Rational and Accelerated Cell Line Development & Engineering

Second in a Series of Application Notes on the integrated Cellular Omics Platform
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Cell line development is a central activity in biomanufacturing. Current approaches for cell line development are time consuming, expensive, labor intensive, and must be repeated for every new production cell line and protein product. The results are variable, unpredictable processes, both in terms of productivity and product quality. A major goal in sustainable biomanufacturing is streamlining the cell line development process while maintaining high titers and product quality.

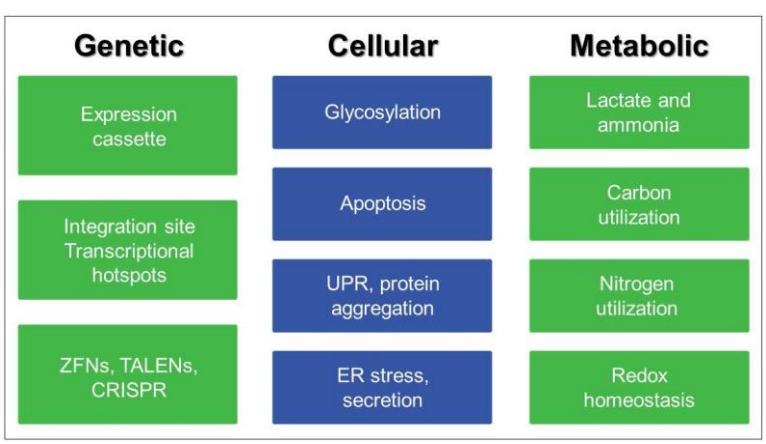
iCOP™ is an integrated Cellular 'Omics Platform developed by ArrayXpress to overcome these limitations. As a Systems Biology platform, iCOP relies on high-throughput 'Omics technologies to provide a system-wide characterization of the cell's DNA, RNA, proteins, and metabolites. Consistent with the QbD philosophy, it is a data driven approach that generates mechanistic insights into the production host physiology and metabolism.

Systems biology is essential for advanced engineering and optimization efforts. While production of data is easy, making use of it is not. AX properly designs the experiment and then integrates the collection, storage, analyses, mining, and visualization steps resulting in actionable information.

Enabling the systematic and directed engineering of production cell lines with iCOP

In contrast to the traditional, random approach, iCOP produces in-depth knowledge that guides the cell line development process. iCOP employs a rational engineering approach to genetically manipulate metabolic and regulatory pathways that determine product quantity and quality to improve process performance and efficiency.

Main areas of cell line development that benefit from iCOP



In GENETIC engineering, transcriptomic data is used to isolate novel regulatory elements for construction of expression cassettes and to identify transcriptional hotspots that support high levels of transgene expression. This information guides site-specific integration strategies using engineered nucleases, such as zinc-finger nucleases (ZFNs), CRISPR/Cas9-based systems, and transcription activator-like effector nucleases (TALENs). The selected genetic site is targeted for single-copy transgene integration in precision genome engineering.

In CELLULAR engineering, enhancement in cell line performance is achieved through genetic manipulation of key cellular targets that control intracellular processes relevant to biomanufacturing. For example, specific glycan profiles are enforced by manipulating selected genes in the glycosylation pathway, improving product safety and efficacy. Likewise, protein turnover, folding, and secretory capacities can be increased by the manipulation of genes involved in these pathways, leading to higher product titers. Signaling pathways and gene networks involved in cellular processes including apoptosis and cell growth can be optimized to increase cell viability and culture longevity.

In METABOLIC engineering, selected metabolic pathways are targeted for modification to maximize cellular productivity and metabolic efficiency. Metabolic by-products such as lactate and ammonia are a common problem in mammalian cell culture that adversely impact production and are prime engineering targets. For example, the metabolic shift from lactate production to consumption has been associated with increased titers and culture viability. This phenotype can be engineered through the genetic manipulation of rate-limiting enzymes in the central carbon metabolism, fine-tuning glycolytic activity, and adjusting the pyruvate flux into the tricarboxylic acid cycle. This improved control of oxidative metabolism results in a balance in intracellular reducing power and, ultimately, increased redox homeostasis.

Next generation cell line development

Bypass random genomic integration, transgene amplification, and clonal selection. Let AX help you to streamline your cell line development program. With iCOP, you will develop your own proprietary collection of engineered cell lines optimized to your specific bioprocess needs. Contact us to find out how.