Enveloped Virus-like Particle Delivery of an Optimized Form of CMV gB Antigen for Prophylactic Vaccination Against Congenital CMV

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Chief Medical Officer

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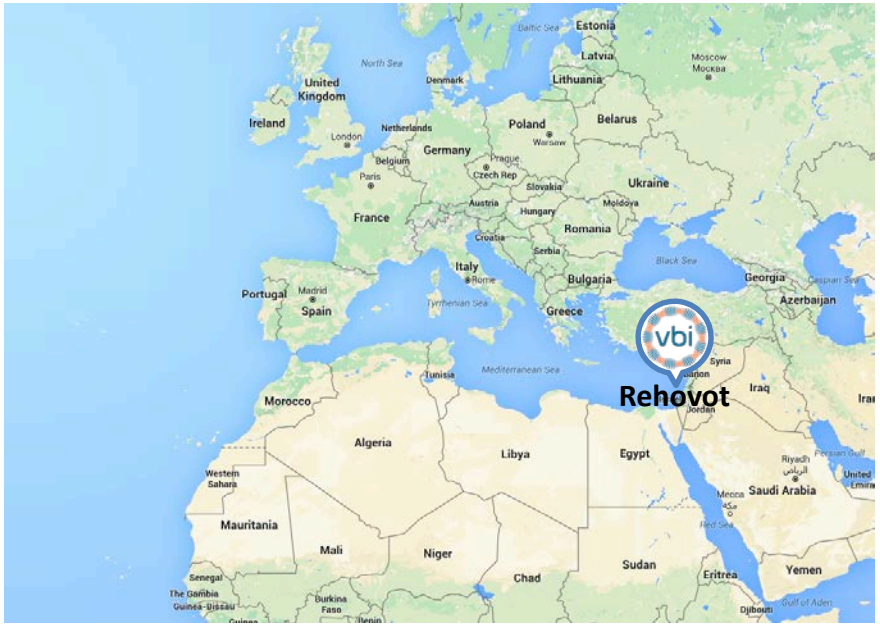
VBI Vaccines Overview



HEADQUARTERS – CAMBRIDGE, MA

- Central location in North America's biotechnology hub
- 8 FTE, including CEO, CSO, CTO & CFO

RESEARCH OPERATIONS – OTTAWA, CANADA

- Exceptional R&D & product development experience across 25 FTEs
- Focused on development of VBI's two platforms
  - **eVLP Technology:** innovative VLP platform with lead candidates in CMV & Glioblastoma
  - **Thermostable LPV:** stabilizing formulation platform including active collaborations with Sanofi & GSK

GMP MANUFACTURING – REHOVOT, ISRAEL

- ~50 FTE focused on manufacturing Sci-B-Vac
- GMP capable for commercial products with early stage process development capability

eVLP Platform & Rationale for Improved gB CMV Vaccine

CMV Unmet 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

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2009, p. 99–126
CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Jan. 2003, p. 1–7

CMV Vaccine Unmet Medical Need: Durable, broadly neutralizing antibody responses

- Naturally acquired immunity confers high protection against CMV infection(Adler[7])
  - Maternal transmission rate: ~50% during primary infection but only 0.5-2% among CMV-immune women
  - CMV-immune subjects: Protected from low to moderate-dose CMV virus challenge
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- 2009: Landmark Phase II CMV vaccine study achieved projected 50% efficacy (Pass[8])
  - **Key Goal 1 -** Need improved potency vs natural immunity:
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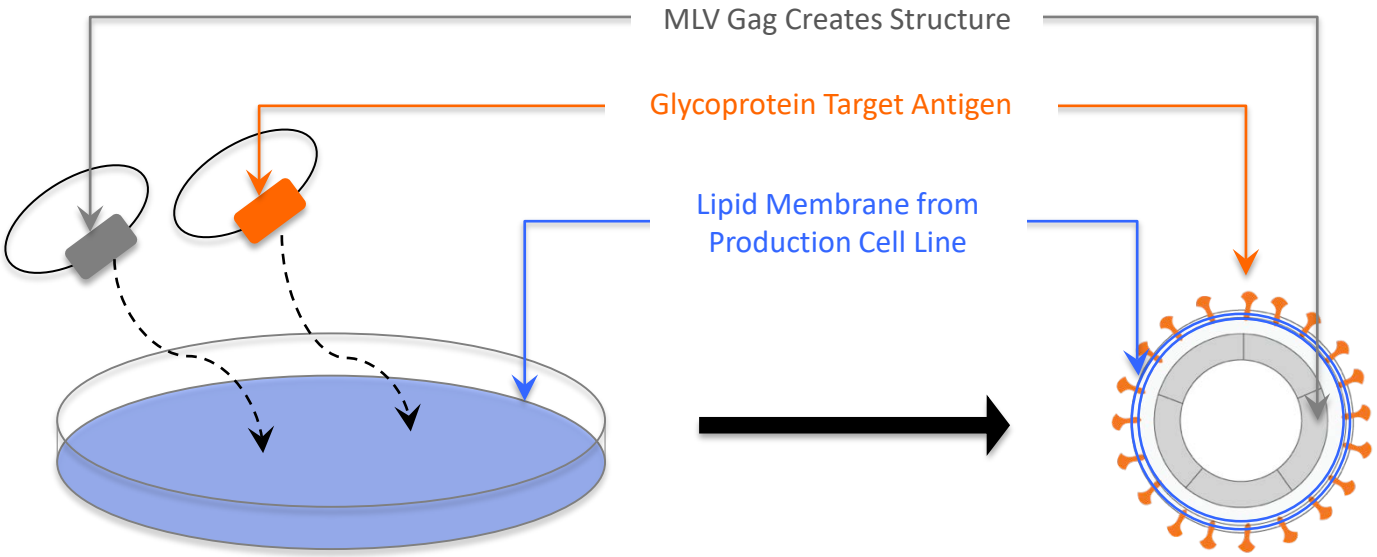
[1] Adler SP (1995) J Infect Dis 171, 26-32; [2] Pass RF (2009) N Eng J Med 360, 1191-1199; [3] Cui X (2008) Vaccine 26, 5760-5766; [4] Lilja AE (2013) Vaccine 30, 6980-6990

