VBI VACCINES

More Foreign than Neo: Harnessing the Power of Viral CMV Antigens in Cancer Vaccines

Mar 30th 2016

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Company Overview

VBI VACCINES INC. (NASDAQ: VBIV) IS DEVELOPING NOVEL TECHNOLOGIES THAT SEEK TO EXPAND VACCINE PROTECTION IN SIGNIFICANT MARKETS OF UNMET MEDICAL NEED

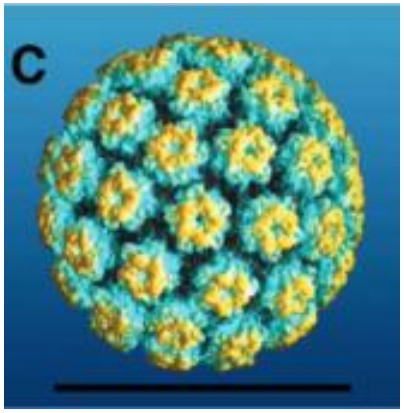
- VBI is developing two complementary vaccine platform technologies:
  - **Enveloped Virus-like Particle ("eVLP") Platform:**
    - Prophylactic CMV Vaccine (Lead Candidate)
    - GBM Immunotherapy
    - Prophylactic RSV Vaccine
  - **Lipid Particle Vaccine ("LPV") Platform**: Proprietary formulation technology enables development of vaccines with preserved stability and potency
    - Active collaborations with Sanofi Pasteur & GSK to stabilize pipeline assets
- Headquartered in Cambridge, MA with its main research site in Ottawa, Canada

eVLP Platform: Potent Antigen Delivery

Virus-like Particle Vaccine Innovation

Early VLPs vs Capsid Virions were a Tremendous Success

- Nature
  - HPV Virion
  - Structure dominated by L1 capsid protein
- Viral Mimic
  - Merck & GSK succeed in a near perfect viral mimic
  - L1 = Major antigenic target AND structural determinant



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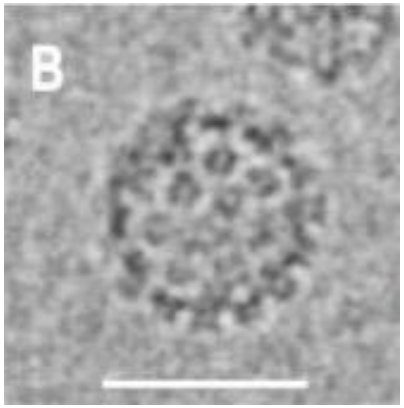

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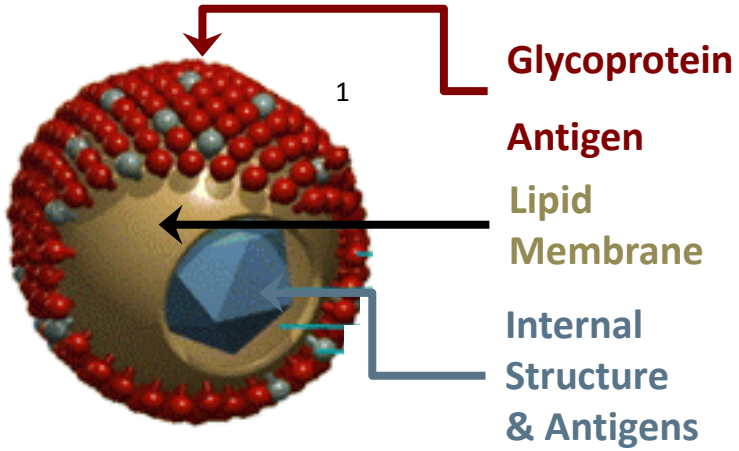
1) Zhao Q, et al Virol J. 2012 Feb 2; 9:52.

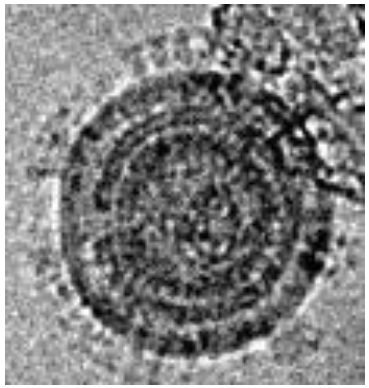
Virus-like Particle Vaccine Innovation

Translation to Enveloped Viruses has been Challenging

- Nature
  - Enveloped virions share three key features
  - Glycoprotein antigens do not natively dictate particle structure



