DEVELOPING AN rAAV PRODUCTION PLATFORM WITH ENHANCED PRODUCTIVITY, SCALABILITY AND BIOSAFETY

LiYing Yang, PackGen Biotech
Liying.yang@packgene.com
Longxiang Sheng, Bo Liu, Ran Li, Huapeng Li

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Recombinant Adeno-Associated Virus (rAAV) remains as one of the most popular modalities in gene therapy due to its many advantages, including low immunogenicity, low risk of insertional mutagenesis, sustained long term gene expression, as well as capability of targeting specific tissue/cell type. With more AAV-based gene therapy being approved for commercial and much more AAV pipelines coming toward clinical proof of concept, the need for large-scale production of rAAV remains a challenge. In this study, various approaches were undertaken to improve productivity and product quality attributes of a suspension triple-transfection rAAV production platform. A development toolbox is established including cell line development, media/feed optimization, transfection condition optimization, as well as process intensification by perfusion. Case studies are presented where challenges were discussed and productivity of AAV is improved by applying DOE principles. At the same time, product and process-related impurities such as the host cell DNA is monitored. Process conditions yielding the lowest levels of host cell DNA are identified via a set of well designed DOEs. Furthermore, successful scale-up from bench-scale to 200L clinical scale is demonstrated by similar genomic titer from lysate in shake flasks, 3L bioreactors and 200L STRs.