eVLP Production – Two Genes & Cell Line Create Natural Viral Mimic

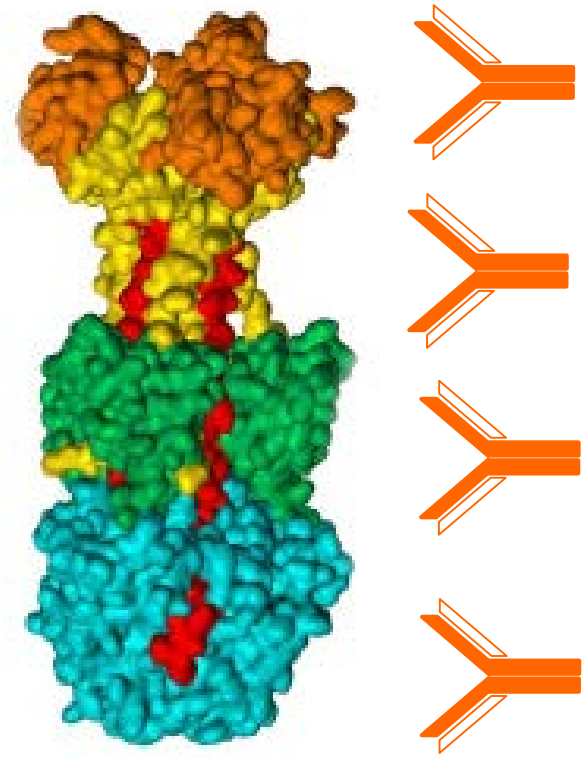
All key structural elements of enveloped viruses represented



- "e" VLP Key Attributes
  - Antigen presented in Virus Like Structure (common to all VLPs)
  - MLV capsid protein creates viral structure (*unique*)
  - Lipid membrane derived from production cell line (*unique*)
    - Multiple cell lines can be used, HEK offers 'human' glycosylation patterns (*as virus does*)
  - Envelope glycoproteins presented in lipid membrane as in nature (*unique*)
    - May allow unique "conformation" benefits

Not All Antibodies to Envelope Glycoproteins are Equal

Multiple CMV gB Epitopes Identified with Distinct Neutralizing Properties



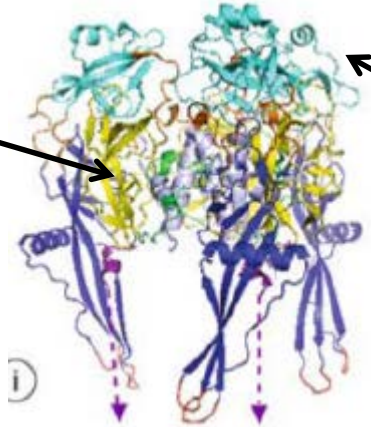
- AD-1 Immuno-dominant Epitope[4]
  - Predominant: 38% of B cell, IgG close bind AD-1
  - Weakly neutralizing: only 2% are neutralizing
- AD-2 Linear Epitope[5]
  - Infrequent but highly potent neutralization
- AD-4 Epitope[4]
  - Very rare: only 5.9% of b-cell clones
  - Strongly neutralizing
- AD-5 Epitope[4]
  - Very rare: only 5.9% of b-cell clones
  - Strongly neutralizing

4) Potzsch S (2011) PLoS Pathlog 7, e1002172
5) Ohlin M (2014) Mol Immunol 60, 95-102

Distinct Envelope Glycoprotein Conformations Expose Different Epitopes - Influence Potency