- Viral Mimic
  - VBI eVLPs mimic key elements of enveloped viruses
  - Glycoprotein antigens find a "native like" home in lipid bilayer
  - T-cell antigens can be fused in-frame with protein capsid core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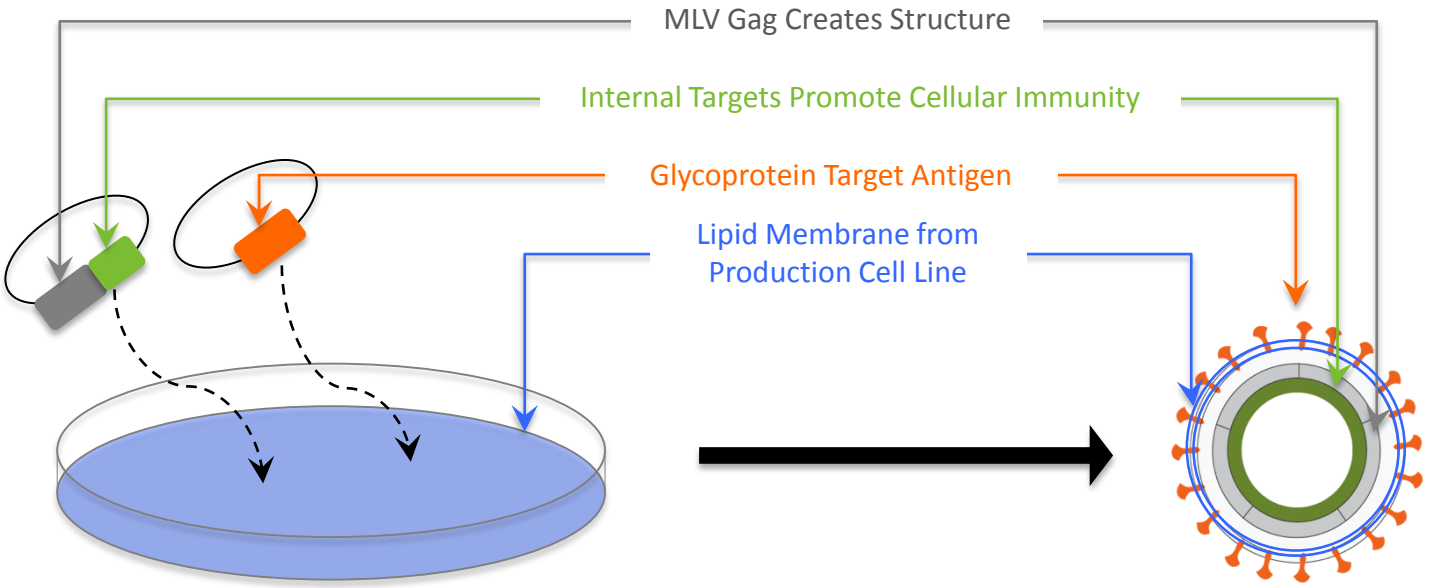
1) Crough et al. Clin. Microbiol. Rev. January 2009 22(1): 76-98, 2) VBI Vaccines Internal Data Courtesy of NanoImaging Inc.

eVLP Production: Multiple Genes and Cell Line Deliver Antigens in Natural Conformations: Within a membrane or internally

Flexible, Customized Antigen Delivery in a Biologically Relevant Construct



- "e" VLP Key Attributes
  - Antigen presented in Virus-like Structure (common to all VLPs)
  - MLV capsid protein creates virus like structure (*unique*)
  - Lipid membrane derived from production cell line (*unique*)
  - Envelope glycoproteins presented in lipid membrane as in nature (*unique*)
  - Internal proteins favor cellular (CTL) immune responses

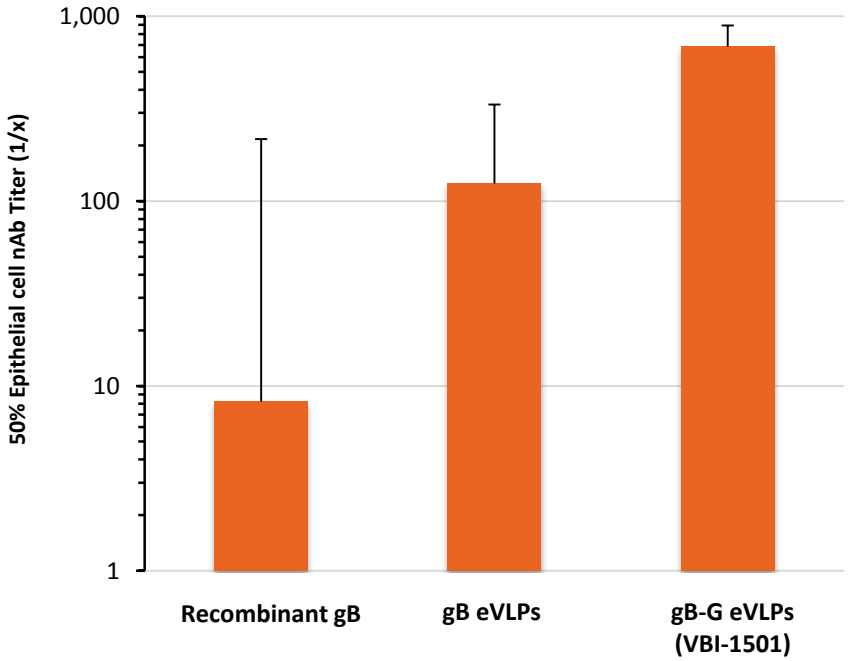
Antigen Presentation in eVLP Improves Potency

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

PRECLINICAL RESULTS

- Structure of the eVLP platform generates stronger neutralizing antibodies than does immunization with recombinant gB
- Proprietary modification of transmembrane domain further improves eVLP potency
- No adjuvant included
- For more details see: Kirchmeier et al, *Clinical Vaccine Immunol.* 2014, 21(2):174.

Neutralizing antibody titers for individual mice immunized with comparable doses of Recombinant gB, gB eVLPs, or optimized gB-G eVLPs (VBI-1501).



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eVLP Application to Immuno-Oncology

Cancer Immunity Cycle:

Potent, "Foreign" Antigen Presentation is Critical to the Solution

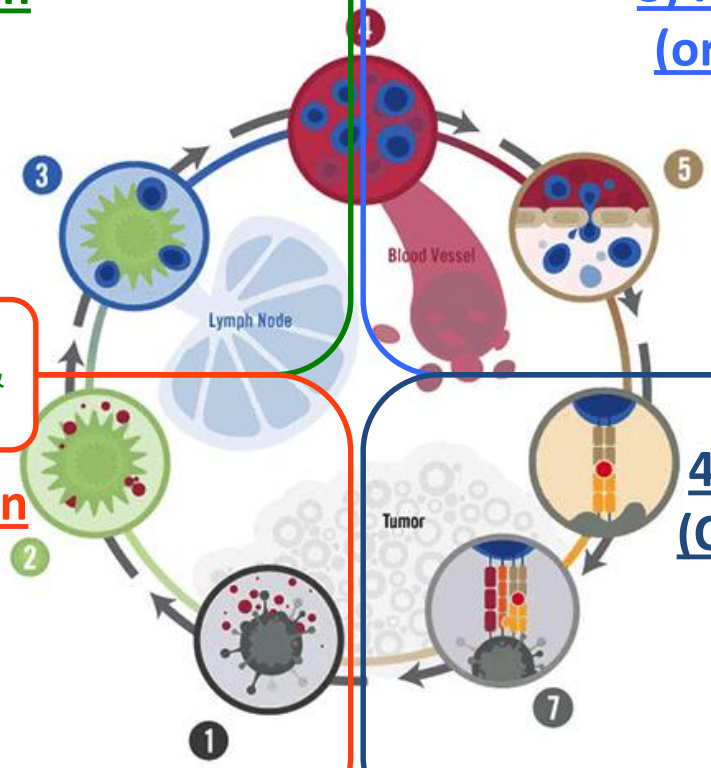
2) Priming & Activation (or GAS)

