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Omics approach for generating a high-yield CHO cell line producing monoclonal antibodies

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OMICS APPROACH FOR GENERATING HIGH-YIELD CHO CELL LINES PRODUCING MONOCLONAL ANTIBODIES

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Chinese hamster ovary (CHO) cells are extensively used for the industrial manufacture of therapeutic antibodies. Generating high producing cell lines for secretory protein production requires knowing the bottleneck in the cellular machinery for protein expression. Integration site of gene of interest (GOI) is one of the important factors that influence the protein productivity. Even though screening of cells randomly integrated GOI can select high producing cells, the selected cell might not stable due to the chromosome instability. Here, we would like to look for host integration sites where GOI is high yield and stable by screening a single copy integration system. We developed several methods to identify integration sites including PCR based, whole genome sequencing based, and a platform to integrate a single copy of GOI into host genome. By determining the integration sites of the high producing clones, we can elucidate the major high yield sites for target gene expression. We have also employed the genome-editing tool, TALEN and CRISPR/cas9 to specifically integrate the vector with an antibody gene into two integration sites of CHO genome. Our data showed, IS1 and IS2 integration sites can be actively edited and specifically integrated an antibody expression vector of 15kb by either TALEN or CRISPR/Cas9. We successfully established site specifically integrated cell pools and expanded the FACS-sorted single cell into a cell line. Each single cell derived cell lines was confirmed by junction-PCR and sequence analysis. Furthermore, these single cells derived CHO cell lines are shown to express antibody gene with high titer. With the combination of omics knowledge and toolbox, including CHO genomics, transcriptomics and CHO specific microarray, GOI can be stably and highly produced.