Pre-fusion structure of Herpes-family virus

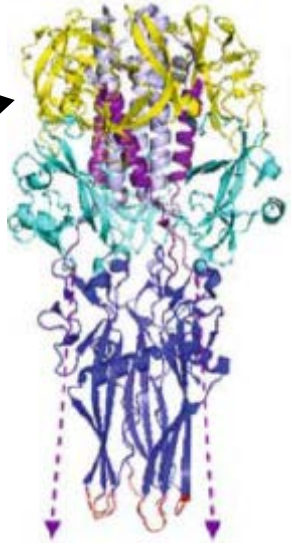
AD-1 is buried in the pre-fusion conformation



AD-4 is more exposed

Post-fusion structure

AD-1 more exposed



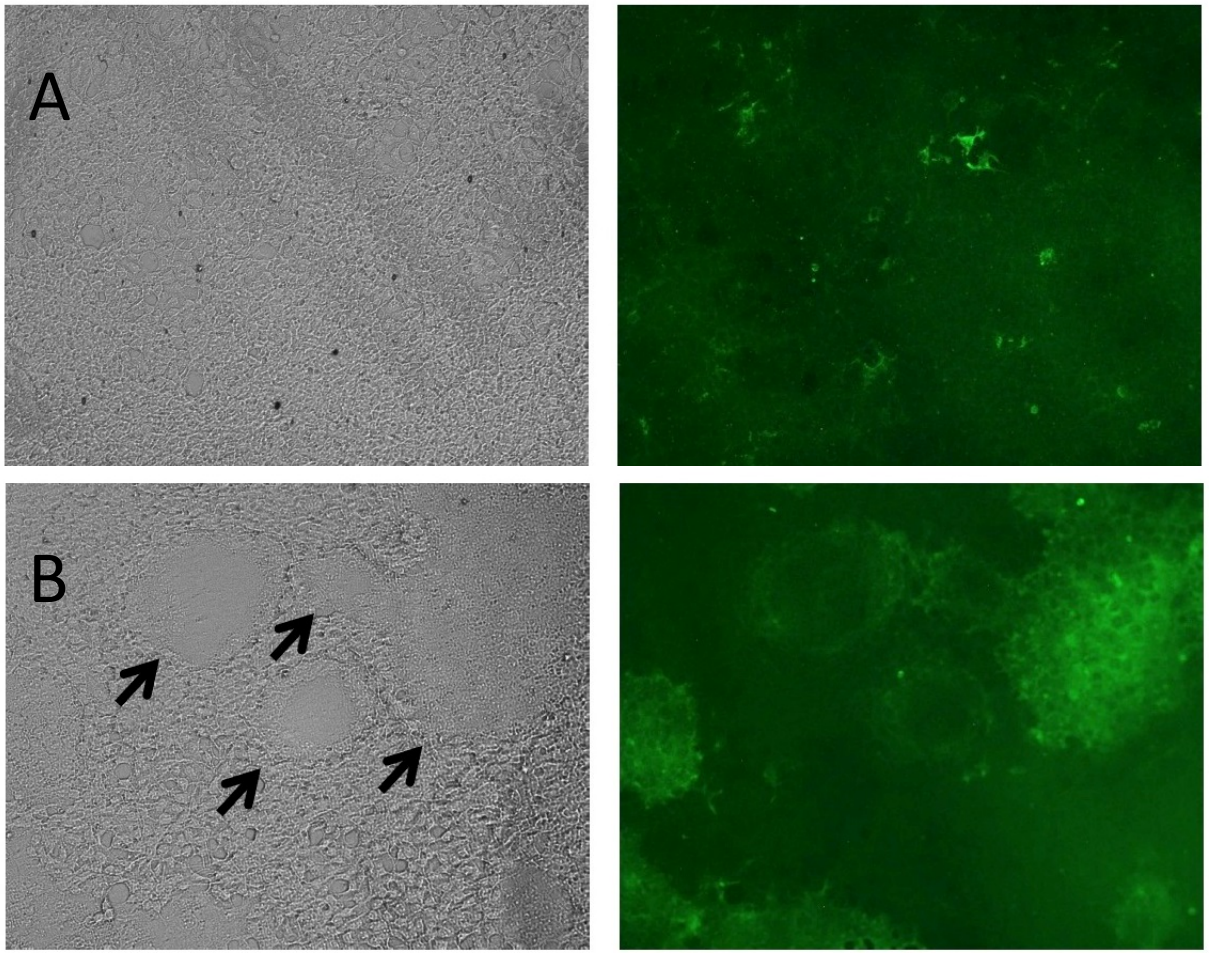
Transition is a biologic process

- Critical to virus infection (cell fusion)
- Happens in context of membrane
- … Soluble recombinant proteins typically adopt post-fusion structures

gB-G Antigen in eVLP Promotes Cell Fusion – Suggests Altered, Biologically Relevant Conformation vs Recombinant gB