Examples:
Positive: GM-CSF, STING
Negative: CTLA-4

CAR-T:
elements of gas & steering

1) Antigen Presentation (or Steering)

Examples:
Positive: Vaccines
Negative: CD40



3) Migration & Infiltration (or GPS & Traffic Control)

Examples:
Positive: TILs
Negative: T-Regs, MDSC

4) Recognition & Killing (Checkpoints = Brakes):

Examples:
Positive: IFN-γ
Negative: PD1

NeoAntigens – Increased Mutation Rates ("Foreign-ness") Provides Immune System with Target for Clearance of Invasion

Checkpoint Blockade Effective Against "Hot', Inflamed, High-mutation Rate Tumors with a Tapestry of Novel Antigens

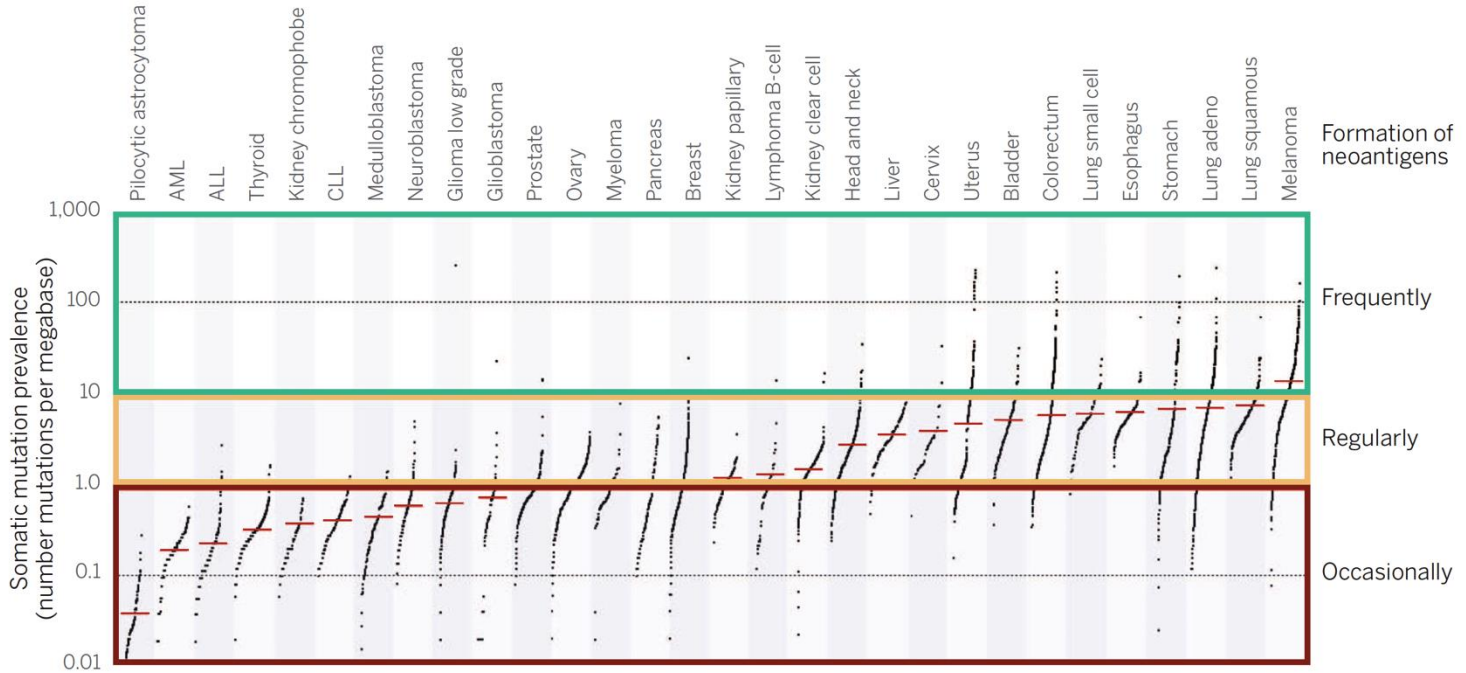
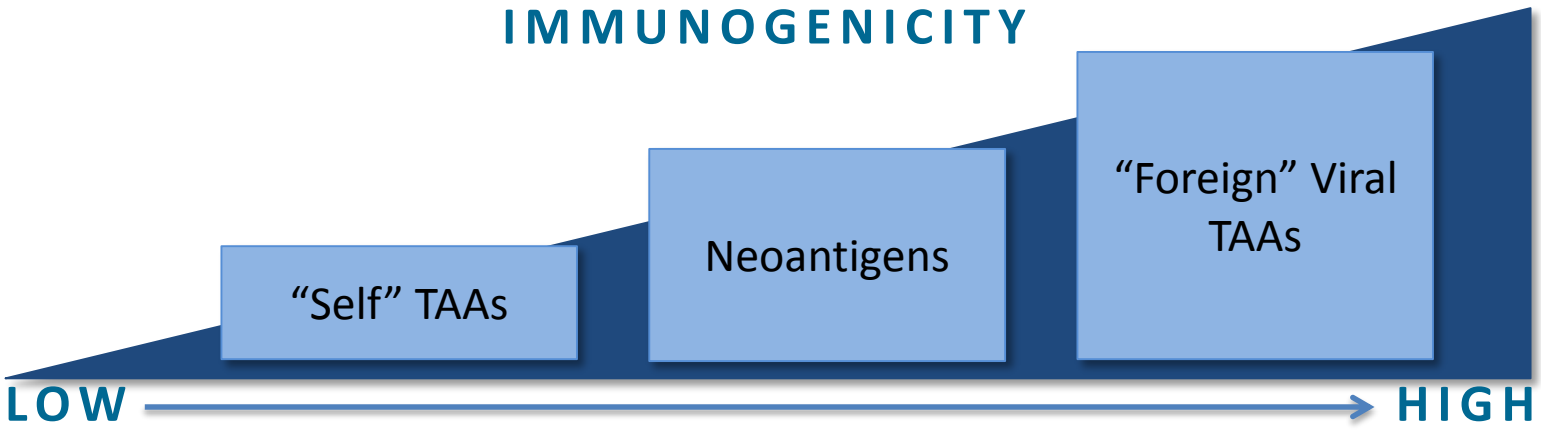


