

HIGH YIELDING LARGE-SCALE TRANSIENT EXPRESSION OF BIOTHERAPEUTICS IN CHO: BEYOND PRECLINICAL DEVELOPMENT

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Traditional stable CHO cell line development (CLD) to generate single clones typically takes 3-5 months. Hence, transient expression of therapeutics in CHO is routinely used to produce small amounts of candidate proteins rapidly for preclinical research to shorten timelines and reduce overall costs. However, low productivity, inconsistent product quality of expressed protein and scalability issues have prevented the use of transient gene expression beyond non-GLP preclinical studies. More recently, improvements in transient technology have enabled high protein yields. Additionally, enhanced cell line and process understanding may allow for transient protein production with product quality profile comparable to stable CHO cell line product. Overall, the recent advancements can provide an opportunity to make transient gene expression a viable option for producing drug substance for toxicology and early-phase clinical trials.

In this work we present a large-scale transient expression platform for rapid generation of proteins using flow-based electroporation technology in BMS-CHO platform. This platform can produce gram quantities of proteins with product quality profile comparable to the stable CHO cell line generated protein. We have implemented Alternating tangential flow filtration (ATF) system to perform perfusion and achieve high host cell densities, followed by buffer exchange in a closed system. This allows for flow-based electroporation followed by 14-day fed batch process in shake flasks, Ambr®250 and large-scale single-use bioreactors. Extensive screening studies were conducted to investigate factors for optimization of cell intensification, transfection, and process conditions to achieve high productivity and desired product quality profile comparable to clonal material. Overall process improvements have led us to achieve transient titers as high as 2g/L for model mAbs and we have established a consistent and scalable CHO transient platform for rapid protein production.