Enveloped Virus-Like Particle (eVLP) Cytomegalovirus (CMV) Vaccine is immunogenic and safe: preliminary results of a First-in-Humans Canadian Immunization Network (CIRN) Clinical Trials Network (CTN) - VBI Vaccines study

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Canadian Immunization Conference 2018 Dec 4

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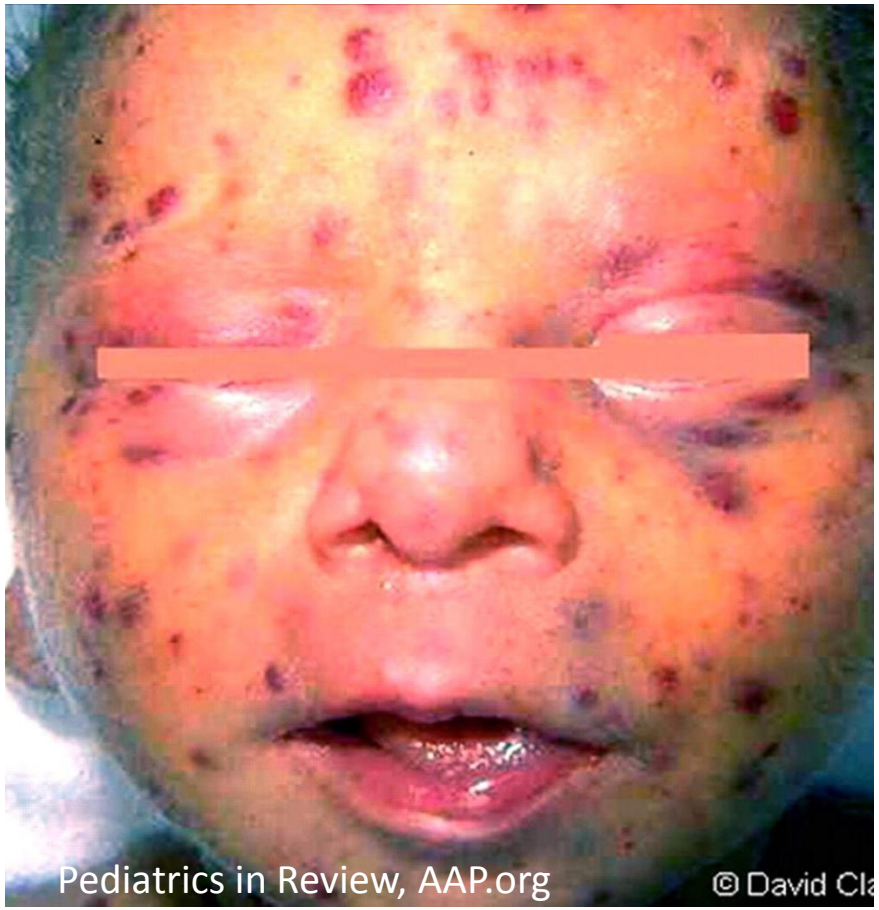
Human Cytomegalovirus (CMV) infection

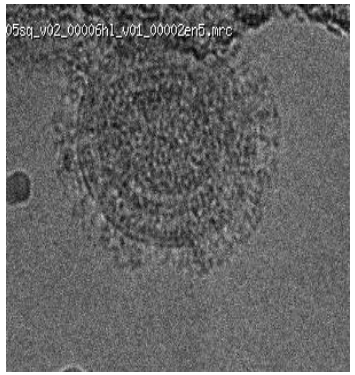
- Most common cause of congenital infection (0.2-2% of pregnancies)
- Maternal viremia can be due to primary or secondary infection, or reactivation of latent infection
- Of infected infants:
  - 10% symptomatic at birth
  - 10-15% of remaining develop permanent sequelae (hearing loss, neurodevelopmental delay)

