DEVELOPMENT OF A CHO PRODUCTION MEDIUM UTILIZING PROTEOMIC AND METABOLOMICS ANALYSIS

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Key Words: CHO, Metabolomics, Proteomics

Traditional CHO cell medium development relies heavily on the stoichiometric analysis of metabolites in spent medium with emphasis on amino acid, glucose and select water soluble vitamin consumption. Analysis of these basic metabolites in an empirical design of experiment (DOE) has consistently resulted in incremental increases in titer generally through increased viable cell density (VCD) and viability of the culture. It has been long hypothesized that an upper limit to titer and product quality would be reached using traditional medium development techniques. Through the use of advanced cellular analytics we are developing a hypothesis based design of media through proteomic and metabolomics analysis of critical pathways focused on specific productivity. Metabolomics and proteomic analysis was conducted on two medium formulations with disparate growth and production characteristics. Medium formulation 1 (M1) demonstrates moderate peak VCD with a high specific productivity (qP) over a 14 day growth performance assay utilizing a recombinant IgG producing CHO-S cell line and DG44 cell line. Medium formulation 2 (M2) demonstrates a high peak VCD with moderate qP under the same conditions and cell line. A comparative analysis of metabolite abundance and enzyme regulation identified that M1 had greater flux in the sorbitol pathway verses glycolysis, the TCA cycle was upregulated to a greater degree than M2. A Design of Experiment (DoE) study was developed to increase the specific productivity of M1 without decreasing the VCD to M2 levels resulting in a superior volumetric titer. Simultaneously, we utilized traditional empirical approaches to increase the qP of M2 in a parallel set of experiments. We describe here the path to develop the medium, metabolic and proteomic pathways which were found to be important, and a comparison of results based on the traditional empirical path verses the hypothesis based advanced cellular analytics path.