COMPUTATIONAL METHODS FOR CELL CULTURE MEDIA OPTIMIZATION AND PRODUCT QUALITY CONTROL

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Biologics development leading to approval can take decades. Acceleration of this timeline is necessary to bring safe and efficacious drugs to patients as early as possible. One research focus to reduce development time is the cell culture process development and optimization. In this study, we will present two computational strategies that cover: (1) enhancing cell culture media by amino acid optimization using Orthogonal-Partial Least Squares (OPLS) regression, and (2) modulating protein glycosylation by altering small molecule compound concentrations based on the Concentration Impact Factor.

Disproportionate nutrient balance in cell culture medium can have a negative impact on cell culture performance. In our study, OPLS regression was used to explain cell growth and monoclonal antibody (mAb) production dynamics from Chinese Hamster Ovary (CHO) cells as a function of amino acid (AA) stoichiometric balances. The OPLS model was trained on metabolic data from 24 concurrent 14-day fed-batch cultures. Metabolic fluxes and respective stoichiometric balances were then generated by calculating the difference between the theoretical biomass demand of each AA and the actual AA usage towards mAb production and experimental consumption. As a result, highly weighted stoichiometric balances represented those AA that could potentially enhance the previous feed medium and aim to achieve a higher intracellular catabolic activity. Accordingly, we used our computational model to generate varied amino acid additions to either a platform feed or a low nutrient feed by means of a 16-run mixture design. The experimental results showed that addition of model generated key AA resulted in a ~55% increase in peak cell density and ~90% increase in mAb production, respectively.

Appropriately glycosylated therapeutic mAb are critical for the proper molecular folding, stability, and in-vivo efficacy of the expressed proteins. Cell culture process conditions and medium compositions have been demonstrated to affect the expression of various glycosylation species. In this study, we evaluated a set of selected small compound for their potential in modifying glycosylation levels in mAb expressed in three different proprietary CHO cell lines. These small molecule compounds were first tested on one cell line to establish a baseline. To quantitate the glycosylation modifications, we have developed a mathematical correlation of a dimensionless number, termed Concentration Impact factor (C_f), to describe the degree changes in glycosylation species. Using the C_f algorithm established for the 1st cell line, we subsequently tested with other two cell lines, and were able to modulate and confirmed the level of glycan expression. This indicates that C_f correlation may serve as a tool to provide early assessment of final glycosylation profiles and levels on therapeutic proteins due to small molecule supplementations.

Overall, the two computational methods presented here are aimed to enhance biologics development speed as well as ensure product quality control.