Empowering CHOZN® GS$^{-/-}$ Cells: Advanced Media & Feed Optimization for Sustained Viability and Exceptional mAb Titers in Extended Fed-Batch Processes

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Introduction

Chinese hamster ovary (CHO) cells are the most common host platform for production of recombinant proteins for biotherapeutics and, in particular, of monoclonal antibodies (mAbs). This is in part due to their ability to perform complex, human-compatible post-translational modifications such as glycosylation. The CHOZN® GS$^{-/-}$ host cell line is becoming increasingly popular in industrial settings due to the detailed documentation associated with the cell line's generation, the greater stability of the glutamine synthetase knockout system, and the overall reduced development time[1]. mAbs continue to be critical players in the life-changing treatments of various diseases; however, the global accessibility of these treatments is hindered by their expensive production costs[2]. Here, we have developed advanced, chemically-defined cell culture media and feeds that sustain CHOZN® GS$^{-/-}$ clone viability and promote exceptional mAb titers in extended fed-batch processes.

Materials & Methods

CHOZN® GS$^{-/-}$ host cells were obtained from Merck KGaA (Darmstadt, Germany). The CHOZN® GS$^{-/-}$ clone utilized here was engineered by the OPM Cell Line Development Department for stable expression of the monoclonal antibody mAb1. Cells were cultured in passaging medium for at least three passages prior to starting experiments. For small-scale experiments, cells were cultured in 125 mL Nalgene shake flasks (Thermo Fisher) with initial volumes of 20 mL in an INFORS HT Multitron incubator shaker. For scale up validation, cells were cultured in an Applikon *my*-Control 3 L Glass Vessel (Getinge) with an initial volume of 1200 mL. For fed-batch processes, cells were inoculated at a density of 1.0 × 10^6 cells/mL in basal medium, fed with feeds/feed supplements, and supplemented with glucose to maintain concentrations above 1 g/L. Cell densities and viability were measured with a Vi-CELL BLU Cell Viability Analyzer (Beckman Coulter), metabolite concentrations were measured with an M-100 Biosensor Analyzer (Shenzhen Sieman Technology) or a Cedex Bio Analyzer (Roche CustomBiotech), and mAb titers were measured using a Cedex Bio Analyzer.

Results

Combo	Basal Medium	Feed	Feed Supplement
A	StarCHO Medium	StarCHO Feed	CDFS12
B	StarCHO Medium	StarCHO Feed Plus	CDFS12
C	StarCHO Plus Medium	StarCHO Feed	CDFS12
D	StarCHO Plus Medium	StarCHO Feed Plus	CDFS12

Table 1. Select combinations of OPM basal media, feeds, and feed supplements tested. Combination D was validated in a bench-scale bioreactor. Data is presented as mean ± standard deviation, where available (*n* = 3).

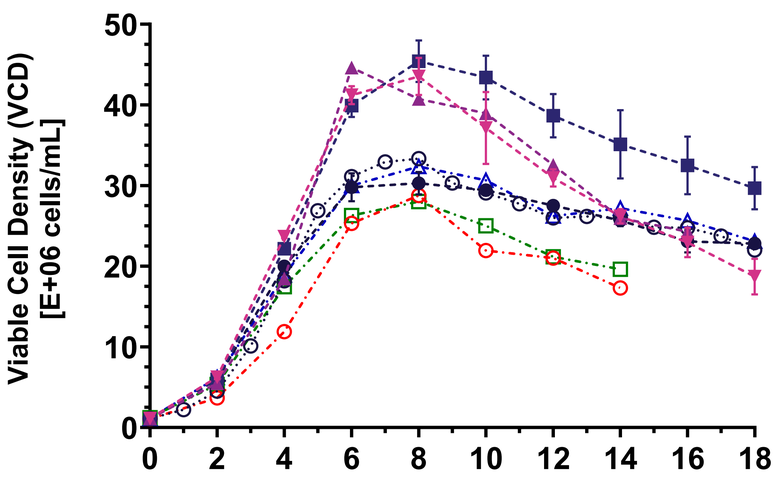

Figure 1. Growth profiles of cells during fed-batch processes. Combinations of OPM media and feeds supported peak viable cell densities (VCDs) similar to or greater than competitor products.

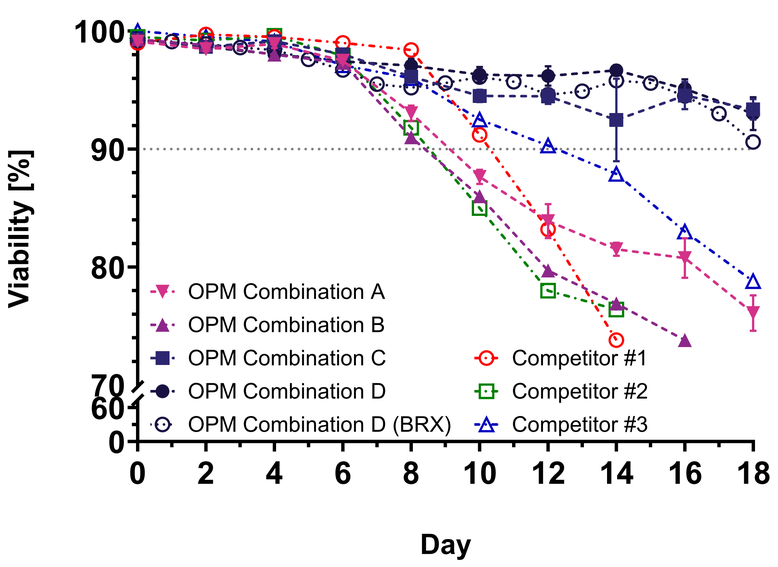

Figure 2. Cell viabilities during fed-batch processes. StarCHO Plus Medium maintained viabilities ≥95% at 14 days and ≥90% at 18 days whereas competitor products led to viabilities <90% by 14 days.