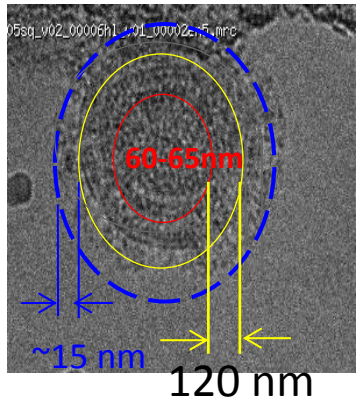


CMV vaccine development

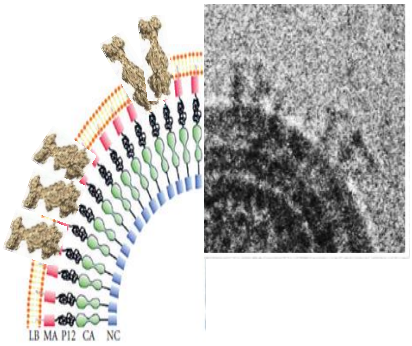
- Institute of Medicine 2000 report “Vaccines for the 21st century: HCMV “highest-level”priority for vaccine development”
- Vaccines currently in development: alphavirus replicon particle vaccines, live attenuated, DNA vaccines
- Evidence that neutralizing antibodies (nAb) confer protection to humans
- Glycoprotein B (gB) viral fusion protein a major target of nAb
- Candidate VBI vaccine: enveloped virus-like particle (**eVLP**) expression of modified **gB antigen** (gB ectodomain fused to fused to transmembrane & cytoplasmic domains of VSV G protein)

Candidate eVLP vaccine presents antigens in a biologically relevant particle morphology





VBI-1501, gB-G



- Modified gB antigen (15 nm spikes) presented in lipid membranes as in nature, a viral mimic
- Compared to recombinant subunit gB, gB-G improves CMV neutralizing responses in preclinical studies
- Neutralizing responses ≥ CMV positive human sera

Randomized, placebo-controlled, dose ranging, observer-blind, first-in-humans study

- Conducted by the Canadian Immunization Research Network (CIRN), a Public Health Agency of Canada (PHAC) – Canadian Institutes of Health Research (CIHR) supported collaboration, at 3 sites (Vancouver, Montreal, Halifax); Sponsor: VBI Vaccines
- Eligibility: CMV seronegative healthy adults 18-40 years of age
- Vaccines administered (0.5 mLs IM) at 0, 2 and 6 months

Study design

- Randomization 1:1:1:1:1(n=25/group) to:
  - 3 dose levels (0.5µg, 1µg, and 2µg gB content) of gB-G eVLPs formulated with alum
  - unadjuvanted 1µg dose of gB–G eVLP
  - placebo
- Outcome measures:
  - Safety, reactogenicity
  - Immunogenicity
    - days 0, 28, 56 (pre-dose 2), 84, 168 (pre-dose 3),196, 280, 336
    - gB binding titers
    - neutralizing antibody titers against CMV infection of fibroblast and epithelial cells

