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Disruptive micro-facility for affordable vaccine manufacturing
Case study for sIPV polio vaccine

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Abstract
Vaccines are the sole preventative measure to eliminate poliomyelitis. The traditional biologic production in stainless steel bioreactors is limited by high capital expenditures and does not provide a sustainable or cost-effective solution for the future. Univercells aims to change the paradigm and produce biologics using small-scale integrated systems, providing a more affordable and flexible approach. The production of a polio vaccine candidate using this compact system paves the way for a worldwide production of affordable vaccines and biologics.

Biologics for all
We notice an increasing demand for affordable biologics such as vaccines, a demand reinforced by the continued efforts of global immunization campaigns. In the case of poliomyelitis, a renewed global immunization effort is combining the use of the OPV and IPV by producing a injected inactivated vaccine using attenuated strains. Due to its high infectivity, Polio vaccine needs to be handled in highly contained environment to ensure operators and environment safety. Facilities complying with GAP III safety levels being usually very complex and expensive to build and operate, new technologies are called for to implement cost-effective sIPV production facilities.

To circumvent the limitations of traditional bioproduction methods (eggs, cell factories or micro-beads), Univercells envisioned a down-scaled high-performance production process, leading to low-footprint infrastructures more affordable (CAPEX & OPEX) and flexible, while achieving high productivity of vaccines.

NevoLine™ micro-facility concept
Univercells designed a self-contained, single-use, closed, low footprint and automated continuous manufacturing platform for GMP pilot and commercial-scale virus production (figure 1). Self-contained upstream and downstream modules reduce the facilityCAPEX, while reducing OPEX at the same time through automation and downsized continuous processing. The first application was developed with Bill and Melinda Gates Foundation funding to meet the goal of reducing the cost of manufacturing inactivated attenuated polio vaccine to $50/dose, presented here.

Materials and methods
- Bench-scale fixed-bed bioreactor (scale-X™, surface: 2.4m² available for cells);
- Case made of 100% pure non-woven hydrophilized PET flors;
- Vero cells grown serum containing media, infection in serum-free media;
- Sabin attenuated polio strains;
- Cell nude count on carriers estimated by crystal violet staining;
- Polio virus production estimated by ELISA assay (5.0-antigen content) and TCID50
- Two steps purification (single step enhanced filtration & single step high affinity OEX chromatography);
- CoGs calculation using BioSolve 2017 (BioPharm Services)

Results
1. Process flow chart
To deliver a low-footprint production unit, Univercells designed a complete sIPV production process of small enough volume & footprint to fit into an isolator (figure 2), based on intensification and chaining technologies.

2. Cell growth & fixed-bed homogeneity
Cultivation of Vero cells in medium with serum was carried out in 2.4m² compact fixed-bed bioreactors achieving high cell density. Cell dispersion results show homogeneity in the fixed bed, ensuring even and predictable growth throughout the structure (figure 4). Thanks to its unique compact structure, scale-X bioreactors seeded with cell densities a quarter of that needed for traditional systems grow nearly 50-fold to reach a final concentration of 200,000 cells/cm³ (figure 3).

3. Purification
First steps of purification, i.e. DNA removal step, pH adjustment and clarification, are performed in-line with positive results. In-line single step purification using CEX chemistry participates in improving overall downstream processing recovery yield & high purity.

4. Production
The process was developed on the three strains of sIPV, achieving promising productivity and purity results (table 1). The overall process achieves high productivity, delivering an equivalent of 0.5 million doses of trivalent at 600m² scale (based on a ratio 51/52/53).

Conclusions
- The successful implementation of intensification and chaining for sIPV production led to a drastically reduced equipment size, enabling the process to be operated within a closed system, in a low footprint isolator, called micro-facility system, NevoLine.
- Thanks to improved recoveries, the intensified process achieves high productivity, delivering $25,000 doses of trivalent sIPV per batch.
- With Univercells NevoLine technology, viral vaccines such as polio can be produced in a miniaturized fully-contained isolator for increased safety, leading to a tremendous impact on the facility design, CAPEX and cost of manufacturing.

Perspectives
- Based on the successful implementation of the intensification and chaining concepts for sIPV, we think NevoLine will provide tremendous value for many applications, like and without limitation:
  i. Other viral vaccines for human and veterinary uses
  ii. Rapid deployment manufacturing capacities to face outbreaks
  iii. Production of gene vectors needed for the ever-increasing gene therapy segment