# VBI VACCINES

## HARNESSING THE IMMUNOGENICITY OF FOREIGN VIRAL CMV ANTIGENS TO TARGET SOLID TUMORS

NASDAQ: VBIV
TSX: VBV

IMMUNO-ONCOLOGY SUMMIT
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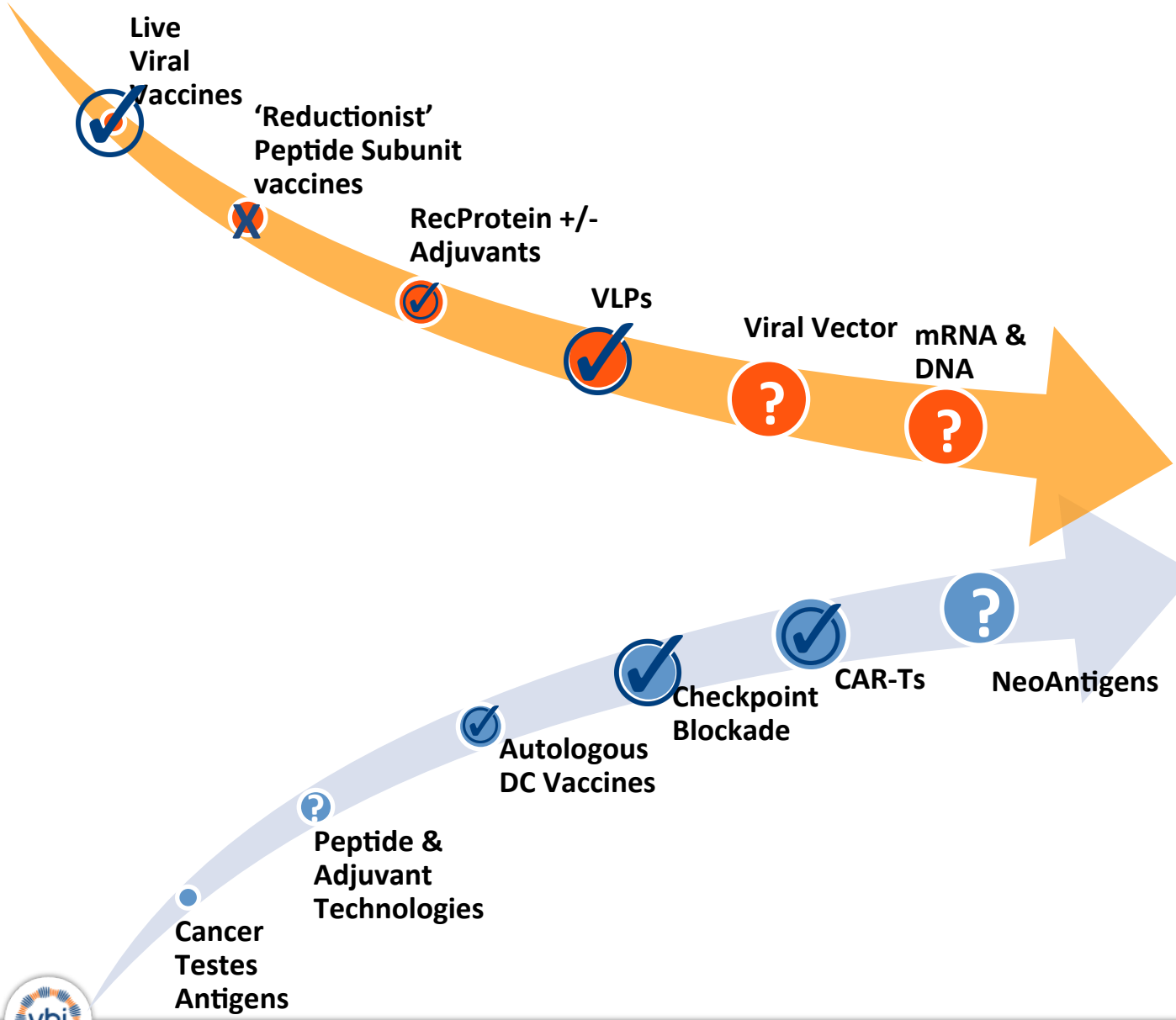
# Agenda