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (*50*). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Traditional Tumor-Associated ("Self") Antigens (TAAs) are Poorly Immunogenic, Newer Mutations ("NeoAntigens") More Promising…

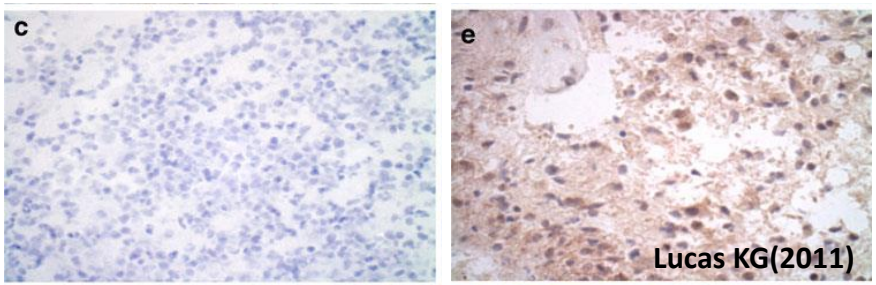


… BUT, NOTHING CAN BE AS FOREIGN AS A VIRAL ANTIGEN

- Immune system exists to fight foreign antigens
- Most successful cancer vaccines (HBV, HPV) are directed against viral targets
- Debating causality (HPV, CMV, EBV) misses the point!
  - Antigen expressed + Antigen is foreign = IDEAL TARGET!!

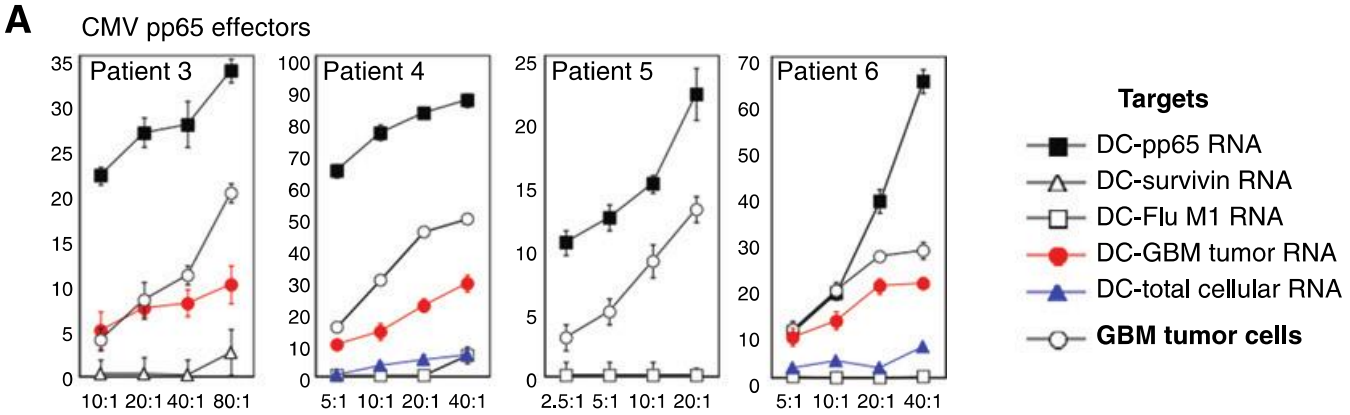
Evidence for CMV as a Target Antigen in GBM

Immuno-histochemical Staining of CMV in GBM Samples



C: negative control Ab
E: pp65 stained GBM sample

Primary GBM Tumors Present Antigens Recognized by CMV Specific T-cells



Nair SK(2014)

Evidence for CMV as a Target Antigen in GBM

Recent Clinical Evidence: CMV DC Vaccination Extends Survival[1]

- DC priming + CMV DC vaccination increased OS of GBM patients
- Overall survival (>36.6 months) vs. control cohort with median OS of 18.5 months

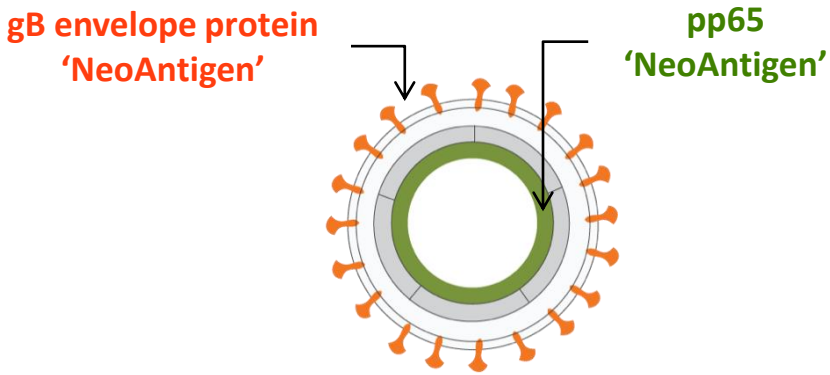
Even Among Viral Antigens: CMV Highly Immunogenic & Highly Expressed in Solid Tumors

