VBI VACCINES

Manufacture and purification of a third generation VLP for Cytomegalovirus

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April 8th, 2015

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eVLP Platform

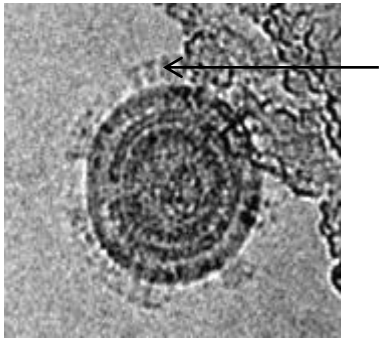
eVLPs are a third-generation class of synthetic vaccines that closely resemble the structure of the virus they mimic

eVLP PLATFORM HIGHLIGHTS

- Same size and structure as enveloped viruses
- Present antigens in their natural state (lipid bilayer) to provoke an optimal immune response
- In animal research, demonstrated ability to trigger strong, broadly neutralizing antibodies in multiple preclinical models (CMV, HCV, and Flu)
- Suitable to a wide array of viruses including CMV, HCV, RSV, Dengue, and West Nile
- Strong intellectual property estate

Proposed structure of CMV gB protein, with shared functional properties with gB proteins from other herpesviruses.

Sharma, S (2013) Virol 435, 239-249.

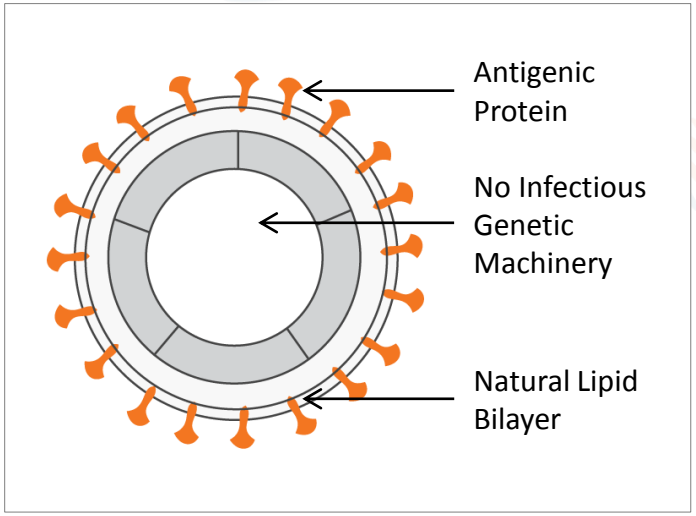


CMV gB protein retains natural conformation in the lipid bilayer of eVLP particle.

Electron microscopy image of VBI's CMV eVLP captured by NanoImaging Services.

Overview of eVLP Design and Production

- eVLPs are produced after transient transfection of cells (e.g. **HEK 293, CHO, Vero, Sf9**) with plasmids encoding:
  - MLV Gag
  - Extracellular domain of gB protein fused with transmembrane (TM) domain of vesicular stomatitis virus G protein (VSV-G)
- Presence of VSV TM domain enhances targeting to cell membrane and optimal protein conformation (greater induction of neutralizing antibodies)
- MLV Gag expression induces “budding” of particles from membrane of transfected cells, with CMV gB protein incorporated into the final eVLP structures
- Formulation of eVLPs with alum phosphate (VBI-1501A) provides product stability *in vitro* and enhanced durability of immunity *in vivo*



Medical Need

Cytomegalovirus (CMV) is a common virus that can cause serious, life-threatening complications in persons with weakened immune systems

