DEVELOPING COST-EFFECTIVE AND SCALABLE MANUFACTURING PLATFORMS FOR AAV PRODUCTION

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ABSTRACT

Cell and gene therapies are becoming increasingly available to healthcare systems worldwide as treatment methods against acute and chronic life-threatening diseases [1]. In the past 3 years a total of 22 new therapies have received regulatory approval with another 916 being in advanced phase II or phase III clinical trials [2, 3]. As the number of commercially available treatments increases so does the demand for synthetic and virus-based gene delivery systems.

Adeno-associated viruses (AAV), which are small non-enveloped viruses, have emerged as the leading platform for gene delivery due to their excellent safety profile and efficient transduction to various target tissues [4]. However, in order to meet increasing global demand, several process and technology related bottlenecks need to be resolved [1]. AAV manufacturing still heavily relies on transient transfection production methods using primarily adherent cell lines, both of which are impractical and cost ineffective to scale up, while stable suspension cell lines have not yet been fully optimized. The complex and demanding purification process that follows further exacerbates the problem, resulting in low final yields [5].

In the present study, process simulation software was used to develop a whole process model of AAV manufacturing with the aim of identifying robust and economically favorable configurations. Initially, a detailed list of suitable alternative technologies for each unit operation was built based on data from technology providers and the scientific literature. Subsequently all feasible technology combinations were simulated in order to estimate the resulting yields and costs per unit mass. Finally, sensitivity analysis was performed in order to characterize each possible configuration based on its robustness against perturbations both in the price of consumables and in critical process parameters (CPPs) for individual unit operations. The results presented herein provide insights into the rate limiting steps as well as the unit operations where a step-change in efficiency would have the highest impact on the overall process yield. Consequently, this study can be used to guide and inform future process development decisions in order to increase manufacturing capacity for AAVs.

KEYWORDS: AAV production, whole process modelling,viral vectors, gene therapy

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