CHALLENGES IN CELL CULTURE PLATFORM DEVELOPMENT OF mAb PRODUCTION WITH SITE-SPECIFIC INCORPORATION OF NON-NATURAL AMINO ACID FOR ADC GENERATION

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Key Words: cell culture platform, non-natural amino acids, ADC, CHO-K1, tRNA, CRISPR/Cas9, cell line engineering, chemically defined media, process development

Ambrx's mammalian expression platform (EuCODE) enables non-native amino acids (nnAAs) through an expanded genetic code to both generate novel bio-therapeutics and to optimize the performance of antibody drug conjugate (ADC), therapeutic proteins, monoclonal antibodies (mAbs), and, bi- and multi-specific medicines. While the ability to control the defined Drug-to-Antibody Ratio (DAR) and payload site can provide an advantage to an ADC, the site-specific incorporation of the NAAs into the antibody heavy chain introduces a unique challenge for antibody production.

To enable higher performance benchmarks in time and resources for process development with stringent product quality requirements, a proprietary cell culture platform is being developed and demonstrated fast-track development of high-quality, high-titer processes for producing recombinant proteins from CHO cells.
We successfully generated a CHO-K1 cell line, stably expressing engineered amber suppressor tRNA and its cognate tRNA synthetase specific for non-natural amino acid para-acetyl phenylalanine (pAF), to achieve high production of monoclonal antibodies (mAbs) containing nnAAs. The stable cell lines were further evolved using CRISPR/Cas9 genome editing technology to sequentially knock out selected genes in glutamine synthesis, and, apoptosis pathways to improve selection efficiency and prevent loss of viable cell mass in production cultures, respectively. Inhibition of apoptosis pathway leads to dramatic increase in viable cell mass and results in extended production time and increased productivity.

In this presentation, we will discuss the challenges in cell culture platform development including cell line engineering, systematic DoE-based approaches on optimal chemically defined media and cell culture processes, and, strategies for scale up to clinical and commercial scales.