1. Intro & eVLP Platform Overview
2. Significance of CMV as a Tumor Target
3. VBI-1901 IND-Enabling Data
4. Summary

# Convergence of Vaccinology & Immuno-oncology – Cancer Vaccines 3.0




***Themes of Convergence:***

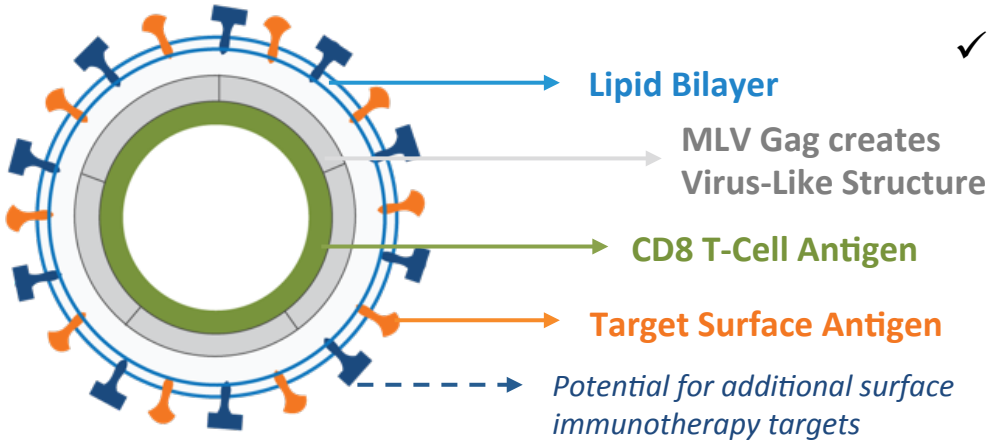
- Antigen selection
  - *Immunogenicity*
  - *Self vs Foreign*
- Antigen delivery
  - *Recognition of Threat*
- Safety
  - Risk-benefit
- Personalized vs. universal

# eVLP Platform: enveloped virus-like particles that leverage innate immune signaling to stimulate anti-tumor immunity

## eVLP Overview

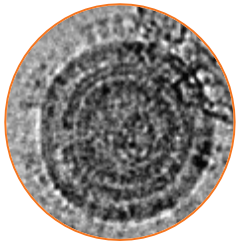
Customizable constructs that mimic enveloped viruses as they occur in nature:

- Key structural components represented
- Antigens in natural conformation
- No replication machinery
- Naturally processed by dendritic cells

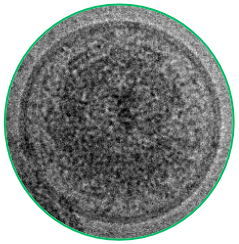



## eVLP Features

- ✓Natively stimulate adaptive and innate immunity
- ✓Promote uptake by antigen-presenting cells
- ✓Internal antigen capacity for CD8 targets
- ✓Surface antigen capacity for CD4 and B cell (antibody) responses
- ✓Scalable and easy to manufacture @ GMP
- ✓Safe in clinic

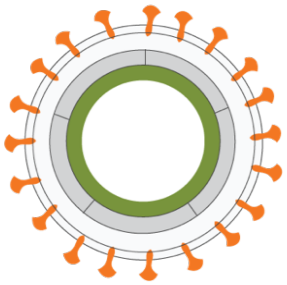


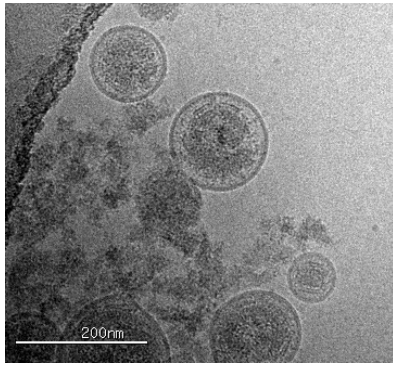
***eVLP Optimized for Surface Antigen***



***eVLP Optimized for Internal Antigen***

# VBI-1901: Rationally designed therapeutic CMV vaccine for solid tumors

| | VBI-1901: Therapeutic CMV for Solid Tumors |
|---|---|
| **Schematic**<br>*Virus-like Structure Stimulates Innate Immunity & Promotes Uptake by Antigen Presenting Cells (APCs)* |  |
| **Antibody Targets** | gB |
| **T-cell Targets** | gB (CD4+), pp65 (CD8+) |
| **Target Indication** | Treatment of CMV+ glioblastoma, breast cancer, other CMV+ solid tumors |
| **Rationale** | Targets both humoral & cellular immunity to promote broad immunity & tumor clearance |