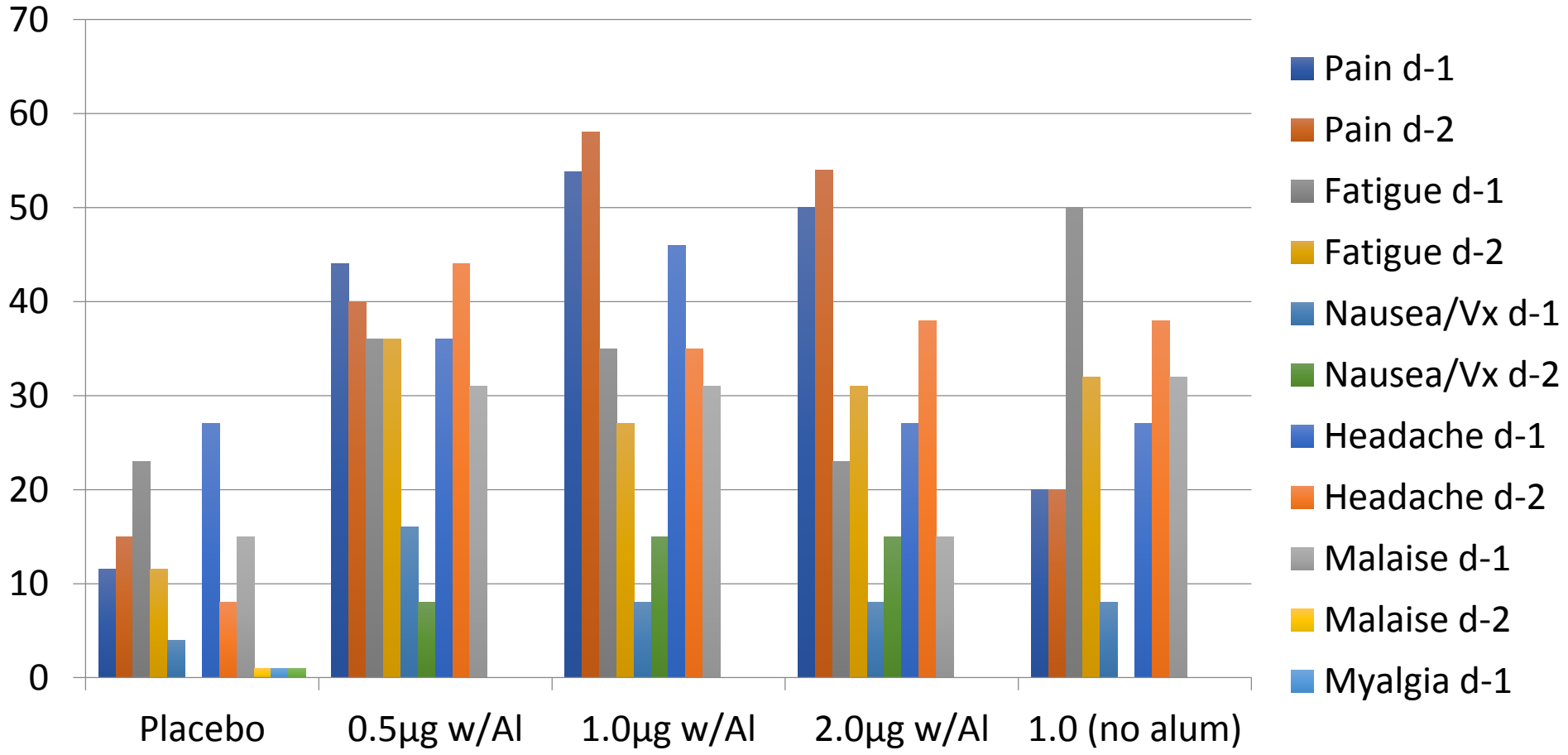
Objectives

- Primary endpoint: safety and tolerability
  - Local and systemic AEs 7 days after each injection
  - Any AE 28 days after each injection and SAEs through Day 336 or early withdrawal
  - Any laboratory abnormality at Days 28, 56, 84, 168, 196, 280, or 336
- Secondary endpoints: immunogenicity
  - gB-binding antibody titers
  - Fibroblast and epithelial cell neutralizing antibody titers

