## Establishing a Reference Cell Culture Platform for Biomanufacturing

The biopharmaceutical industry has emerged as a major manufacturing engine of the U.S. economy. With new biological information brought about through technology innovation and data acquisition, ample opportunities exist to improve biomanufacturing efficiencies.

The Advanced Mammalian Biomanufacturing Innovation Center (AMBIC), supported by the National Science Foundation's Industry-University Cooperative Research Centers Program (IUCRC), seeks to transform upstream cell culture bioprocessing in three areas: industrially relevant biology; process monitoring and control; and consensus and standardization.

Supported by 17 industrial members representing a cross-section of the biopharma industry, AMBIC is based at Johns Hopkins Univ. (JHU), Clemson Univ., Univ. of Delaware (UD), and Univ. of Massachusetts (UMass) Lowell, and has an affiliate site at the Univ. of Maryland, College Park (UMD).

AMBIC seeks to make biopharmaceutical manufacturing processes more efficient and cost-effective by bringing together leaders from industry, academia, and government to foster upstream mammalian cell culture innovation.

One major objective of this partnership is to develop a reference cell culture platform for biomanufacturing. While Chinese hamster ovary (CHO) cells are the principal platform used to produce the great majority of biopharmaceuticals worldwide, no common CHO cell line, culture media/feed, or process exists as a standard or baseline for innovation and comparison across the field. The availability of such a platform will facilitate a better understanding of cells and cell culture processes in a manner that is impossible today, given the diversity of cell lines and media currently used.

Other AMBIC projects are building on this reference platform effort, such as an investigation by Winston Timp (JHU) to elaborate the epigenetic state of cells and identify favorable expression conditions. Similarly, Kelvin Lee and Bramie Lenhoff (UD) are characterizing host-derived proteins in industrially relevant conditions.

Maciek Antonowiecz (UD), Seongkyu Yoon (UMass), and Mike Betenbaugh (JHU) are evaluating how cells in culture utilize nutrients and identifying potentially inhibitory waste metabolites that can accumulate in culture. This information is also used to enhance a genome-scale metabolic model of CHO cell culture performance. Additionally, Sarah Harcum's lab at Clemson Univ. is developing control strategies to maintain the cell cultures in a highly productive state.

Projects are also under way to investigate culture conditions. For example, surface-enhanced raman spectroscopy (SERS) technologies developed by Jake Khurgin (JHU) and wireless multicomponent sensing developed by William Bentley and colleagues at UMD can provide more efficient process monitoring within bioreactors. All of these efforts are being applied to optimize CHO cell growth, bioproduct yields, and product quality.

Alhough AMBIC is only a year and a half old, it has already established a framework for cooperation and collaboration between teams of academic, industry, and government scientists. Industry mentors meet virtually with university researchers on a monthly basis, enabling more direct interactions between graduate students and industrial engineers and scientists. These experiences help focus students' training and address workforce development needs in a way that has not been attempted at this scale in the U.S.

Ultimately, AMBIC's activities will have a lasting impact on the cell culture community through innovation and workforce development in a critically important sector of the economy that provides life-saving medicines to patients around the world. CEP

### Key outcomes of AMBIC

- *Establishing a CHO cell reference platform*. This reference platform includes two CHO cell lines that produce antibodies at levels compatible with or near industrial levels. A production process is being established for this production host. In addition, a defined AMBIC medium, AMBIC 1.0, has been developed.
- *Epigenomics research*. An initial characterization of the epigenome has been established for the two mammalian production cell lines.
- *Metabolic tracking*. A series of 13C labeling experiments has been performed to track the allocation of amino acids to the AMBIC cell lines. And, a genome-scale mathematical model is being applied to mammalian cell culture processes.
- *Proteomics research*. Mass spectrometry and other analytics have been implemented for characterizing post-translational modifications and host-cell proteins.
- *Media properties*. The chemical properties of specific components in the media are being defined. Analytical methods are being established to identify potential inhibitory metabolites in cell culture fluids.

This technology was funded through the NSF Industry-University Cooperative Research Centers Program (IUCRC).

This article was prepared by the National Science Foundation in partnership with *CEP*.