PRODUCT QUALITY CONTROL STRATEGY DEVELOPMENT FOR NON-MAB COMPLEX MODALITIES BY USING COMBINATORIAL CELL ENGINEERING AND OMICS SCREENING TOOLS

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Product quality control without compromising productivity has been a major goal in biotherapeutics process development. The challenge is further increased for new modalities using complex and hybrid protein structures, such as nanobodies and bispecific antibodies. New product-related impurities and unique product quality attribute (PQA) species have been found to accompany these new protein scaffolds, which usually don't exist in standard mAb production. Undesired attributes include unique patterns of glycosylation, conformation heterogeneity, mis-pairing, and partial molecules. Many of these PQAs are related to protein folding and assembly efficiency inside the cell, which impact post-translational modifications such as disulfide bond formation and glycosylation processes, directly or indirectly. We have identified multiple intracellular causal factors that link some PQAs directly to host cell lineage. To improve understanding and increase options in developing a successful production cell line with desired product quality profile, we have used this information to develop diversified CHO host lineages using both conditioned-culture adaptation and CRISPR genome editing approaches. The resulting CHO hosts showed significant differences in cell growth and recombinant protein production, including productivity and quality attribute profiles. Furthermore, the hosts respond differently to changes in medium components and process conditions. These differences were more significant for complex/ hybrid proteins such as nanobodies and bispecific antibodies. OMICS tools were systematically utilized to identify the evolutionarily significance of genetic and epigenetic variability of individual host cell lineages, which determine the specific PQA profile of the expressed recombinant protein. Overall, our presentation will illustrate the importance of selecting the appropriate host cell line through screening and/or engineering, as part of quality control strategy to obtain the desired recombinant protein PQA profile. .