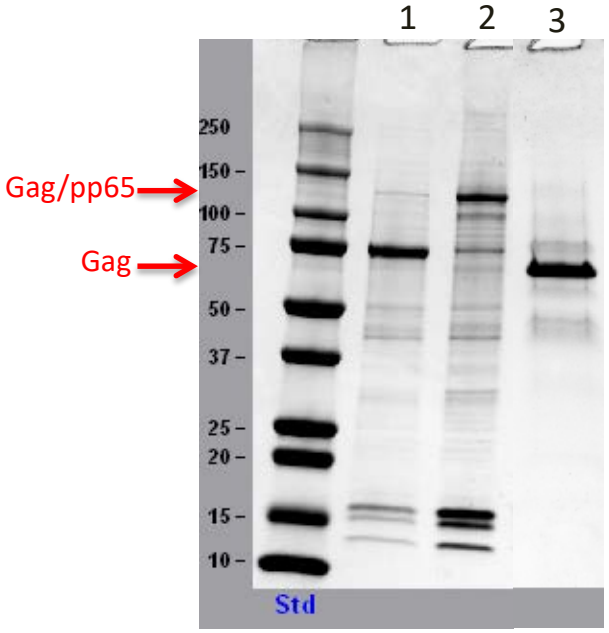
Native gB Antigen

Optimized gB-G Antigen
(VSV –G protein transmembrane domain induces altered conformation that drives significant cell fusion)

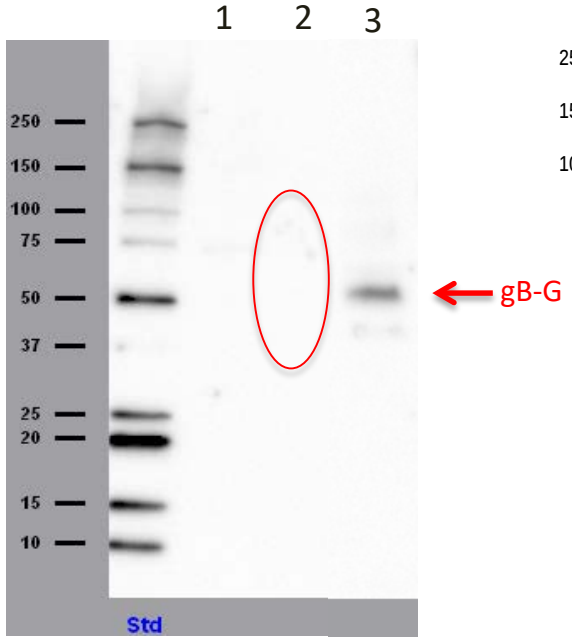


Antibodies generated with gB-G eVLPs bind to gB-G but not gB-expressing eVLPs

SDS PAGE



CMV gB Western Blot
(anti-gB-G mAb)



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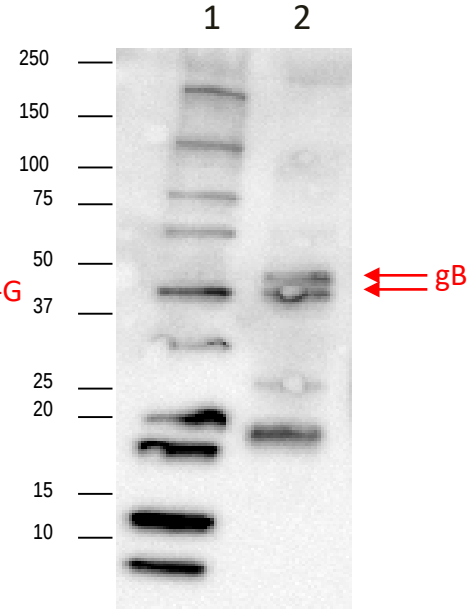


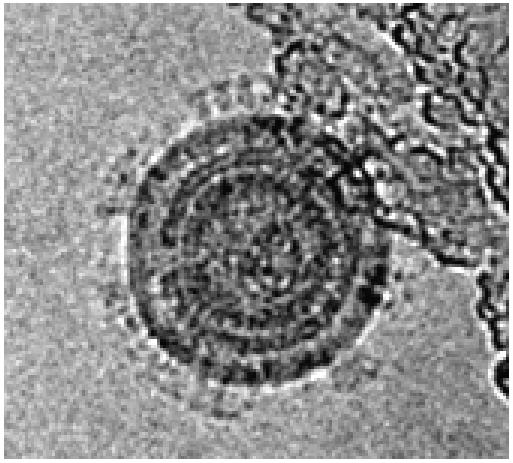
Samples:

Lane 1: VBI bivalent gB/pp65 eVLPs
Lane 2: Paragon bivalent gB/pp65 eVLPs
Lane 3: Paragon gB-G eVLPs (tox batch)

Cryo-EM Analysis Demonstrates Bivalent gB/pp65 eVLPs Differ Structurally From gB-G eVLPs

Structure of VLP core (with fused CMV pp65) and surface gB appear unique

gB-G eVLP



Note 1) the presence of surface gB-G spikes not seen with fully native gB expression in bivalent gB/pp65 eVLPs and 2) the expected ring structure of MLV Gag core protein not seen when pp65 is fused with Gag.