Results: Safety

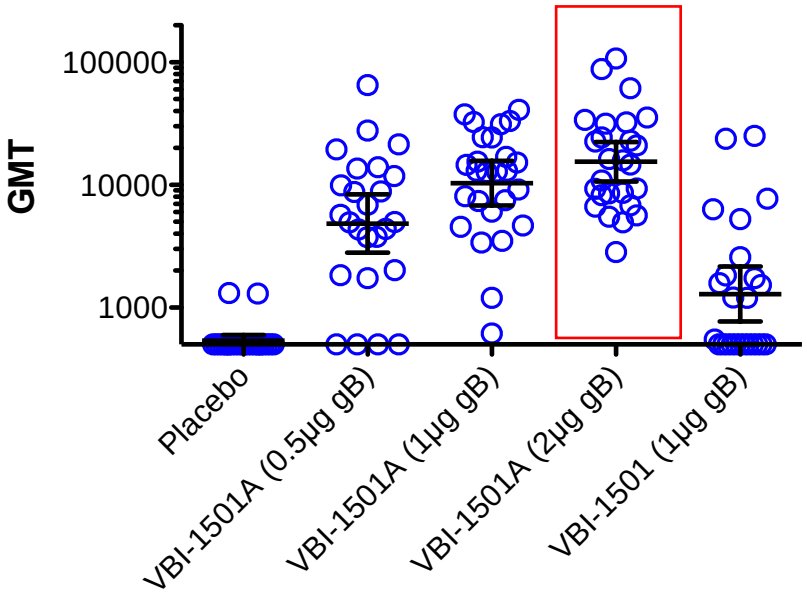
- Most frequent AEs: headache, infections, and fatigue
- Vaccine was not associated with clinically significant AEs compared to placebo
- No significant differences in abnormal laboratory results compared to placebo
- Events were generally mild to moderate in severity
- No event led to an early withdrawal from the study
- Severe events were relatively infrequent and did not appear to be dose-related
- Only one SAE was possibly related to vaccine
  - Aseptic meningitis 114 days after 2nd dose of 2ug VBI-1501A

Solicited adverse events days 0-6 after CMV eVLP gB-G vaccine dose (d) 1 & 2

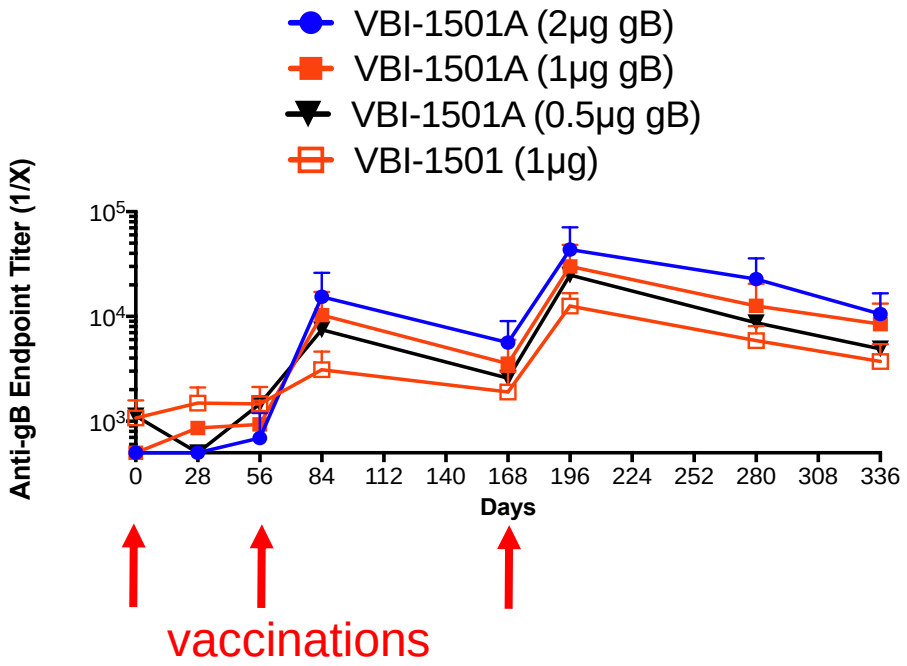


Results: Antibody Binding Titers

- Response after 2 doses
  - Clear dose response
  - 100% seroconversion in highest dose level
  - Alum enhances immunogenicity

