Production of Rabies Virus Using the TideCell Bioreactor System

Case Study of Virus Production Using Vero Cells
Comparison Study

• Due to pronounced differences in virus strain and host cell line characteristics, the ideal process for virus production can significantly differ.

• The following slides compare process condition requirements for the production of the Rabies virus based on using the TideCell bioreactor and other commonly used systems.
1. Required high cell density to achieve high titer, and reduce media consumption

- TideCell: high surface area increases cell density to approx. 4x10^6 cells/ml.
- Roller bottle: low cell density due to limitations of surface area
- Micro-carrier system: bead density is limited
- Fixed bed bioreactor: feasible, but the scale is limited
- Hollow fiber bioreactor: feasible, but the scale is limited.
2. Required sampling to determine infection time and MOI

- TideCell: capability to sample carriers from the matrix vessel. Quick/convenient cell count due to carrier’s known surface area and carrier quantity in matrix vessel.
- Roller bottle: cell density and morphology can be observed under microscope. MOI, however, is difficult to estimate.
- Micro-carrier system: carrier sampling is possible.
- Fixed bed bioreactor: difficult, due to inability of sampling carriers.
3. Required long term harvesting due to slowly occurring CPE

- **TideCell**: Cells are immobilized in a fixed-bed containing porous carriers. Media exchange is straight-forward resulting in no damage or loss of cells.
- **Roller bottle**: media can be directly exchanged
- **Micro-carrier system**: additional separator is required to separate micro-carriers from media. Long term perfusion is difficult.
- **Fixed bed bioreactor**: cells are immobilized, therefore media can be directly exchanged
4. Required reduction of host cell protein and DNA residues to increase recovery rate

- TideCell: even lysis after virus infection, cells remain entrapped inside the carrier matrices without being flushed into the harvest media. The host cell protein and DNA/RNA nucleic acid residues is several folds lower than conventional systems.
- Roller bottle: cells are retained on the bottle wall.
- Micro-carrier system: cells can be detached and milled by the micro-carrier beads during agitation after infection, releasing increased host cell protein and nucleic acids.
- Fixed bed bioreactor: cells will detach and be disrupted after infection, releasing host cell protein and nucleic acids.
Cycle Batch Virus Titer Profile

![Graph showing the relationship between Post-Infection Time (hour) and Log TCID50.](image)

- **Log TCID50**
- **Post-Infection Time (hour)**

www.bioreactorsciences.com  |  bioreactorsciences@gmail.com
Process Profiles

- Virus Titer (log LD50/ml) vs. Post-Infection Day (day)
- Cell Density (cells/ml) vs. Culture days (day)

Graphs showing comparison between TideCell and Stir tank.
3D Growth of Vero Cells

VERO cells form 3D in BioNOC II carriers, which helps cells to mimic the in vivo situation and enhance virus productivity.
Cell Morphology after 96 hours post-infection

Cells after infection becomes illness and fragile. Carriers protects cells and extend their life.
1. Virus production time can be extended,
2. Yield increased
3. DNA residue decreased.
DNA Residues Profile

[Graph showing DNA residues (ng/ml) over Post-Infection Days (day).]

- TideCell
- Stir Tank
Extended Post-Infection Time

![Graphs showing virus titer and cell density over time.](image)
# Summary of Results

<table>
<thead>
<tr>
<th>Type</th>
<th>Roller Bottle</th>
<th>Microcarrier, stir tank bioreactor</th>
<th>TideCell bioreactor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PERFORMANCE ANALYSIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale</td>
<td>15 L (3000 cm²)</td>
<td>50 L</td>
<td>10 L</td>
</tr>
<tr>
<td>Carrier</td>
<td>none</td>
<td>750 g (Cytodex I)</td>
<td>650 g (BioNOC II)</td>
</tr>
<tr>
<td>Max. cell density</td>
<td>4-6x10⁷</td>
<td>4x10¹¹</td>
<td>4x10¹¹</td>
</tr>
<tr>
<td>Culture days</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Consumed culture medium (during cell culture)</td>
<td>1.5 L</td>
<td>600 L</td>
<td>300 L</td>
</tr>
<tr>
<td>Harvest days</td>
<td>8</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Consumed culture medium (during post infection period)</td>
<td>6 L</td>
<td>1200 L</td>
<td>1040 L</td>
</tr>
<tr>
<td>Total Yield Equivalency</td>
<td>1/800</td>
<td>1/2</td>
<td>1</td>
</tr>
<tr>
<td><strong>COST ANALYSIS (based on the same productivity)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Space</td>
<td>200 m²</td>
<td>10-15 m²</td>
<td>3-6 m²</td>
</tr>
<tr>
<td>Man power</td>
<td>30</td>
<td>4-6</td>
<td>2</td>
</tr>
<tr>
<td>Carrier</td>
<td>500 roller bottle</td>
<td>1,500 g (~USD 12,000)</td>
<td>650 g (~ USD 2,600)</td>
</tr>
<tr>
<td>Culture Medium</td>
<td>3,750 L (~USD 75,000)</td>
<td>3600 L (~USD 72,000)</td>
<td>1340 L (~USD 26,800)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Process development time</td>
<td>short (~ 3 months)</td>
<td>long (~24-36 months)</td>
<td>moderate (~6 months)</td>
</tr>
<tr>
<td>Process development cost</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>
Thank You for Watching

Please Visit Us at:

www.bioreactorsciences.com