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Challenges and exciting solutions to downstream bioprocessing operations for the manufacturing of therapeutic vaccine candidates

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Abstract

The cultivation and fermentation processing using fed-batch fermentation or perfusion is rather inexpensive in delivering high yields of target proteins. However, the downstream processing for the recovery and purification of the proteins can be challenging. This presentation summarizes the systematic methodology for the clarification of bacterial and viral vaccine proteins. The methodology pertains to the clarification of vaccine proteins that are extracellular (i.e. viral or bacterial product) or intracellular (i.e. bacterial soluble protein or inclusion body). The methodology was established based on data related to process economics, recovery and purity of the clarified material prior to downstream column purification. Based on the analysis, we have found that the initial step of clarification after fermentation should be centrifugation. This centrifugation step serves to separate the protein of interest from cells, if the product of interest is extracellular, or to concentrate the cells to an optical density for homogenization, if the product of interest is intracellular. In the case of an extracellular protein, a final ultrafiltration step is usually performed to concentrate and condition the product before column purification. In the case of proteins that are intracellularly expressed, the clarification of soluble protein is best recovered, after homogenization, using microfiltration followed by a final ultrafiltration step to concentrate and condition the protein prior to column chromatography. The clarification of inclusion body is best recovered and purified using centrifugation where the centrifugation helps facilitate better separation of the denser inclusion body particles from the lighter cellular debris. In addition, other methods such as a direct capture step (i.e. modified suspended bed chromatography) were economical in proteins as it reduced additional downstream columns due to its selectivity. Other membrane technologies (Q, HIC, His) are discussed in their ability to reduce column chromatography steps downstream for improve recovery, purity and cost

Biography

Dr. Tim Lee received his Ph.D. in Biochemical Engineering. The area of research was focused on the mechanical and catalytic stability of immobilized enzymes. He then did a post-doctoral fellowship at Sanofi pasteur, Canada, where he was involved in the optimization of primary recovery processes for bacterial systems, mainly focusing on micro-filtration, centrifugal and chromatographic separations. As a senior development scientist within sanofi pasteur, Dr. Lee has played a key role in the development of different bacterial media, fermentation and purification optimization and scale-up as well as the transfer of processes to Industrial operations for manufacturing and externally to CMOs. He has also published many patents and scientific papers and has presented extensively, globally, over the last several years, outlining the work performed in the industry. As a director of bulk manufacturing and operations, he was involved extensively in cGMP commercial manufacturing, facility qualification, process validation and continuous improvement initiatives for the global organization utilizing Lean six sigma training for the biopharmaceutical industry. He is currently a Senior Scientific Consultant for Latham Biopharm Group specializing in CMC and winning of government contracts and continues to interact with vendors to find new technologies to improve and simplify the industrial operation for the manufacture of vaccines.