- CMV stimulates powerful immunity – 1-2% of circulating T-cells in infected individuals[2]
- CMV is highly expressed (> 90%) on multiple solid tumors:
  - Glioblastoma (GBM)[3]
  - Medulloblastoma[4,5]
  - Meningioma[5]
  - Breast cancer[6,7]

Sources: [1]Mitchell DA(2015) Nature 519, 366-369; [2] Sylwester AW (2005) J Exp. Med. 202, 673-685 ; [3]Cobbs CS(2013) Curr Opin Oncol 25, 682; [4]Baryawno N(2011) J Clin Invest 121, 4043-4055; [5]Libard S(2014) PLoS ONE 9, e108861; [6]Taher C(2013) J Clin Virol 54, 240; [7]Harkins LE (2010) Herpesviridae 1, 8

Design of GBM CMV eVLP Vaccine Candidate

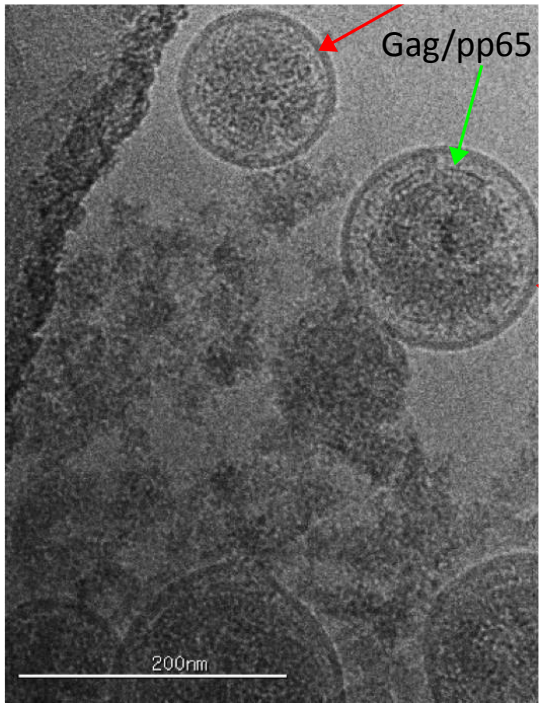
Rationale for vaccine components/mechanisms of action



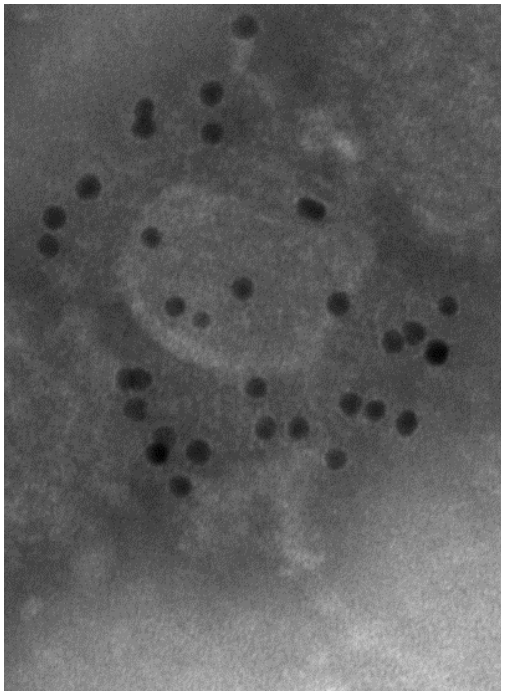
Vaccine Component	Immune Response	Scientific Support
CMV gB	Anti-gB Antibodies	• Prevent gB activation of GBM survival signals (Cobbs C et al, 2014) • Antibody-dependent cell cytotoxicity (ADCC)
CMV pp65	Polyvalent T-cell Responses: $CD4^+$ & $CD8^+$	• CMV pp65 DC vaccination prolongs overall survival of GBM patients (Mitchell DA et al, 2015) • Responses against multiple epitopes and antigens (gB & pp65) avoid immunoselection/tumor escape
eVLP formulation with GM-CSF	Stimulation of IFN-g and CCL3	• IFN-g and CCL3 are key biomarkers of efficacious tumor immunity (Galon J et al, 2006)

