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Special Focus: an 'omics approach to Chinese hamster ovary based pharmaceutical bioprocessing

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Chinese hamster ovary cell 'omics 2.0

Chinese hamster ovary (CHO) cells are the most widely used mammalian cell for the production of recombinant therapeutic proteins. For over a decade, industrial and academic research groups have used 'omics technologies to profile CHO cells to understand the biological processes that make them effective cellular factories. The goal of these efforts is to realize more efficient and predictable biopharmaceutical production.

The release of the CHO-K1 cell line genome in 2011 signaled the beginning of a revolution for the CHO cell biology community [1]. Since then, five additional CHO cell line genomes and two *Cricetulus griseus* genomes have been published [2,3]. The availability of these data have accelerated research dramatically allowing us to develop accurate expression profiling platforms, apply modern gene editing technologies and for the first time carry out genome-scale analyses. The CHO cell 'omics 2.0 era has begun.

This timely special focus issue of *Pharmaceutical Bioprocessing* presents a series of reviews, editorials and perspectives from academic and industrial scientists on recent developments and emerging trends in the CHO cell biology area.

Applications of 'omics technologies

Kyriakopoulos and Kontoravdi review recent 'omics analyses of CHO cell productivity and growth rate [4]. The authors examine outputs of several transcriptomic, metabolomic and proteomic studies and highlight biomarkers for selecting high producing clones as well as cell line engineering targets. Until recently, the CHO epigenome has received little attention. Dahodwala *et al.* outlines how processes such as DNA methylation and chromatin organization have been shown to play an important role in gene expression and stability in other species [5]. The experimental methods utilized to study epigenetics and potential applications for CHO cell bioprocesses are also discussed. Kumar *et al.* presents the current state-of-the-art for proteomic analysis of CHO cells [6]. The authors review sample preparation and protein labeling and their detection using MS as well as discussing areas of application for bioprocess improvement such as media development. Finally, the proteomics resources available at CHOgenome.org are presented [7].

Industry perspectives on CHO cell 'omics

Two articles from industrial scientists share opinions of how the industry can benefit from a systems level understanding of CHO cell biology. Laux discusses the potential of genomic sequence and expression profiling platforms to improve productivity, ensure stable expression of transgenes and optimize media formulations [8]. The author also discusses the need for a better understanding of post-translational modifications to facilitate rapid biosimilar development. Wright and Estes present their vision that 'omics techniques, particularly RNA-Seq, will be central to the bioprocess industry in the future and they can forsee a potential regulatory role for NGS technology [9]. The authors argue that 'omics data acquired from the users own host cell lines and processes are most likely to lead to meaningful discoveries.

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Characterizing & engineering product quality

The ability of CHO cells to produce correctly post-translationally modified proteins is essential to their dominance in the biopharmaceutical industry. Spearman *et al.* presents a review of the production of recombinant glycoproteins that spans a range of areas including the pathways responsible for glycosylation in CHO cells and the experimental techniques (e.g., MS) utilized to characterize glycan structure [10]. Pamela Stanley discusses the utility of currently available CHO cell glycosylation mutants [11]. The potential applications of gene editing technology such as the the CRISPR-Cas9 system to manipulate glycosylation and optimize recombinant protein production during cell line development is also discussed. Chan *et al.* focus on cell engineering to improve sialylation, a critical factor in the efficacy of glycoproteins [12]. The article summarizes research in the area and describes a recent study from the author's laboratory utilizing the CHO-gmt4 cell line to increase erythropoietin sialylation.

Data mining & modeling approaches

The community is generating 'omics data from CHO cells at an ever increasing rate. The utilization of CHO-specific bioinformatics resources coupled to powerful statistical and genome-scale modeling tools will be essential if the community is to make sense of these complex multidimensional, multilevel datasets. Clarke *et al.* present a review of the statistical methods utilized so far to mine expression profiling data to prioritize biomarkers and cell line engineering targets [13]. A number of approaches are reviewed from straightforward differential expression analysis to machine learning algorithms to the integration of data from multiple levels of the biological system. Since the publication of the CHO-K1 genome several groups have been utilizing sequence and expression profiling data to generate and validate genome-scale models for CHO cells. Kaas *et al.* describes the utility of genome-scale models across a number of species and outlines their potential application in areas such as CHO cell metabolic engineering and genome annotation. [14].

A systems biology approach to CHO cell engineering

Hefzi and Lewis present a tantalizing vision of the promise offered by convergence of multiple technologies (genome sequencing, genome-scale models and genome editing technology) to enable the reproducible and predictable manipulation of CHO cells [15]. Examples outlining the achievements of systems biologists in manipulate bacterial systems manipulating bacteria are described and the challenges to be overcome in order to replicate those successes in CHO cells are discussed.

Collaboration in the post genomic era

It is now evident that great strides have been made by the CHO cell community in a very short amount of time and the genome sequence is a driver for collaboration amongst researchers. Nicole Borth provides a summary of the 'Genome scale science for CHO production cells: Genomes, -omics and Big Data' meeting recently held in Vienna [16]. That meeting brought together scientists with expertise across a broad range of areas including genome sequencing, 'omics analysis, bioinformatics and genome-scale modeling. The main outcome of the meeting was the agreement that the Chinese hamster should be used as a reference with a new reference assembly planned for release in 2015.

Sarah Harcum outlines current barriers to academic/industrial collaboration in the USA [17]. Areas such as funding, education, communication and intellectual property are discussed and potential solutions to issues are presented. It is clear that if recent advances in CHO cell genome-scale science are to continue and the promise of better biopharmaceutical production is to become reality we must continue to foster collaboration between academics and researchers in industry.

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