PERSONS LIKELY TO DEVELOP CMV COMPLICATIONS

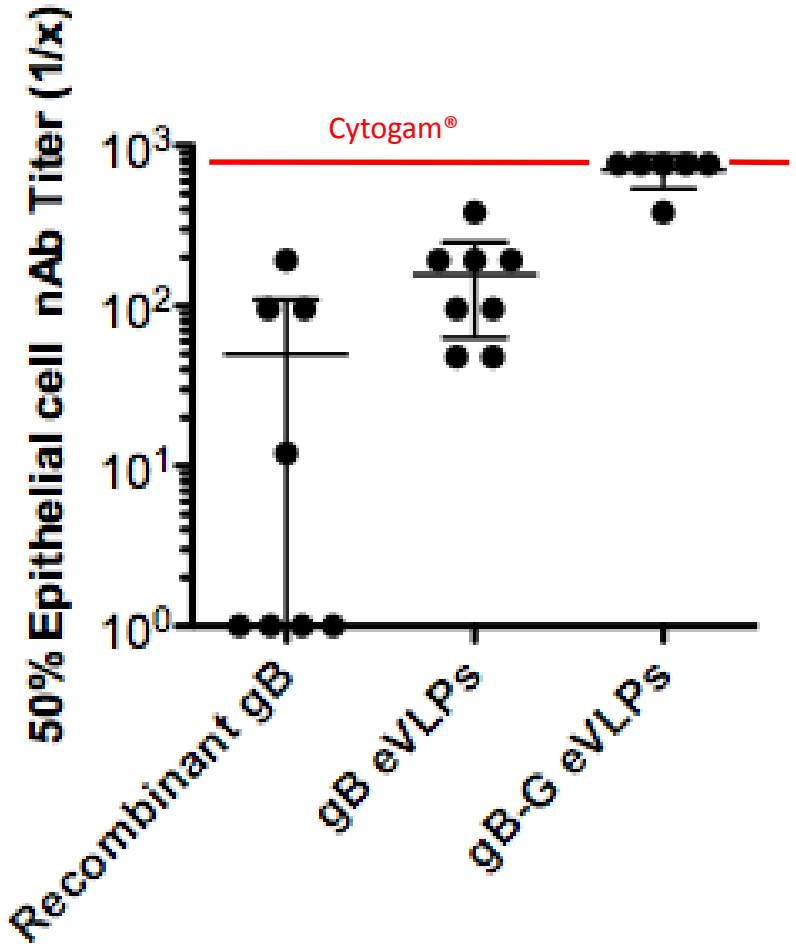
- **Congenital CMV:** Unborn babies whose mothers become infected with CMV during pregnancy are at high risk
  - Congenital CMV infection causes more long-term problems and childhood deaths than Down Syndrome or Fetal Alcohol Syndrome
  - In the U.S., congenital CMV causes one child to become disabled every hour
- **Immunocompromised:** A primary CMV infection can cause serious disease in organ and bone marrow transplant recipients, cancer patients, and patients receiving immunosuppressive drugs