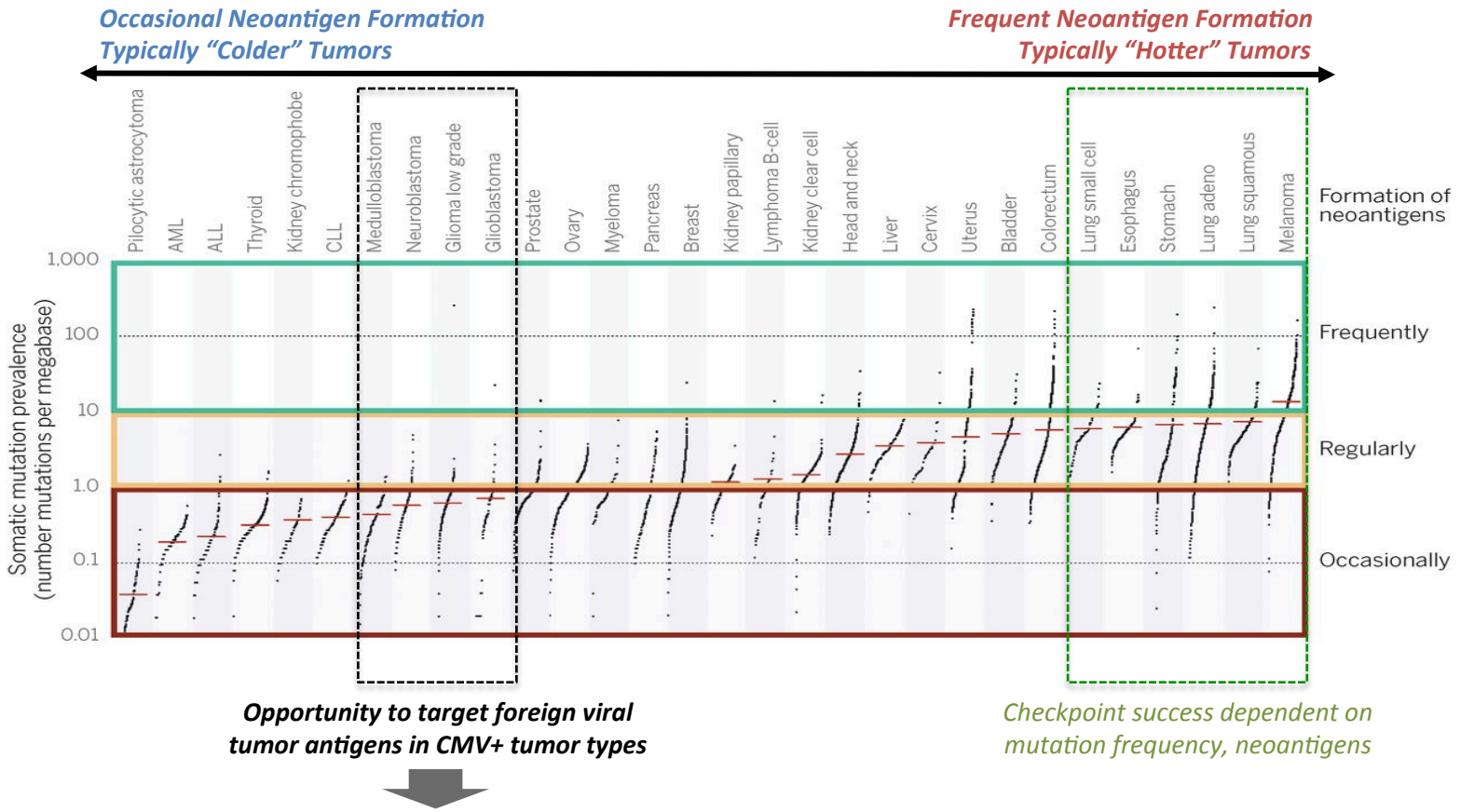



*'Foreign' Tumor Associated Viral Antigens (TAVA) are naturally immunogenic*

| Target | Rationale |
|---|---|
| CMV-gB | • *Viral fusion protein for APC uptake*<br>• *Major antibody & CD4 T-cell epitopes*<br>• *Stimulates innate immunity* |
| CMV-pp65 | • *Primary CD8 T-cell target*<br>• *Full length overcomes HLA restriction* |

# Significance of CMV as a Tumor Target

# Foreign viral antigens, like CMV, enable immune targeting in “cold” tumors where checkpoints inhibitors have been less successful




- Foreign viral tumor antigens are highly immunogenic and inherently ‘hot’
- VBI-1901 can drive potent responses against CMV+ tumors where neo-antigens and ‘self’ tumor-associated antigens have weaker immunogenicity

*Note: Image derived from Nature Review Article on “NeoAntigens”: Schumacher & Schrieber, Science, April 2015*

# Broad evidence supports CMV as a cancer immunotherapeutic target

## GBM

***Body of Evidence Suggests a CMV Vaccine That Can Stimulate DCs & Restimulate CMV-Specific T-cells Has Potential for Clinical Efficacy***

- Prins RM (2008) – Autologous, GBM tumor lysate DC vaccine
  - Single imzn. increased CMV pp65-specific $CD8^+$ T cells from 0.2% to 4.4%
- Crough T (2012) – Single patient receiving 4 infusions of autologous CMV-specific T-cells
  - MRI revealed improvement with stable disease reported for 17 months
- Schuessler A (2014) – 10 patients receiving 3-4 infusions of autologous CMV-specific T-cells
  - 10 recurrent GBM pts, 3-4 infusions of autologous CMV-specific T cells
  - Achieved median OS of 403 days and only minor adverse events
- Mitchell DA (2015) – CMV-specific DC vaccine with tetanus pre-conditioning
  - OS (>36.6 months) vs. control cohort with median OS of 18.5 months
  - ***Survival was correlated with increased levels of CCL3***
- Batich K (2017) – CMV-specific DC vaccine with GM-CSF & Temozolomide
  - OS increased (>41.1 months) vs historic control
  - ***Survival correlated to CMV-pp65-specific INF-gamma T-cells***