gB/pp65 eVLPs

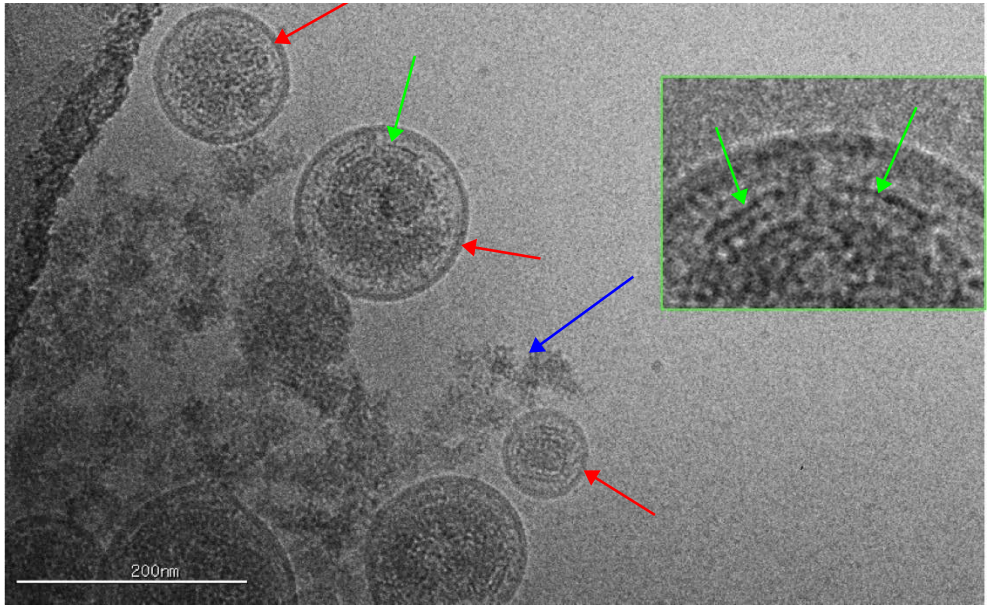


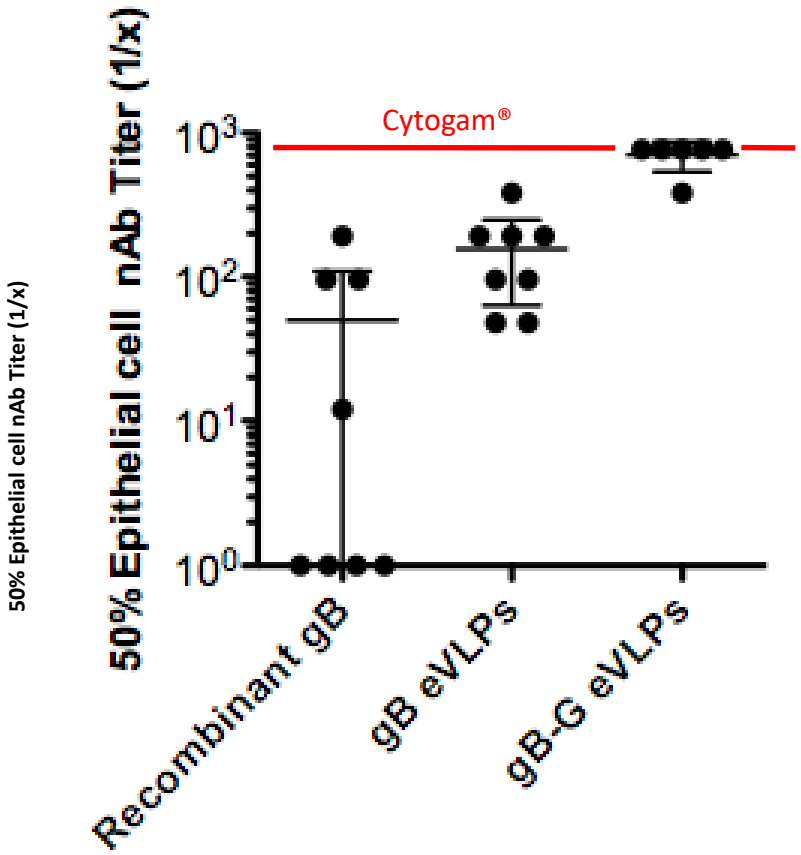
Figure 1d. Selected image of Post TFF/UC Pellet Ref #153-190 at a magnification of 52,000x**.** Observed in the sample are: spherical particles with dense material in their interiors (red arrow) and a visible not intact second layer surrounding the dense material (green arrow, inset), proteinaceous aggregates (blue arrow). Scale Bar: 200 nm**.**

eVLP Presentation Improves Potency of gB Antigen

Presentation of gB antigen in an eVLP improves relevant functional CMV neutralizing responses relative to recombinant gB protein.[1]

PRECLINICAL RESULTS

- gB in eVLP generates higher levels of CMV nAbs than recombinant (gB)
- Modification of transmembrane domain further improves eVLP potency
- No adjuvant included
- For more details see: [6]Kirchmeier et al, *Clinical Vaccine Immunol.* 2014, 21(2):174.