Cryo-EM Analysis Demonstrates Location of CMV Antigens in VBI gB/pp65 eVLPs

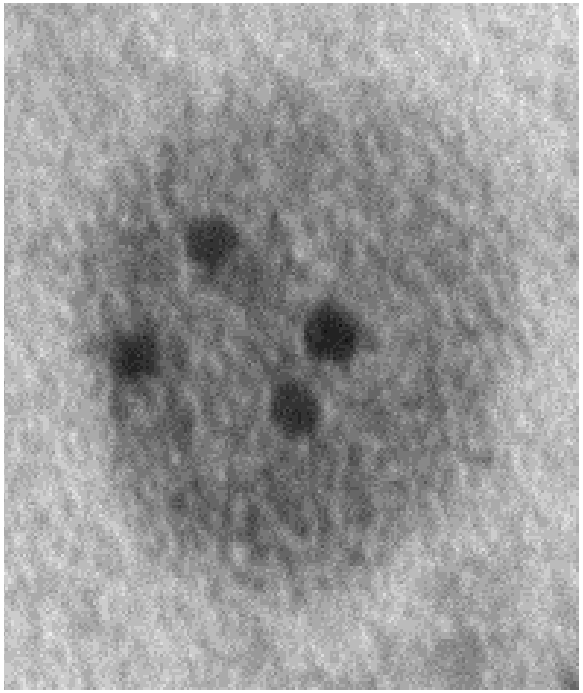
Lipid bilayer



gB expression on eVLP surface

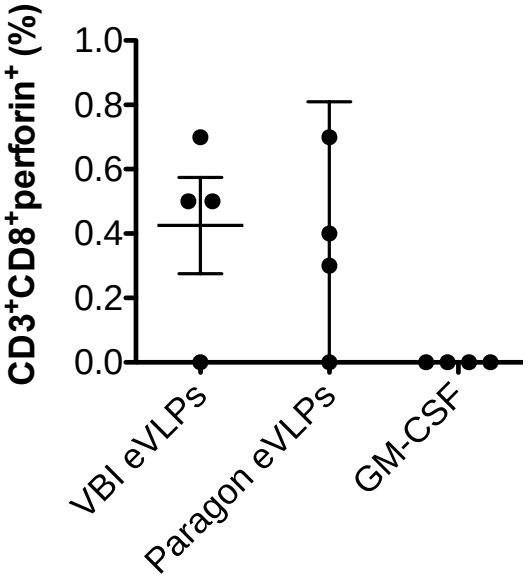


pp65 expression within particle

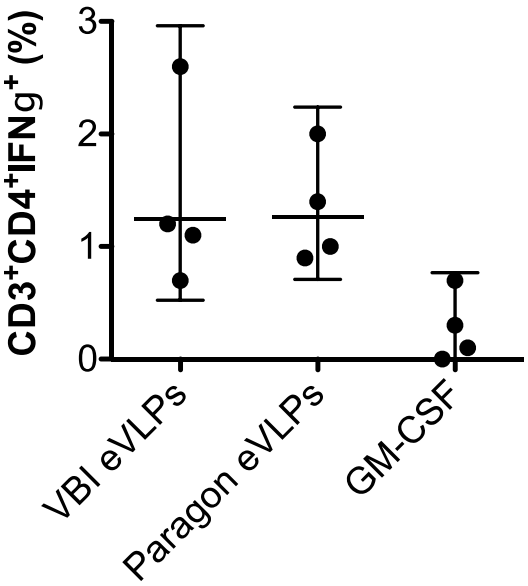


Balanced Humoral & Cellular Immunity in Mice

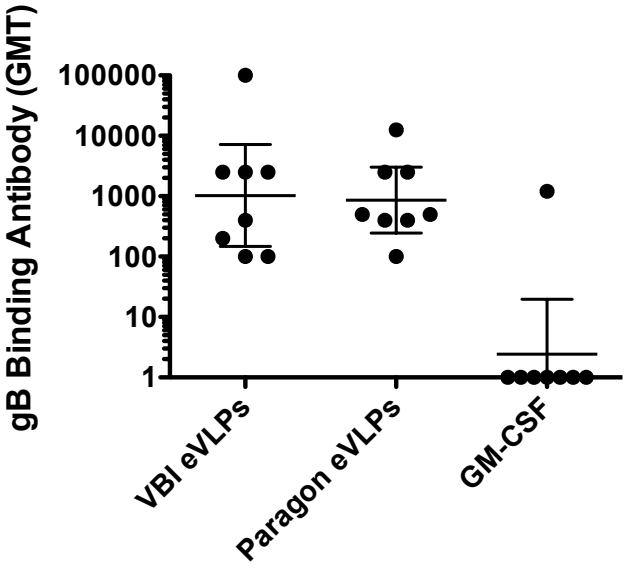
CMV Anti-PP65 CTL Responses



CMV Anti-PP65 T Helper Responses



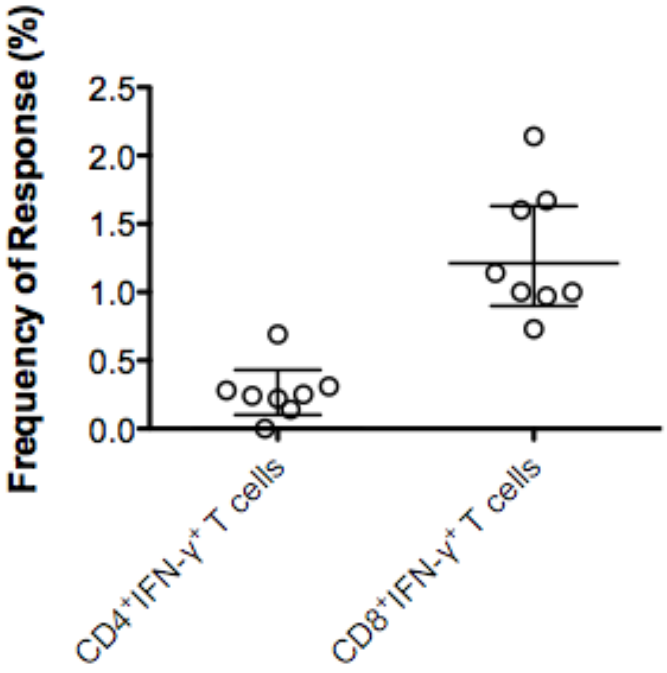
CMV Anti-gB Antibody Responses

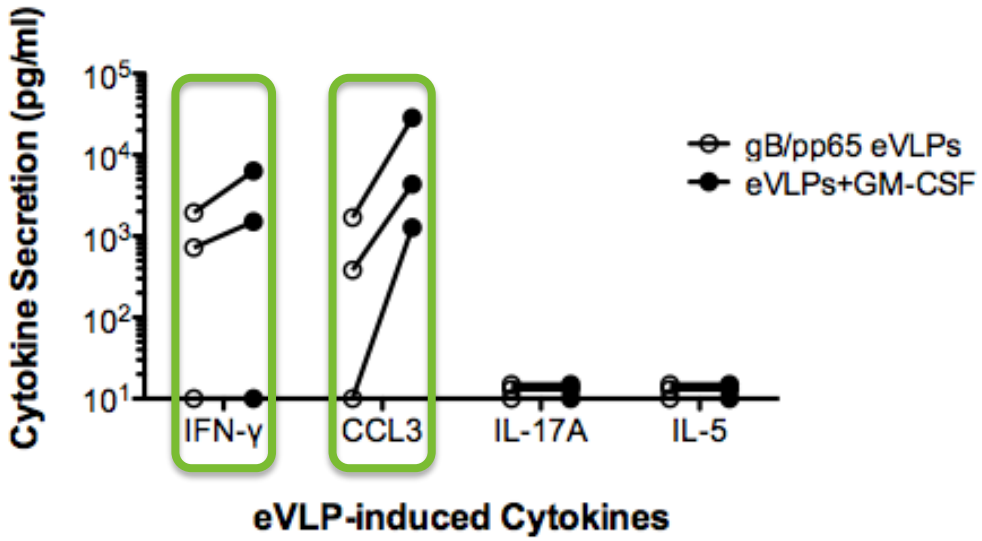