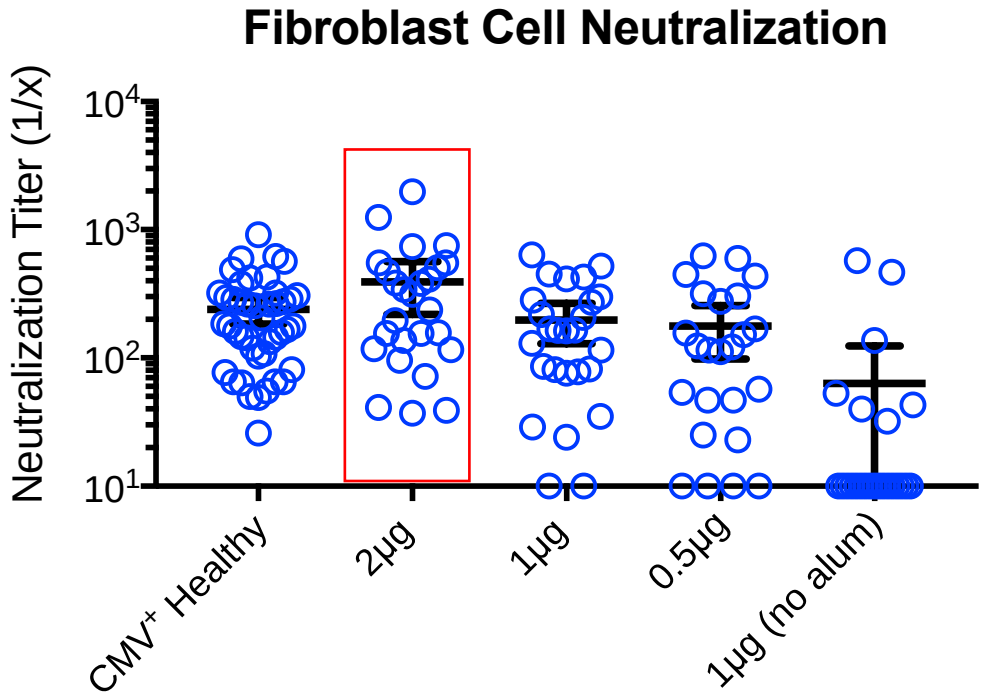


- Antibody kinetics
  - Boosting after 2nd and 3rd doses
  - Peak responses 28 days after 3rd immunization



Potent Neutralization in Fibroblasts

- 100% nAb responses 1 month after 3rd 2ug dose
- Rapid onset of nAb responses
  - 85% of 2.0ug dose seroconverted after two doses
- Neutralizing titers comparable to CMV+ subjects



Conclusions:

- eVLP CMV gB vaccine appears safe and well tolerated at all doses tested
- VBI-1501A is immunogenic
  - 100% seroconversion in highest (2μg) alum-adjuvanted group
  - **gB binding titers** induced at all dose levels, with clear evidence of dose-dependent boosting
  - **Neutralizing activity in fibroblasts** in 100% of subjects at highest dose with titers comparable to CMV-positive controls
  - **Neutralizing activity in epithelial cells** correlate with higher gB binding titers
- Discussions with regulatory bodies ongoing to plan the design of the next stage of development

