and regulations.

SMEs are looking for a CDMO with expertise and experience. The high diversity and complexity of viral vectors used in gene therapy and the strict regulations required for good manufacturing practice (GMP) production limit the number of companies willing to take on the challenge. The expertise takes years to build. For example, some clients change their processes between clinical trials and commercial manufacturing. Although challenging, this is doable by a CDMO that is flexible and willing to make an effort.

GEN: ***What can a CDMO like Biovian offer potential clients who are developing gene therapy products?***

Dr. Gustafsson: Biovian can provide manufacturing knowledge. Building viral vector processes from almost any starting point is the expertise of Biovian. Over 80% of people working here have higher education from Finland's top-ranking education system. Because of a

Biovian headquarters in Turku, Finland

low employee turnover rate, experience has been accumulating among the personnel for almost two decades. The result is a CDMO that has a track record and scientific skills needed for challenging projects.

Many of our clients need to demonstrate successful Phase I results before their investors provide more funding. The objective is to establish a robust, scalable, and cost-effective AAV manufacturing process while adhering to GMP regulations.

GEN: ***What expertise and experiences does Biovian bring to the table for its clients?***

Dr. Gustafsson: Biovian has been manufacturing viral vectors since 2004. With this experience, we can guide clients through all the steps. Biovian is a one-stop-shop CDMO, which means that the offered AAV vector services span from the laboratory bench to clinical trials. Switching providers at various stages could cause costly delays and risks, so Biovian is licensed for GMP production of both investigational drugs and commercial gene therapy products. Teaming up with a one-stop-shop CDMO can make it easier for gene therapy developers to achieve their project goals.

Dr. Padzik: Biovian has more than doubled its viral vector manufacturing capacity by opening a new state-of-the-art production facility in 2020. It provides the space we need for an even greater technical variety of bioreactors and cell factories to address the growing demand for AAV production flexibly.

Artur Padzik, PhD

Biovian develops processes with easy scale-up scenarios to avoid delays and costs associated with late changes. We also provide and develop analytical methods as part of our expert services. Being able to analyze samples in-house makes a huge difference. It speeds up the development of the process because time is not wasted on cross-audits or responsibility issues between different parties. Aseptic filling is also provided under the same roof, which minimizes the risks related to transfer logistics.

GEN: ***Please talk about the AAV production process from a technical perspective. What are the key issues, and how are these addressed?***

Dr. Padzik: Today, triple transfection is the most accessible method. It is a practical approach for clients who emphasize swift delivery and aim at a range of drug candidates for screening. When the number of candidates narrows down and clinical phases progress, other approaches may be needed. It is because triple transfection produces low to moderate titers, and the crude AAV product is known to contain a high percentage of empty capsids or inactive particles.

Biovian can address this need in multiple ways. We have a 200-L bioreactor available to support production on a larger scale for clients who want to continue with the triple transfection method. If requested, we

can implement more efficient and scalable processes using, e.g., baculovirus and Sf9 insect cells or newly introduced transduction-based technologies. These approaches can increase the physical titer 10–50-fold and the functional titer 1,000–2,000-fold compared to triple transfection. They also free the projects from another bottleneck—the availability of plasmids. Stable cell lines may be a solution for Phase III and commercial scale, but they will take 5–10 months to generate. Clients require a more flexible and faster system to progress with early clinical trials.

Many projects benefit from suspension cultures, where scale-up is more predictable than for adherent cultures. The great benefit of our range of bioreactors is that the process can be scaled. We are currently optimizing our process, intending to remove cell lysis which will significantly simplify the purification process.

Everyone is trying to increase the proportion of full capsids. The current AAV downstream dilemma lies in setting up a purification protocol optimized for a single serotype as opposed to a protocol that applies to multiple AAV serotypes but struggles to achieve high efficiency for each one of them. Our focus is on providing an adequate but, at the same time, flexible AAV purification system that is applicable for various AAV serotypes.

Dr. Gustafsson: It would be wonderful to have an academic/commercial initiative with open-source AAV platform process development, something like Linux. Technology innovation will be the driver for the success of gene therapy. ■

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