CMV Vaccine: Preclinical Immunology

CMV Vaccine Unmet Medical Need: Durable, broadly neutralizing antibody responses

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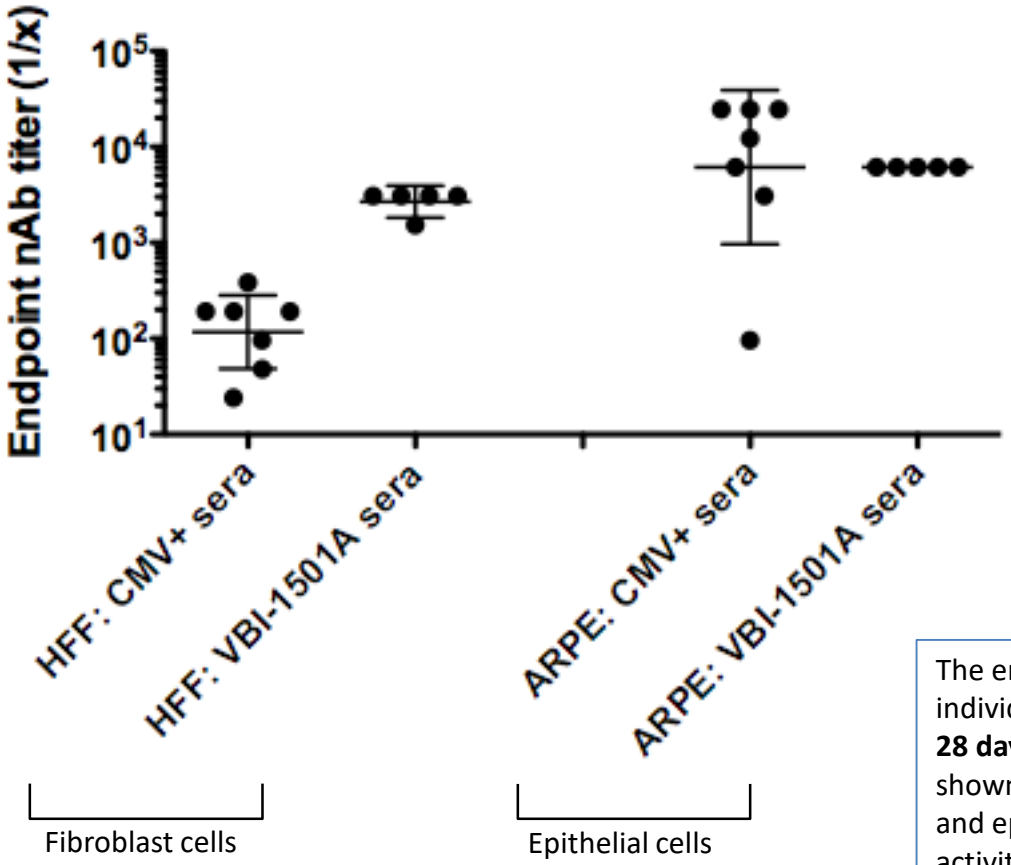
VBI 1501A Induces Neutralizing Antibody Titers in Rabbits Equivalent to or Exceeding Natural Infection

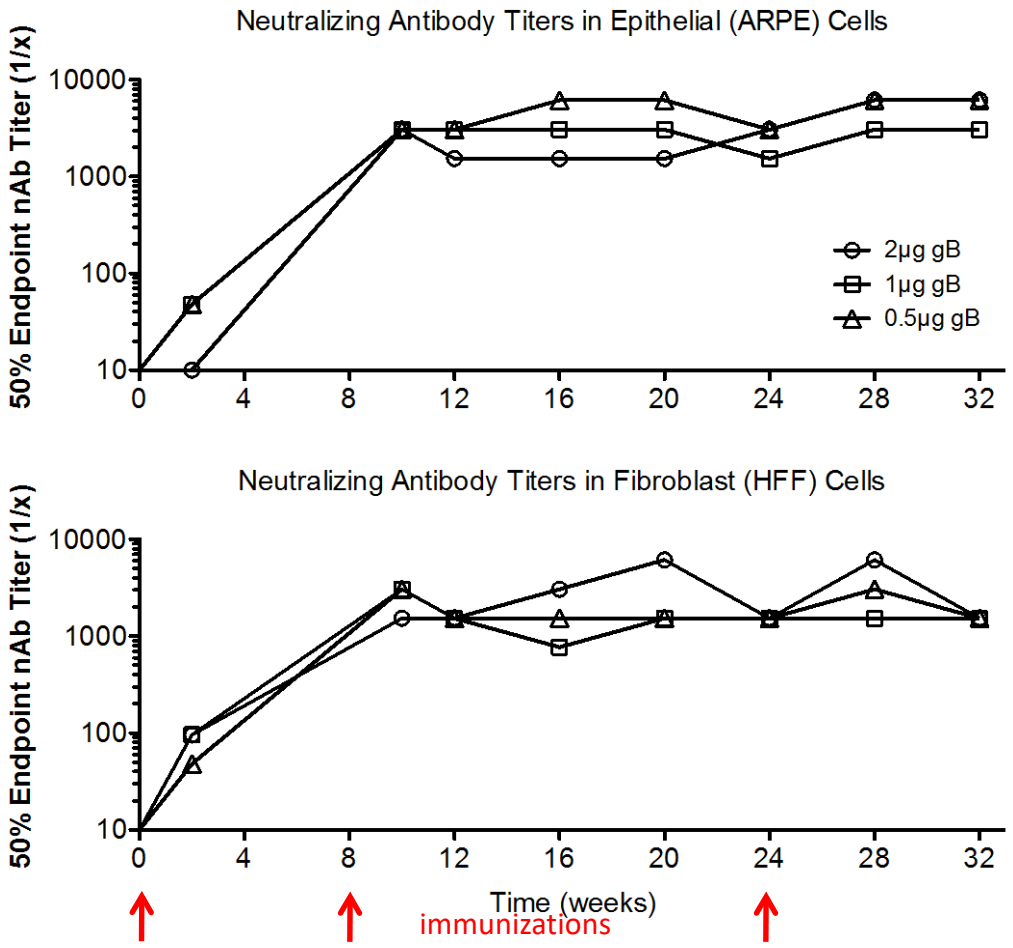
Key Achievement 1 & 2: Neutralization of CMV matches natural levels of immunity in Fibroblasts AND Epithelial Cells