CMV Vaccine Landscape: need for enhanced potency and durability

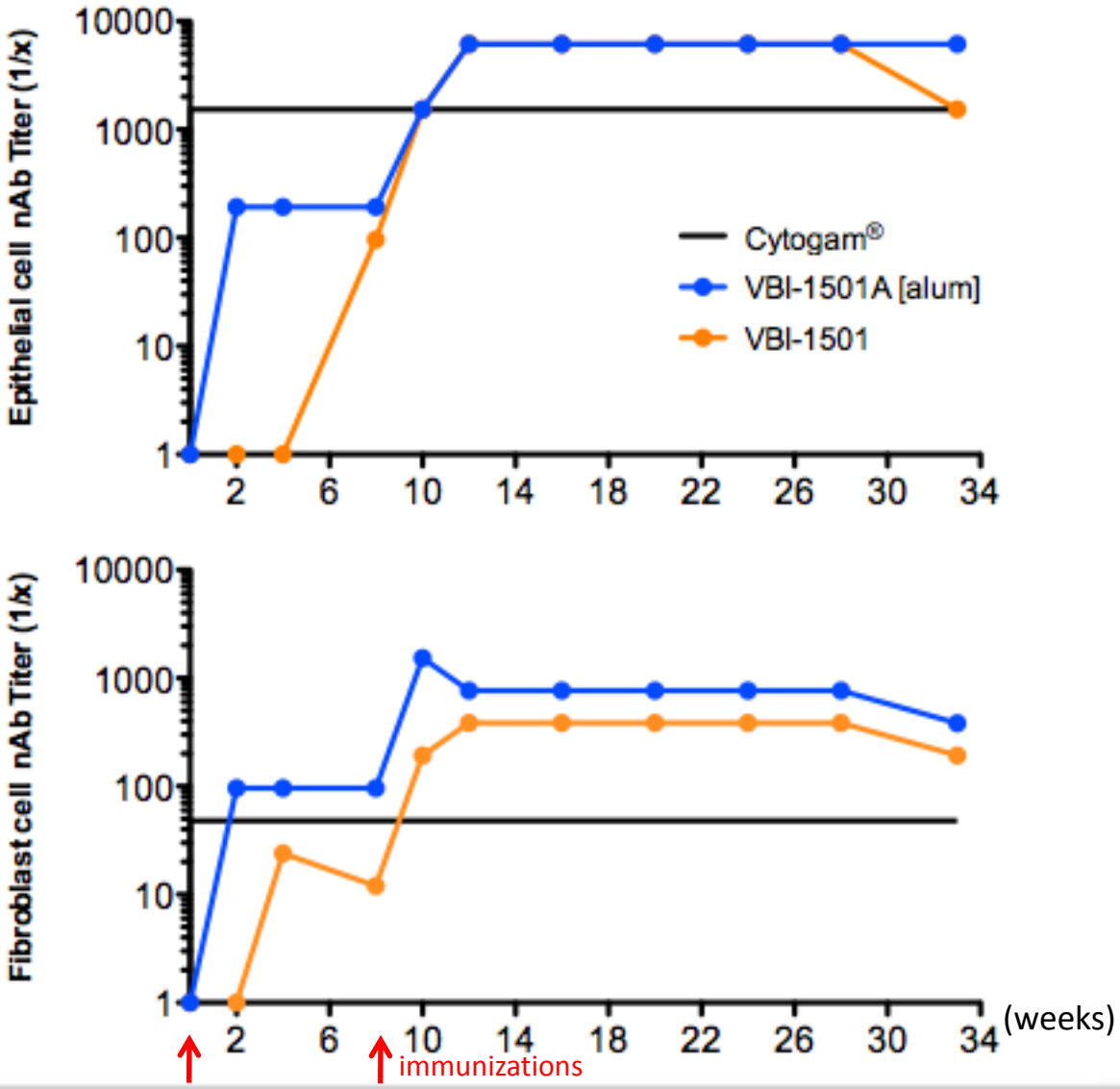
- Naturally acquired immunity confers high protection against CMV infection[1]
  - Maternal transmission rate: ~50% during primary infection but only 0.5-2% among CMV-immune women
  - CMV-immune subjects are protected against low- and intermediate-dose CMV virus challenges
- 2009: Phase II study of a prophylactic CMV vaccine had projected 50% efficacy[2]
  - Natural immunity imparts ~90% protection[1], but vaccine-induced nAb titers against epithelial cell infection were 10X lower[3]
  - Efficacy appeared to wane quickly after 1st year[4]