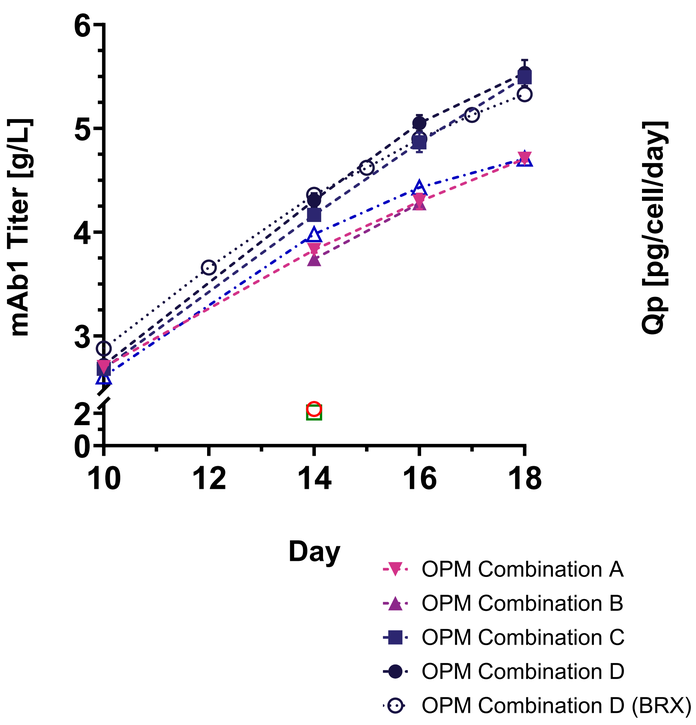

Figure 3. mAb1 titer measurements during fed-batch processes. All combinations of OPM media and feeds resulted in titers similar to or greater than the best competitor products. OPM Combination D resulted in the highest titers with 4.31 g/L and 5.53 g/L after 14 days and 18 days, respectively, in shake flasks.

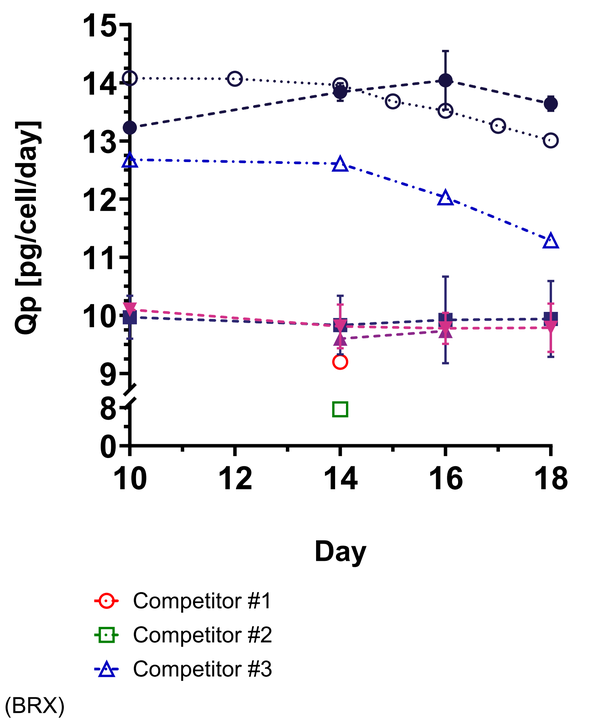

Figure 4. Cell-specific productivities (Qp) during fed-batch processes. OPM Combination D promoted the greatest productivity for the specific clone tested with 13-14 pg/cell/day in shake flasks, which was validated in a bioreactor.

Discussion & Future Work

Advanced cell culture media and feeds developed by OPM support CHOZN® GS$^{-/-}$ clone growth, sustain high cell viability, and maintain good cell-specific productivities. These characteristics allow for extended fed-batch processes with increased cell densities, ultimately enabling greater overall production of mAbs. As a result, OPM products promote exceptional mAb titers with performance similar or superior to the leading competitor products. Future work will include product characterization to ensure consistent product quality attributes. Because OPM media and feeds are specifically designed with the economics of production in mind, our products offer substantial opportunity for biotherapeutic manufacturers to reduce the overall cost of goods sold (COGS), ultimately increasing accessibility of mAbs and benefitting patients globally.

References

[1] Kiss B, *et al*. *New Bioprocessing Strategies* **165** (2018).
[2] Kelley B. *mAbs* **1** (2009): 443-452.

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