The endpoint neutralization titer of individual rabbit sera (n=5/group) collected **28 days after a 2nd immunization** are shown against CMV infection of fibroblast and epithelial cells. The neutralizing activity of CMV$^+$ human sera were also evaluated.

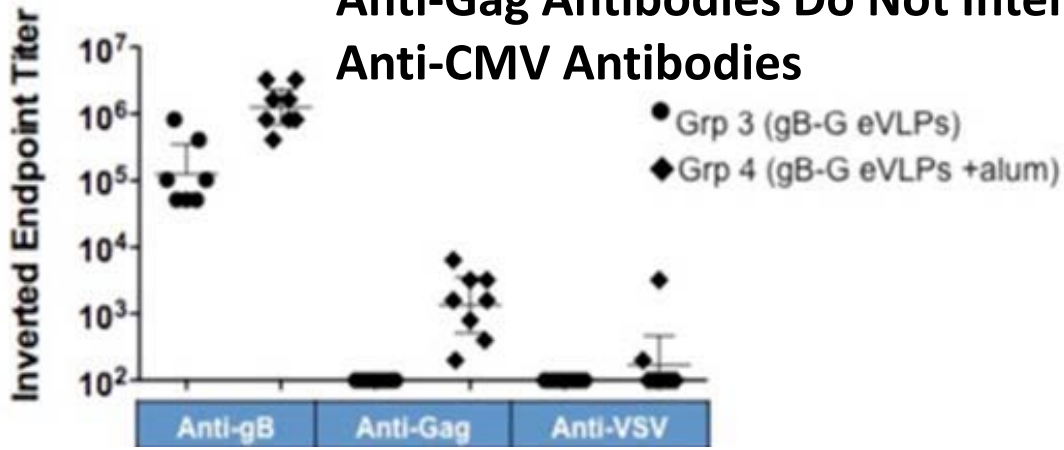
Potent Durability of nAb Responses in Rabbits Vaccinated with Planned Human Doses of CMV Vaccine Candidate

Key Achievement 3: Durability of Immunity has been a barrier to past approaches



Anti-Gag Antibodies Do Not Interfere with Induction of Anti-CMV Antibodies

A



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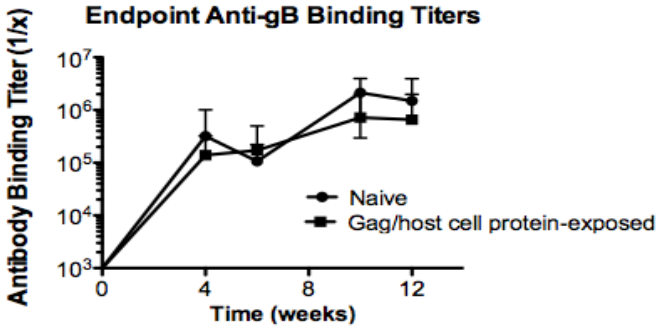

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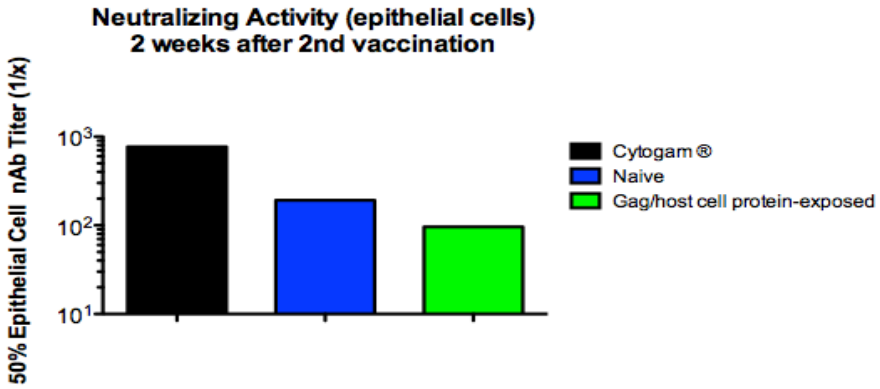