[1]Adler SP (1995) J Infect Dis 171, 26-32; [2]Pass RF (2009) N Eng J Med 360, 1191-1199; [3]Cui X (2008) Vaccine 26, 5760-5766; [4]Lilja AE (2013) Vaccine 30, 6980-6990

Strong Potency Induced Using eVLP Presentation of a Modified gB Antigen



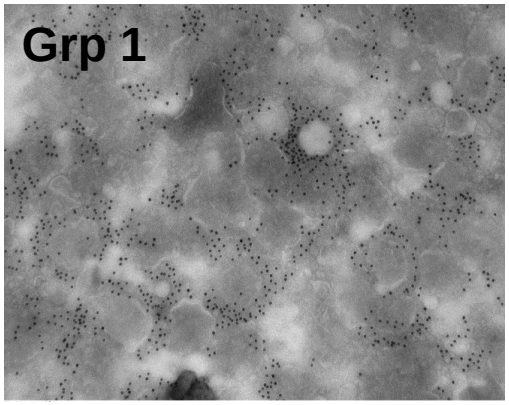
VBI-1501A: Rapid, Potent & Durable Immunity

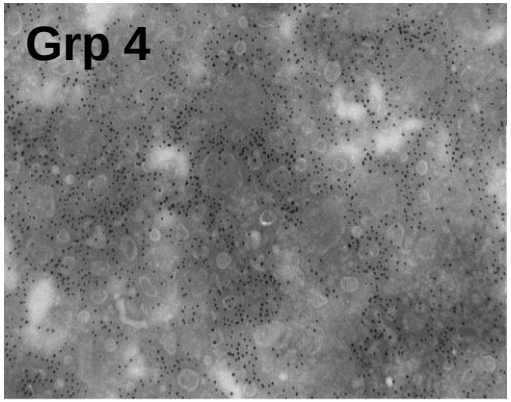


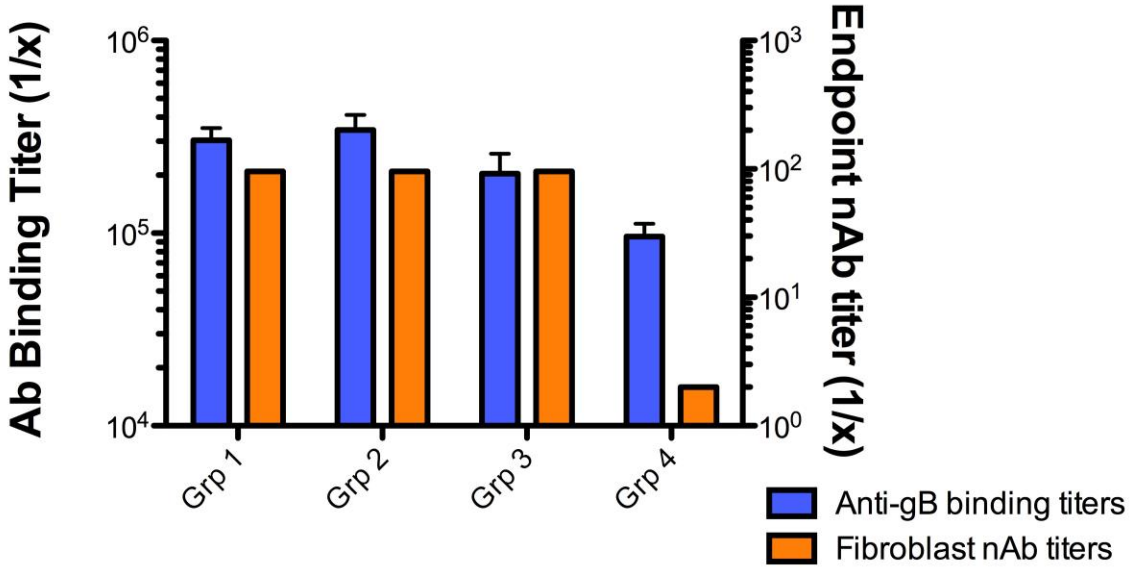
VBI-1501/A were produced using a GMP compliant HEK 293 cell line and purified to meet FDA standards.

Pooled sera from vaccinated mice (n=8) were tested for the ability to neutralize CMV infection in both Fibroblast and Epithelial cells, two clinically relevant cell types susceptible to CMV infection.

