ACCELERATED PROCESS DEVELOPMENT FOR INTEGRATED END-TO-END BIOLOGICS MANUFACTURING

Laura Crowell, Massachusetts Institute of Technology, USA
lcrowell@mit.edu
Kerry Love, Massachusetts Institute of Technology, USA
Steven Cramer, Rensselaer Polytechnic Institute, USA
J. Christopher Love, Massachusetts Institute of Technology, USA

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With the exception of monoclonal antibodies, biologics typically require bespoke manufacturing processes that vary widely in the type of and number of unit operations. This constraint leads to custom facility designs and unique strategies for process development for every new molecule. To enable flexible, multi-product manufacturing facilities and to reduce the speed to clinic for new molecules, streamlined manufacturing processes and associated strategies for process development are needed. We have developed a bench-scale, integrated and automated manufacturing platform capable of rapidly producing a variety of recombinant proteins with phase-appropriate quality for early development[1]. The system comprises three modules for fermentation via perfusion, straight-through chromatographic purification, and formulation. To facilitate the production of multiple products on the same system, we have also developed a holistic strategy for process design to manufacture new products in as few as twelve weeks after obtaining the product sequence. While upstream process development in our host (*Pichia pastoris*) has been relatively straightforward, there are not many tools currently available for developing fully integrated straight-through chromatographic processes. Therefore, we developed an *in silico* tool for the prediction of fully integrated purification processes based on a one-time collection of host-related data combined with conventional high-throughput chromatographic screening data for each new target molecule[2]. We used this tool to develop fully integrated, end-to-end production processes for three molecules (hGH, IFNα-2b, and G-CSF) with at least 45% fewer steps than traditional processes. While our *in silico* tool allows for rapid resin selection, it may not predict the optimal process for each individual molecule since it is based on conventional high-throughput screening techniques which seek to optimize each chromatographic step independently rather than optimizing a fully integrated, multi-column process. To address this limitation, we have also developed a DoE-like framework for the optimization of fully integrated purification processes once the resins have been selected. First, a series of range finding experiments are carried out on each individual column, similar to conventional screening but with limited analytics. Next, we carry out fully integrated (multi-column) testing of the proposed operational area with more extensive analytics, including host cell protein, DNA, and yield measurements. We use this methodology to develop optimized processes for the end-to-end production of a variety of single domain antibodies with high yield and purity. Further, we present a method for predicting the optimal operating conditions for a new molecule within the same class based only on its biophysical characteristics, reducing the timeline from sequence to early stage, phase-appropriate product to only six weeks. Using these holistic strategies for process development, we have produced over ten different recombinant proteins on our manufacturing platform including enzymes, cytokines, singe domain antibodies, and vaccine subunits. We believe that such integrated strategies for process design could enable the rapid translation from sequence to early stage clinical development of products for a variety of molecules and potentially allow clinical testing of a greater number of high quality molecules for vaccines and biopharmaceuticals.

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