Mice (n= 4 or 8/group) were immunized at 0 and 4 weeks, and splenocytes harvested 10 days later. Splenocytes from the above groups were stimulated with recombinant CMV gB or pp65 antigens; responses against empty eVLPs were subtracted from all responses. The endpoint titer (EPT) is based on the highest dilution of sera reactive with recombinant gB protein in ELISA with an O.D. of 0.1 or greater.

CMV eVLPs Re-stimulate T-cell Responses & Desired Immunity Profile in CMV-positive Human Subjects *Ex Vivo*

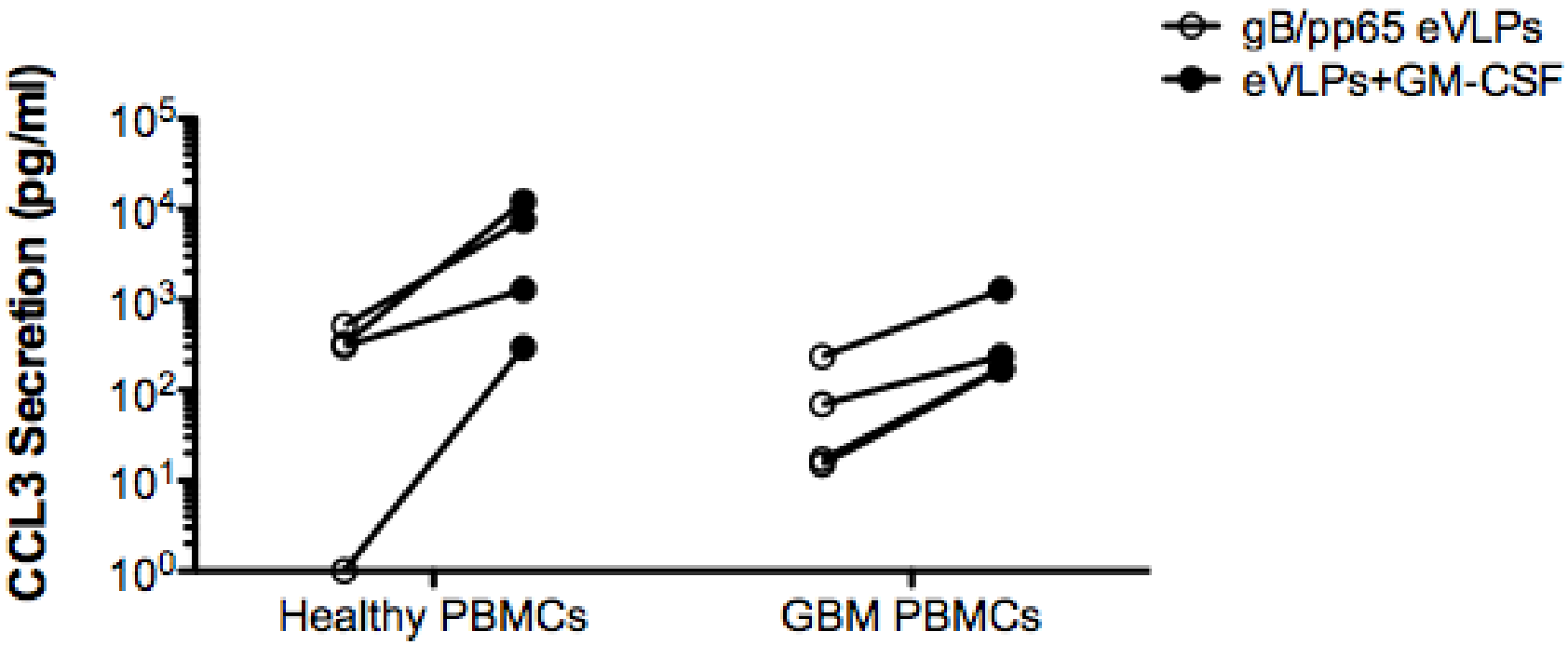
Restimulation of CD4+ & CD8+ T-cells in Ex Vivo Human Samples