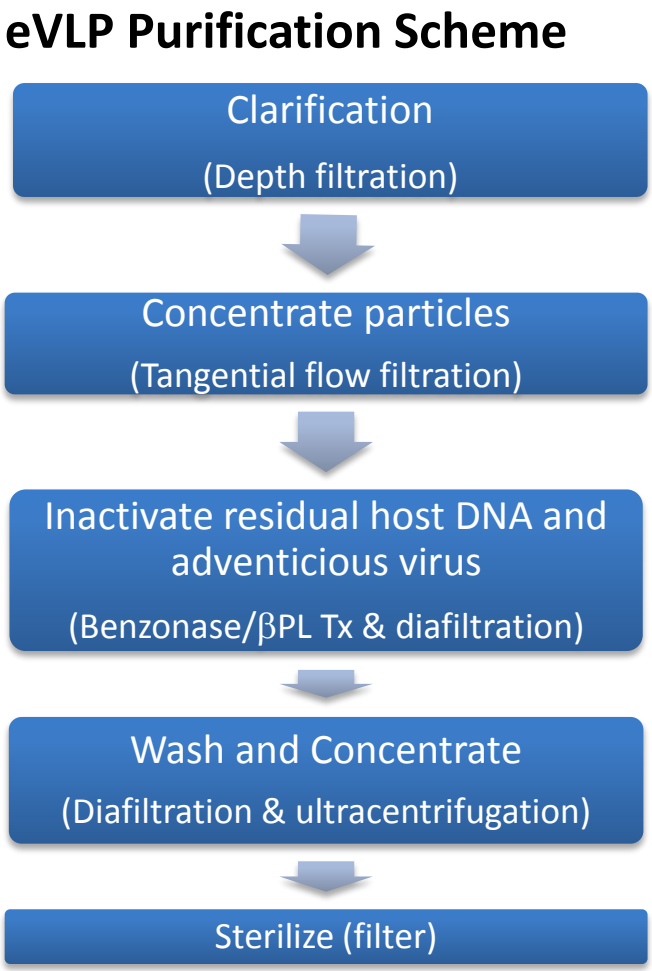
gB Density on eVLPs Influences Potency





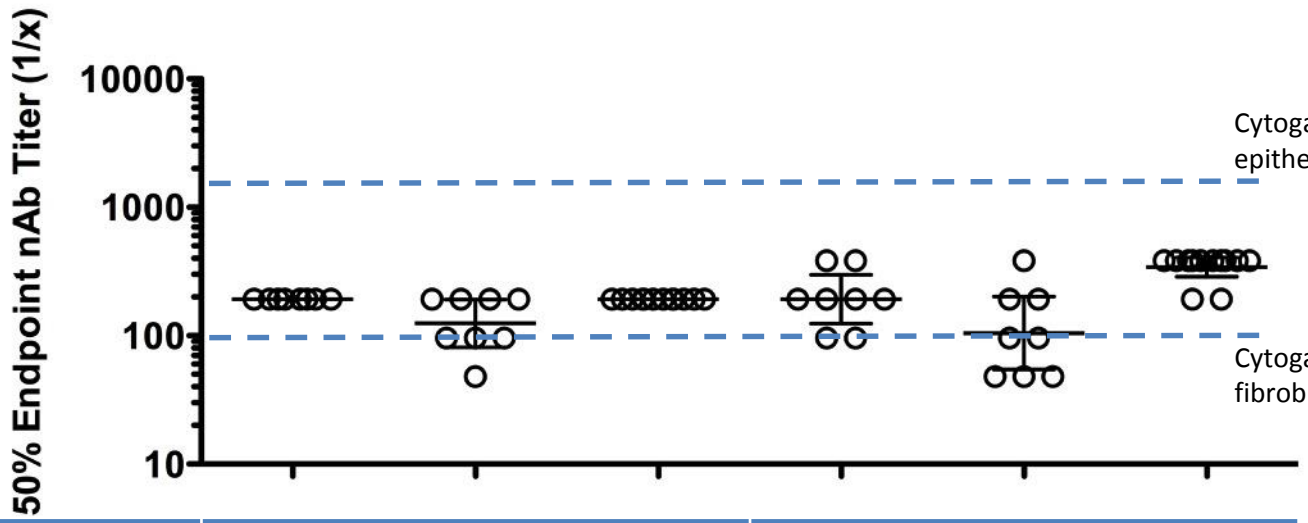


Overview of VBI-1501 Purification Process



VBI-1501A: Batch consistency based on *in vivo* potency assay (nAb titers measured 14 days after a single dose)

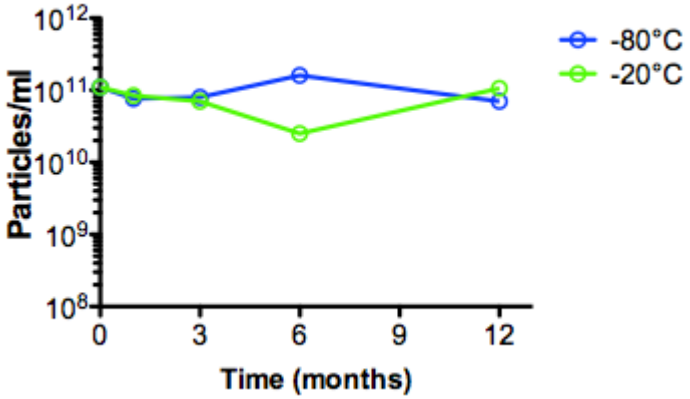
Mice (n=8-12/grp) immunized i.p. with 0.4µg gB/dose. GMT and 95% CI are represented.



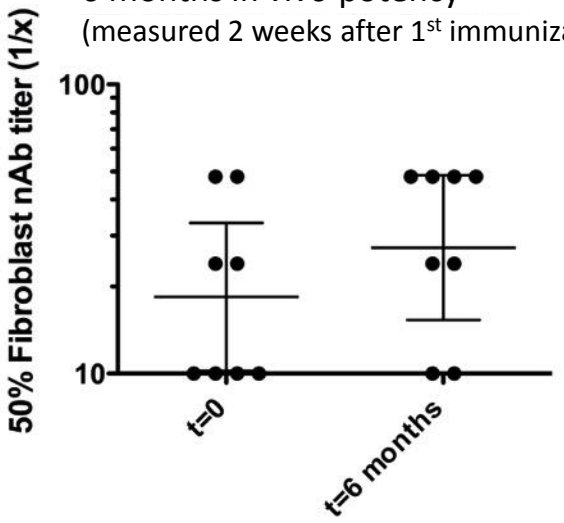
nAb Titers (P1Vd14)	(HFF-1) fibroblast cells			ARPE-19 epithelial cells		
Batch run	NRC	CMO batch 1	CMO batch 2	NRC	CMO batch 1	CMO batch 2

