BIOPROCESS ENGINEERING OF INSECT CELLS FOR ACCELERATING VACCINES DEVELOPMENT

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The majority of novel protein-based biologics require animal cell technology for discovery and production. The costs and complexity associated to these production platforms are commonly high making mandatory further improvements in product yields. Technological breakthroughs and/or new producer hosts allied to classical systems/molecular biology tools and engineering methodologies are therefore necessary for accelerating biologics manufacturing process, including vaccines.

Two case studies will be presented where bioprocess engineering assisted/accelerated vaccines development. In the first case study, the aim was to generate an Influenza VLP in which the surface antigens are presented in their native conformation as membrane-bound proteins and are comprised of several hemagglutinin (HA) variants specifically designed to target B cells capable of mounting broad neutralising antibodies. The platform herein adopted for production of enveloped Influenza VLP enclosed certain drawbacks, namely (1) instability of baculovirus vectors encompassing multiple HA genes, and (2) low expression levels and recovery yields. To tackle these issues, a set of bioprocess engineering schemes were designed and subsequently implemented, which included (1) combination of stable and baculovirus-mediated expression of HA in insect High Five cells for production of difficult to express multi-HA VLPs (pentavalent VLP of H3 subtype), (2) DoE for identifying best infection strategy and evolutionary engineering of insect cells phenotype, and (3) development of a scalable, “universal” and “All-Filtration” purification platform of Influenza VLPs.

In the second case study, the aim was to develop a fast and flexible insect cell platform for production of enveloped VLPs pseudo-typed with membrane proteins of interest. Stable insect cell lines have been successfully generated using site-specific gene integration based on flipase-mediated cassette exchange (FMCE) technology. Influenza M1 and HIV Gag proteins were evaluated as scaffolds, and proof-of-concept demonstrated using two membrane proteins, the Influenza HA protein (e.g. for vaccines) and the human beta-2 adrenergic receptor (e.g. for drug screening or antibody discovery). Bioprocess engineering schemes have been designed (adaptive laboratory evolution to hypothermic culture conditions and supplementation with productivity enhancers), allowing to improve Gag-VLP production in the developed stable insect cells.

Overall, the insect cell platforms and bioprocess engineering strategies herein assembled have the potential to assist/accelerate vaccines development.

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