Thank you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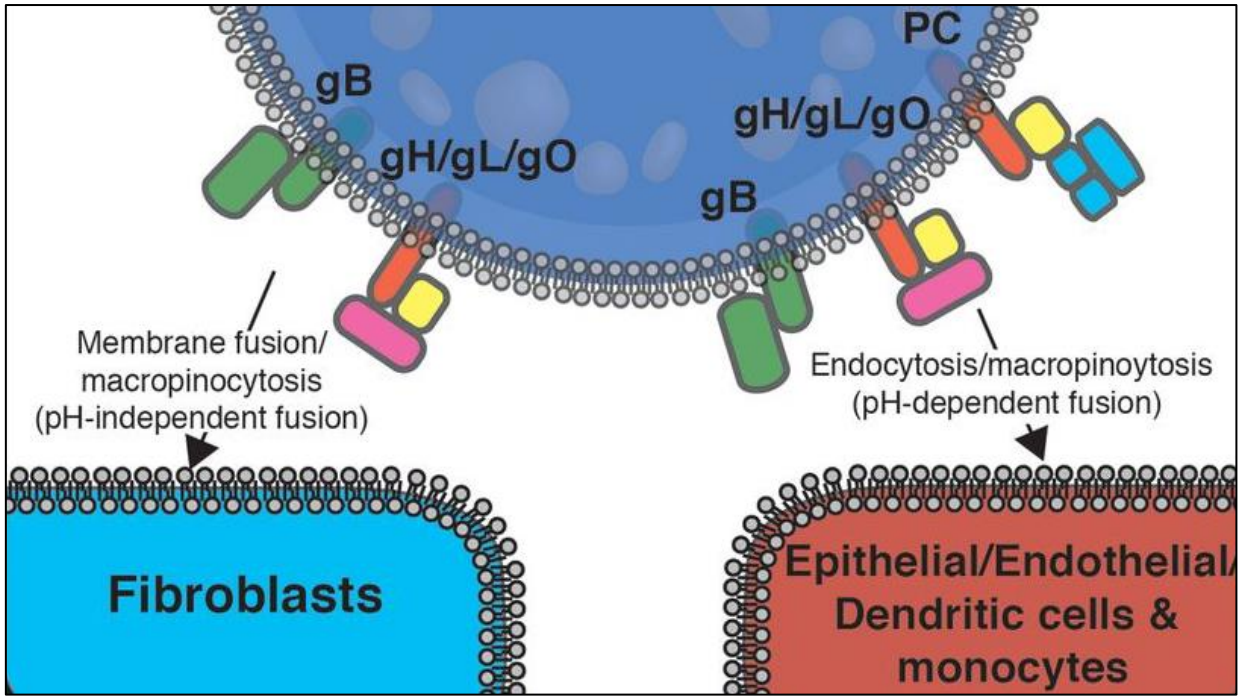
VBI VACCINES

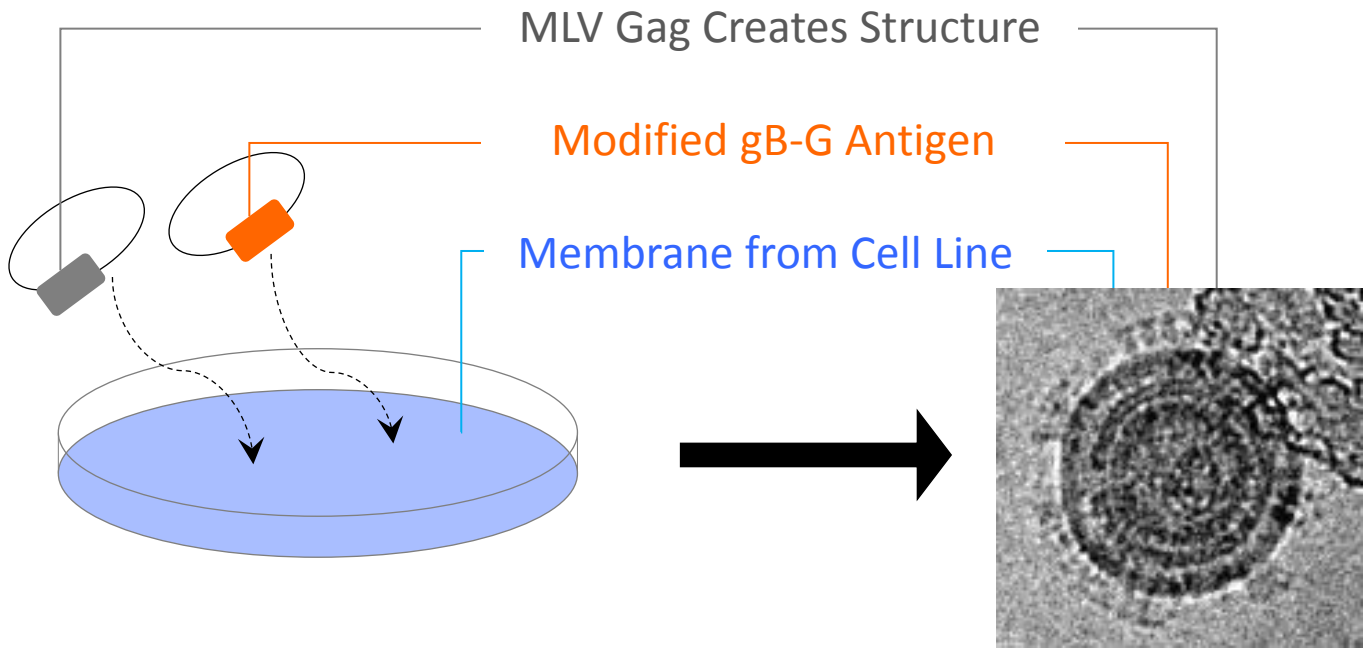
Anti-gB antibodies can neutralize infection of multiple cell types Soren



