

PRODUCER CELL LINE ENGINEERING FOR LARGE VOLUME MANUFACTURING OF THERAPEUTIC AAV

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Recombinant adeno-associated viruses (rAAV) are among the most promising gene therapy delivery vectors for treating patients with genetic abnormalities. rAAV can safely deliver long-lasting expression of a therapeutic transgene to target cells. Multiple studies using rAAV have demonstrated sustained transgene expression in cultured cells and pre-clinical models, suggesting that rAAV could provide a cure for certain diseases. Moreover, bioengineering advancements have expanded the viral tropism beyond the constraints of naturally occurring AAV capsids, increasing the cell types that can be thought of as targets. Taken together, rAAV therapies have attractive qualities to safely address the needs of patients where other modalities may fall short.

One challenge with therapeutic rAAV is the ability to generate enough virus for clinical trials and commercial supply. This challenge is particularly true with neuromuscular or hemophilia patients in which doses can exceed 1×10^{14} viral genomes per patient. Typical yields from a rAAV production are around 10^4 viral genomes per cell, meaning batch cell numbers would need to exceed 10^{10} for a single dose. These doses require a robust, scalable platform to generate quantities of rAAV to meet patient demand. Biogen has selected the producer cell line (PCL) platform to meet the large demand for therapeutic rAAV. A PCL is a stable cell line engineered to contain the ITR flanked transgene of interest and AAV sequences needed to produce rAAV upon addition of helper virus. We will present our rationale for selecting the PCL platform as a cost-effective manufacturing strategy for gene therapy programs as well as current technical improvements and our vision for the next generation PCL platform.