BIOLOGICS 4.0: EMERGENCE OF THE CHO BIOFOUNDRY

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Mammalian cell factories are required for most, high-value biopharmaceuticals and CHO cells have proven most versatile. Routine transformation yields a highly diverse pool of production clones from which production lines can be isolated using high-throughput screening, e.g., FACS sorting. The flipside to clonal variation is that every production clone must be characterized for stability and product quality, and the production process generally has to be re-optimized. Moreover, the process relies on inexpensive screens of product, which is difficult to deliver for complex products or where the product needs particular posttranslational modifications (e.g., blood factors or bio-similars). For these purposes, the design-build-test cycle of modern biofoundries would be superior. The availability of the CHO and Chinese Hamster genomes together with advances in mammalian genome editing has renewed interest in using systems and synthetic biology to guide rational strain design. In this talk, we will present recent work on model-based design strategies, efficient multigene genome editing (Fig 1), as well as multi-omics characterization. We will highlight outstanding challenges that need to be resolved before a CHO Biofoundry can be fully realized.

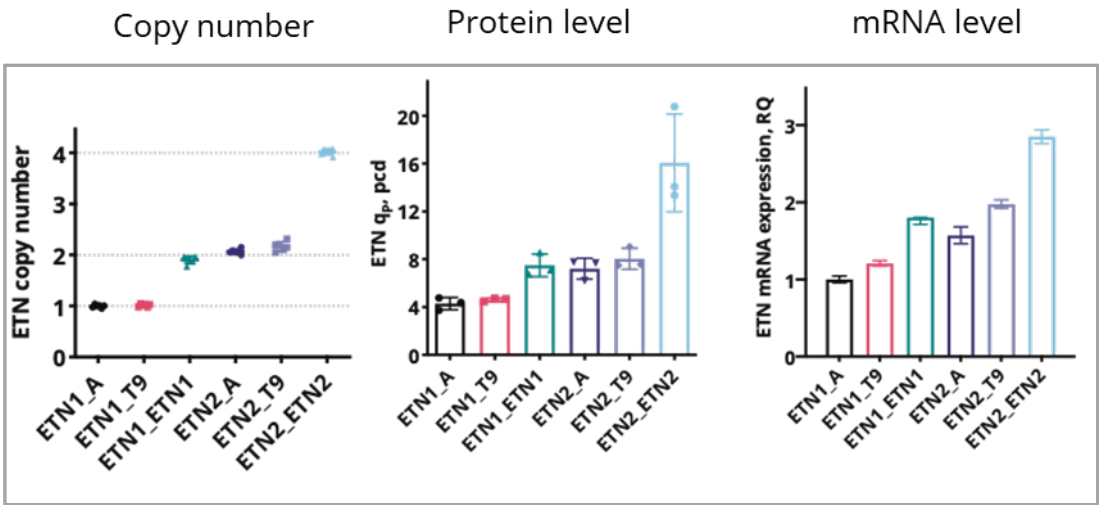

Figure 1: Efficient targeted integration using recombinase-mediate cassette exchange (RMCE) is critical to reduce clonal variation. Unlike Crispr mediated engineering RMCE can be used to create cell lines with almost no clonal variation (1). Using multi-copy targeted integration titers in excess of 1 g/L is readily achieved (2).

1. Grav LM, Sergeeva D, Lee JS, Marín de Mas I, Lewis NE, Andersen MR, Nielsen LK, Lee GM, Kildegaard HF (2018) Minimizing clonal variation during mammalian cell line engineering for improved systems biology data generation. ACS Synth Biol 7: 2148-2159. doi:10.1021/acssynbio.8b00140.

2. Sergeeva D, Lee GM, Nielsen LK, Grav LM (2020) Multicopy targeted integration for accelerated development of high-producing Chine Hamster Overy cells. ACS Synth Bio 9: 2546-2561. doi:10.1021/acssynbio.0c00322