Development of Advanced Feed Media and Supplements

with Yaron Silberberg

Cell culture media play a crucial role in upstream process (USP) development. Their compositions are made of complex mixtures that affect the entire development process as well as product quality. Yaron Silberberg (chief scientist at Ajinomoto CELLiST Korea) discussed a multiomics (digital twin) technology that can identify crucial bioreactions and media components by creating global network visualizations of metabolic pathways. The genome-scale metabolic model (GEM) can simulate >7,000 individual bioreactions to better represent cells, identify bottlenecks in development, and improve bioprocess productivity.

Silberberg's Presentation

The traditional method of culture media development is to perform multiple wet experiments and statistical analyses. However, that technique doesn't provide an in-depth view of cells, and it would take thousands of experiments to examine all correlations between media components and cell culture performance. The use of multiomics replaces experiments with computer-based simulations, resulting in identification of metabolic bottlenecks and crucial media components. This approach leads to faster, more effective basal and feed media development.

Case Study: Silberberg presented a case study demonstrating the development of advanced feed medium using GEM in collaboration with Dong-Yup Lee's team at Sungkyunkwan University. The team tested two feeds prototypes (A1 and A2). Data were gathered using Chinese hamster ovary (CHO) cell cultures, measuring performance indicators such as viable cell density (VCD), titer, and amino acid concentrations in spent media throughout the culture process. The strategy identified contrasting pathways and metabolic reactions between the two feeds using the metabolic model. The team used partial least squares (PLS) regression to determine the variable importance in projection (VIP) and target specific metabolites exhibiting high correlations. Then, using the metabolic model, pathways with >20% difference in flux rates between the feeds were screened and filtered to help target specific bioreactions and metabolites. Additional selection steps identified metabolites and factors that had greater effects on culture performance and productivity. Once components were selected, the team adjusted the relevant media components, producing a new formulation. As an example, Silberberg presented how glutamate was adjusted in this study. Glutamate metabolism performed better with feed A2, so the team increased the amount of glutamate in feed A1 to balance. This alleviated the bottleneck in the citric acid cycle, allowed for greater lactate metabolism, and increased overall productivity by 20%. This formulation is now commercially available as the CELLiST F7 feed medium. Silberberg compared the performance of the CELLiST F7 feed with the team's previous feed, as well as competitors' feeds. The CELLiST F7 feed resulted in a >2× increase in titer productivity and significantly lower lactate accumulation.

Media Supplements: Ajinomoto has developed supplements (Cys1 and Cys2 supplements) to reduce precipitation and increase stability of feed media. Precipitation occurs when L-cysteine oxidizes and forms highly insoluble cysteine dimers. Ajinomoto's Cys1 and Cys2 supplements inhibit cystine-dimer–formation, increasing free L-cysteine by >5×. As a result, the amount of cysteine made available to cells increases, and productivity and liquid feed stability increase. Cys1 supplements are designed to be added to any single-component feed media, while Cys2 supplements replace high pH feeds in dual-feed platforms. In such platforms, one feed is kept at pH 7, and another feed is added from a separate feed tank at pH >11. In his slides, Silberberg illustrated how, instead of using two different dedicated feed lines, they can be combined into a single line at pH 7 by adding the Cys2 supplement. The combined line reduces feed precipitation in a dual-feed system to provide high productivity and cost-effectiveness.

Questions and Answers

Can we predict or control protein quality attributes and media effects on them? We are working on a technique to predict and control specific protein quality attributes using digital twins, artificial intelligence (AI), and machine learning (ML).

What is the advantage of switching from one cell culture medium to another at later stages of development? Drug development can take a few years. It starts with one type of medium, then during the process, higher quality media may become available. Switching to another media provider can improve productivity, quality control, and cost-effectiveness.

How do multiomics reduce the time to market for a biologic or biosimilar pipeline? They minimize the number of experiments required for media and process development and therefore reduce overall development time.

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