ADVANCING THE PRODUCTIVITY, ROBUSTNESS, AND SCALABILITY OF AAV PRODUCTION PROCESS BY TRANSIENT TRANSFECTION IN SUSPENSION CELL CULTURE

Jenny Shupe, Biogen, USA
Jenny.shupe@biogen.com

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Recombinant adeno-associated viral vectors (rAAV) are the vehicle of choice for therapeutic gene delivery in the gene therapy field. The transient transfection method of production remains one of the most attractive processes for the manufacture of rAAV due to its fast turnaround and versatility towards the production of a wide range of rAAV constructs. To meet the increasing drug substance demand, further productivity improvement has been one of the primary focuses of process development. Process robustness and scalability challenges are also well-known obstacles to the wide application of the transient transfection process for AAV manufacturing in the industry. In this work, we have identified process parameters with significant impacts, and successfully demonstrated the effectiveness of comprehensive process optimization through the Design of Experiment (DoE) approach to improve AAV productivity as well as process robustness. During process optimization a >10x productivity increase was achieved through medium supplementation targeting the reduction of PEI induced cytotoxicity. Additionally, to address the well-known scalability challenge of the transient transfection process, novel complexation technology was developed and optimized for production scales larger than 250L. High productivity (above 1e11 vg/ml ddPCR titer) has been achieved for multiple programs using different AAV serotypes and demonstrated at 250L and 1000L production scales.