Gardiner Micro Mol Biol Rev 2016

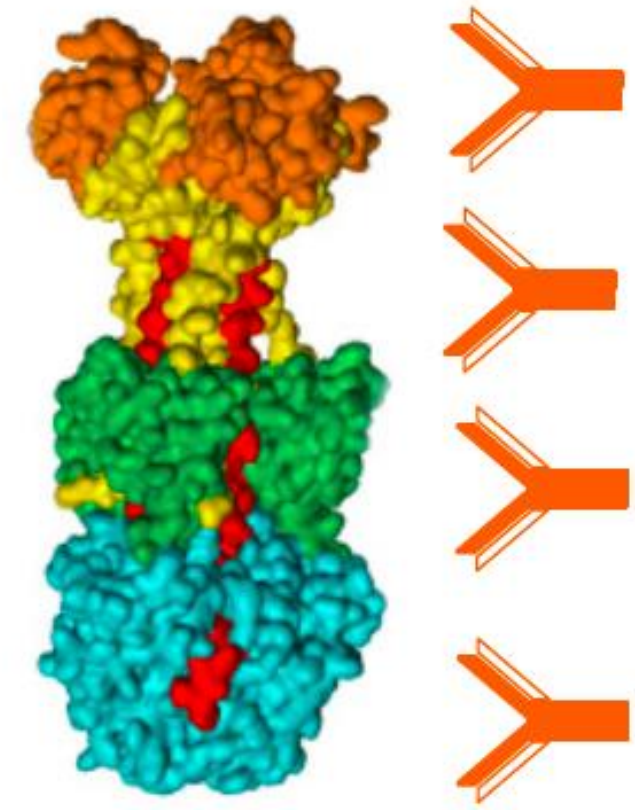
- Pentameric complex required for infection of epithelial/endothelial cells but not fibroblasts
- gB required for fusion/entry in all cell types

Enveloped Virus-like Particle (eVLP) VBI-1501 Soren



Electron micrograph of VBI-1501 showing native conformation of gB envelope spikes

AD-2 is recognized on VBI-1501-Soren



- AD-1 immunodominant domain
  - Antibodies detected in ~all CMV+
  - Poorly neutralizing
- **AD-2**
  - **Antibodies detected in ~50% CMV+**
  - **Broadly potent nAb block fusion**
- AD-4
  - Antibodies detected in ~all CMV+
- AD-5
  - Antibodies detected in ~all CMV+

Potzsch PLoS Pathogens 2011; Ohlin Mol Immunol 2014; Baraniak J Infect Dis 2018