

**Title:** Advances in bioprocessing and analytics to accelerate vaccine production

**Author(s):** Antonio Roldão

**Affiliation(s):** iBET & ITQB NOVA

**E-mail:** aroldao@ibet.pt

**Address:** Av. República, Qta. do Marquês, Edifício IBET/ITQB, 2780-157 Oeiras-Portugal

**Abstract:** Vaccination is the most effective method of disease prevention, being responsible for controlling and/or eradicating some of the worst diseases in history. Development of new vaccines has become critical with the growing concerns about public threats such as Ebola, Zika, Dengue, or pandemic strains of influenza and coronavirus. Nonetheless, vaccine manufacturing remains incredibly challenging and complex. Here, current limitations and complexities in vaccine manufacturing will be reviewed, specifically related to process development and analytics implementation, with an outlook into the future. In addition, an overview of the bioprocess and analytics innovations and technologies designed at iBET to overcome production challenges will be presented. This includes:

- Cell line development:
  - combining RMCE technology with FACS high-throughput screening for generation of stable (insect and mammalian) cell lines;
- Upstream processing:
  - combining stable insect cells with baculovirus-mediated expression for multivalent influenza HA-VLPs production;
  - adaptive laboratory evolution as a bioprocess engineering strategy to improve production of monovalent influenza HA-VLPs in insect cells (either in stable cells or using the baculovirus expression system);
  - a new, scalable process for PPRV vaccine production in Vero cells using microcarrier and bioreactor technology, in-situ cell detachment from microcarriers, and perfusion;
- Downstream processing:
  - membrane-based approaches for purification of influenza VLPs;
- Analytics:
  - MFA to assess the metabolic modulation of insect cells by baculovirus infection during production of mono- and multi-valent influenza HA-VLPs;
  - click-chemistry and biolayer interferometry technologies to assist process optimization and product (influenza HA-VLPs) monitoring and control.