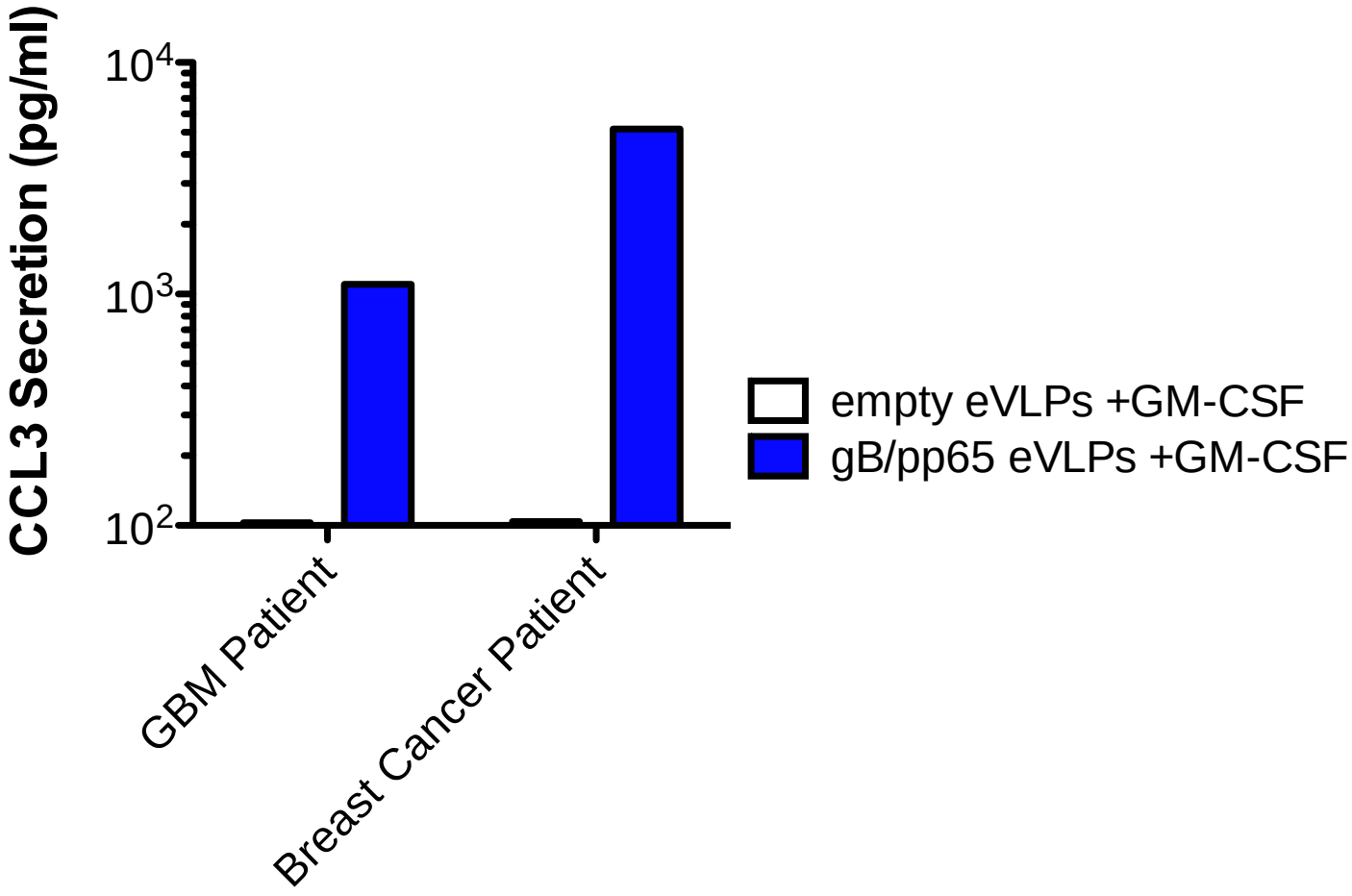
Bivalent gB/pp65 eVLPs were used to stimulate freshly isolated PBMCs from 3 healthy subjects. Background responses to empty eVLPs have been subtracted from all data points.

GBM Patient PBMCs Respond to Bivalent CMV eVLP & GM-CSF Stimulation

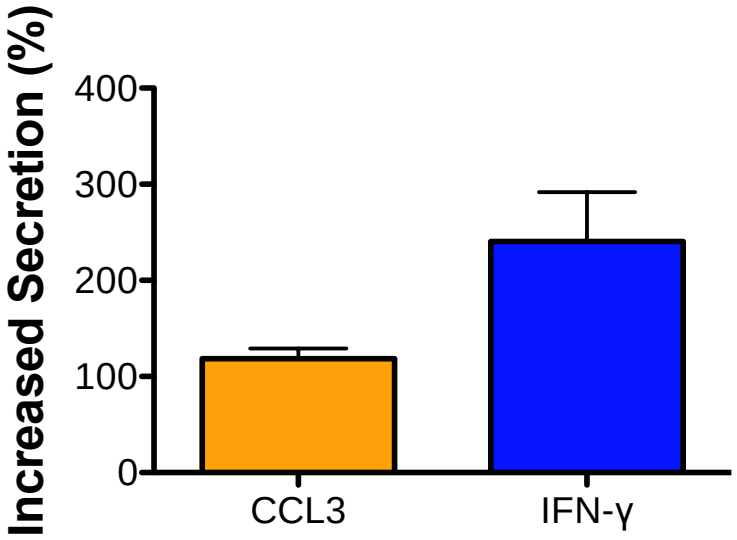


Bivalent gB/pp65 eVLPs were used to stimulate **frozen/thawed PBMCs** from 4 healthy subjects and 4 primary GBM patients. CCL3 secretion after stimulation with empty eVLPs has been subtracted from all values.

CMV eVLPs Elicit Responses in PBMCs Obtained From Patients with GBM and Breast Cancer



Checkpoint Inhibitor (anti-PD-1 mAb) Blockade Enhances CMV eVLP-induced IFN-γ



Increases in CCL3 and IFN-γ secretion are based on 5 healthy CMV+ subjects, comparing gB/pp65 eVLP stimulation in the presence or absence of anti-PD-1 mAb (Opdivo).

Summary

VBI eVLPs Represent a Novel Targeted Approach to Cancer Vaccination

- eVLPs present proteins in a biologically relevant particle & conformation
- Expression of proteins is customizable to optimize desired anti-tumor immunity
- CMV vaccination provides a potent foreign antigenic target with anti-tumor potential & desired biomarker profile
  - Potential application to multiple solid tumors: breast, medulloblastoma, GBM
- eVLP anti-tumor immunity can synergize with checkpoint blockade

Thank You!

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