VBI-1501: Drug substance stability at 12 months

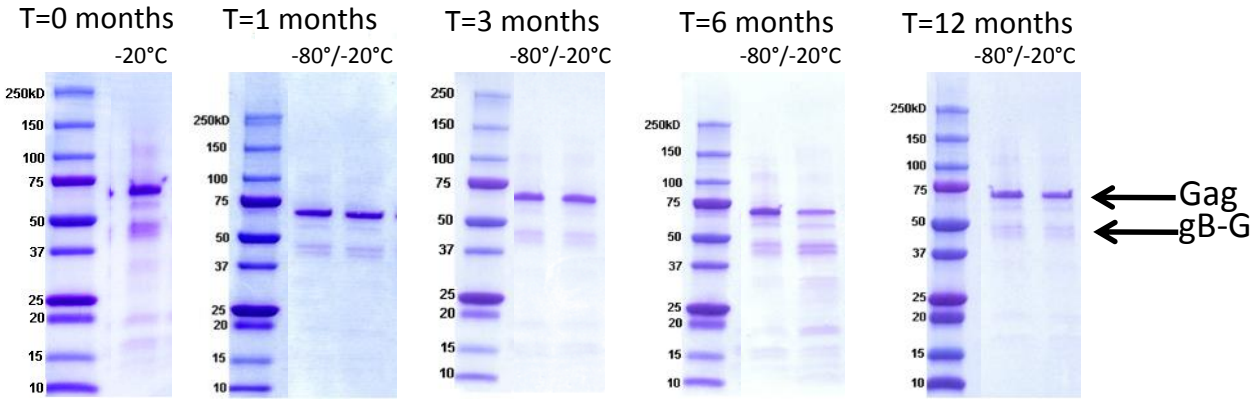
eVLP particle stability based on nsTEM analysis



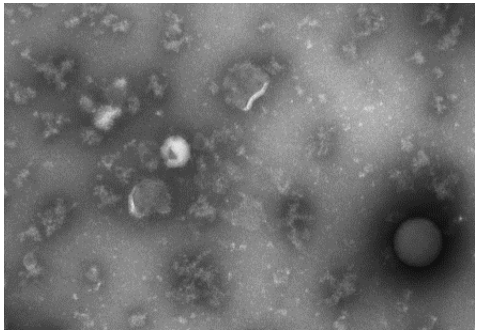
6 months *in vivo* potency
(measured 2 weeks after 1st immunization)



gB and Gag stability assessed by SDS PAGE

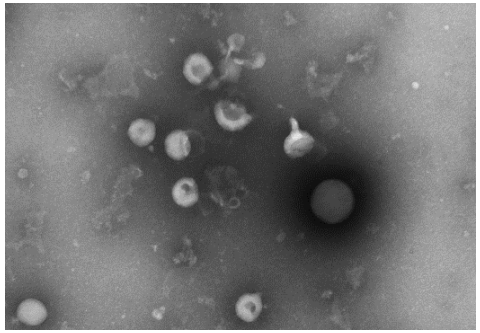


VBI-1501: Electron microscopy imaging confirms particle integrity and debris removal through purification process



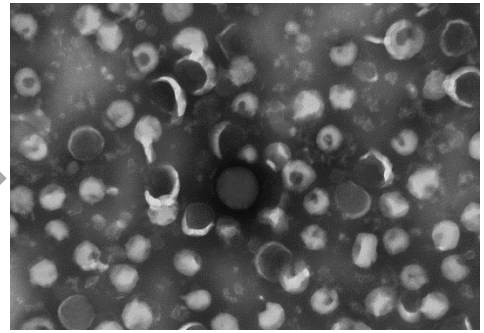
eVLP density = 9.60×10^6 particles/mL

TFF & BZ Tx



1.15×10^{10} particles/mL

Diafiltration & UC



1.44×10^{12} particles/mL

Total particle count (~5×10^{12}) remains consistent throughout process → little particle loss

CMV eVLP Manufacturing Summary

- Rapid, potent and durable immunity demonstrated with both drug substance (VBI-1501) and drug product (VBI-1501A)
- Batch consistency demonstrated using *in vivo* potency release assay
- eVLPs expected to meet Phase I release criteria:
  - **Toxicology batch (50L production scale)**
  - Purity (based on 1 µg gB content):
    - Residual DNA: Picrogreen: 26.2 ng/dose; PCR: 0.2 ng/dose
    - Residual HCP: 12.1 ng/dose
  - Yield: ~150 doses/L purified drug substance
- Ratio of Gag to gB (or target of interest) a key determinant of potency
- **Opportunity to begin new eVLP vaccine candidates internally and with partners**

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