Overview of VBI-1501 Purification Process

Process Optimized to Preserves Particle Integrity & Meet FDA Standards

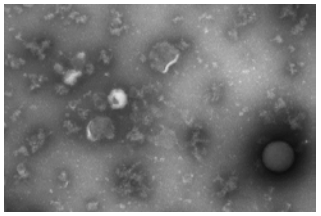
Clarification
(Depth filtration)

Concentrate particles
(Tangential flow filtration)

Inactivate residual host DNA and adventicious virus
(Benzonase/βPL Tx & diafiltration)

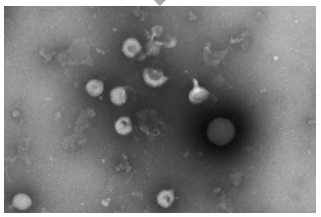
Wash and Concentrate
(Diafiltration & ultracentrifugation)

Sterilize (filter)



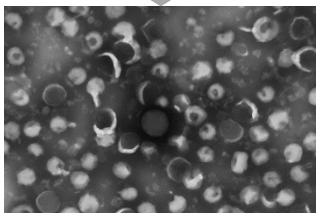
eVLP density = 9.60×10^6 particles/mL

TFF & BZ Tx



1.15×10^{10} particles/mL

Diafiltration & UC



1.44×10^{12} particles/mL

Total particle count (~5×10^{12}) remains constant through process

Analytical Characterization of Purified and Sterilized eVLPs

Test	Test Method/Assay	Test Result
Particle Count	Quantitative nsTEM	$2.93x10^{11}$ eVLP/mL
gB Concentration	Sandwich ELISA	29.4 µg/mL
Total Protein	Bradford Assay	415 µg/mL
Residual Host Cell DNA	Quantitative PCR	1.97 ng/mL
Residual Nucleic Acid	Picogreen Assay	240 ng/mL
Host Cell Protein	HEK 293 ELISA	436 ng/mL
Residual Benzonase	ELISA	<0.25 ng/mL
Osmolality	Osmometric Meas.	275 mOsm/kg
pH	pH Measurement	7.2
Residual Betapropiolactone	LC-MS	<LOD

Summary of eVLPs Yield & Purity

- Consistent, high yield production achieved in HEK (~200 purified doses/L)
  - Final sterile filtration step identified as focus of further process improvement (expect ~500 doses/L)
- Exceptional purity achieved for GLP toxicology and GMP clinical batches:
  - Residual host cell DNA: 0.06 ng/dose
  - Total nucleic acid: 8.1 ng/dose
  - Residual host cell protein: 14.9 ng/dose
    - ~40 total proteins present (2D gel/Mass Spec); only 1 membrane protein (CD81)
- Qualitative & quantitative release criteria established
- Robust viral clearance step confirmed (16 hrs Tx with 10mM βPL)
  - Minute Virus of Mice (MVM): 6.97 log reduction (average)
  - Murine Leukemia Virus (MLV): 6.24 log reduction (average)

CMV Phase I Clinical Trial Overview

Opportunity for Human Potency Proof of Concept with Ph I Data

TRIAL DESIGN

- **Target Population:** ~125 CMV-Negative Healthy Adults (18-40 yrs)
  - Grp 1: 0.5µg (gB content/dose) VBI-1501A (gB-G eVLPs+alum)
  - Grp 2: 1.0µg VBI-1501A
  - Grp 3: 2.0µg VBI-1501A
  - Grp 4: 1.0µg VBI-1501 (unadjuvanted gB-G eVLPs)
  - Grp 5: Placebo (buffer/sucrose used for VBI-1501 suspension)
- **Design:** Staggered Enrollment with Vaccinations at 0, 2, and 6 Months
- **Expected Duration:** 20 Months
- **Primary Endpoint:** Safety and Tolerability
- **Secondary Endpoints:**
  - gB binding titers – ITR
  - nAb titers in fibroblast and epithelial cells – Charles River
  - gB avidity measurement – Adler/McVoy

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- **VBI Team**
  - Dave Anderson, Anne Catherine Fluckiger, Catalina Soare, Abebaw Diress, Tanvir Ahmed, Jasminka Bozic, Barthelemy Ontsouka, Isabel Yang, Diana Duque, Matt Yorke, Jonathan Hodgins, Melissa Lemieux, Misha Nossov

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NRC Industrial Research Assistance Program | Programme d'aide à la recherche industrielle du CNRC

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    - NRC-IRAP supports innovative technologies developed in Canada