NOVEL ENGINEERED CHO DG44 HOST CELL LINE DEMONSTRATES LOWERED UPR, INCREASED TITERS AND SUPERIOR QUALITY OF RECOMBINANT VACCINES

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The Chinese Hamster Ovary (CHO) DG44 platform is routinely used at the Vaccine Production Program (VPP) for manufacturing Vaccine Research Center (VRC) pipeline therapeutic proteins. Clonal cell lines have been generated that express broadly neutralizing monoclonal antibodies (bNmAbs) against HIV-1 with titers ranging between 1 and 5 g/L.

In the analysis of data from high and low productivity clones across a range of projects, high-producing clones were found to display increased viable cell density (VCD) and viability at later days in fed-batch culture. With an objective to understand the underlying mechanism for the observed differences in titer, we investigated the Unfolded Protein Response (UPR) pathway and found that multiple genes were differentially regulated among high- and low-producing clones. UPR-induced apoptosis was observed to be significantly higher in lower-producing clones and significantly lower in higher-producing clones at late days in culture.

Our initial analysis emphasized a need to generate a platform host cell with lowered UPR and more efficient protein secretion capacity to achieve maximum yields. Through the course of developing and characterizing a panel of cell lines expressing varying levels of human furin for use in a trimeric viral antigen project, a CHO DG44 clone expressing low levels of human furin was identified that had high VCD and viability in later days of fed-batch culture. Reduced UPR at late days in these cells, particularly the lowered expression of apoptotic genes, was seen to correlate to the late day increases in VCD and viability. When the low furin expressing host CHO DG44 cells were used for recombinant protein expression, the increases in VCD and viabilities were maintained compared to platform CHO DG44 host and we achieved a 3 X increase in viral antigen titers without any change in the existing upstream process. It is our goal to characterize the quality of recombinant proteins expressed in DG44- furin engineered clones. The extent of unfolded protein response in viral antigen expressing clones, furin level, and the influence of these factors on the quality of protein is currently under investigation. Our work describes a successful effort to rationally develop a superior host cell for increased and efficient yield of difficult-to-synthesize recombinant targets and points to a potential path forward for generating higher-producing clones for bNmAbs as well.