## Other CMV+ Tumors

***Broad Support for High CMV Expression, Potential for VBI-1901 Clinical Efficacy***

| | |
|---|---|
| **Neuroblastoma** | • Wolmer-Solberg N (2013) Int J Cancer, 133, 2351-61 |
| **Medulloblastoma** | • Baryawno N(2011) J Clin Invest 121, 4043-4055;<br>• Libard S(2014) PLoS ONE 9, e108861 |
| **Breast** | • Taher C(2013) J Clin Virol 54, 240;<br>• Harkins LE (2010) Herpesviridae 1, 8 |
| **Colorectal** | • Wolmer-Solberg, International CMV Conference – April 2017 |

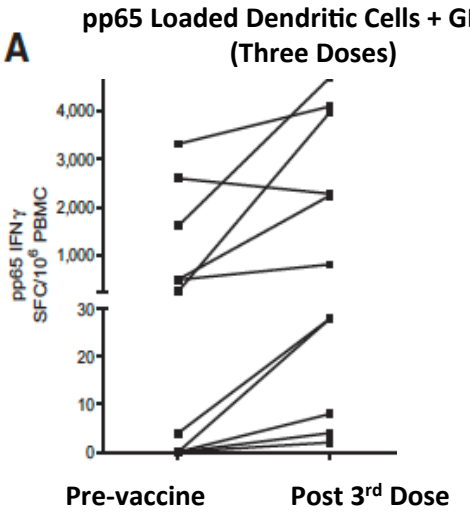
# Duke-led study demonstrates that CMV dendritic cell vaccines can increase pp65 immunity (Batich et al, 2017)

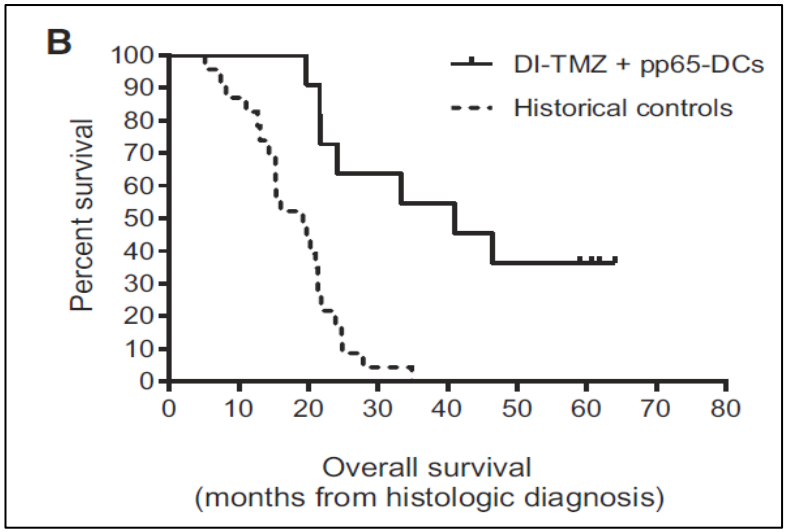
## Trial Design

- 11 patients received at least 3 doses of pp65-dentritic cells after dose-intensified temozolomide

## Clinical Results

- >3 times longer progression-free survival
- >2 times longer overall survival
- pp65 cellular response increased



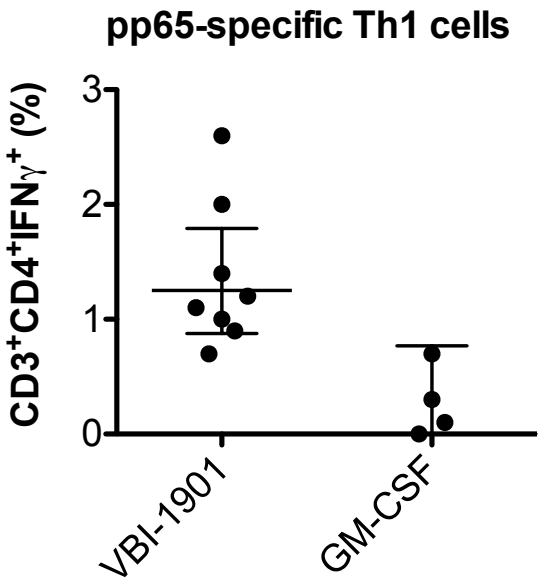

## Relevance for VBI-1901:

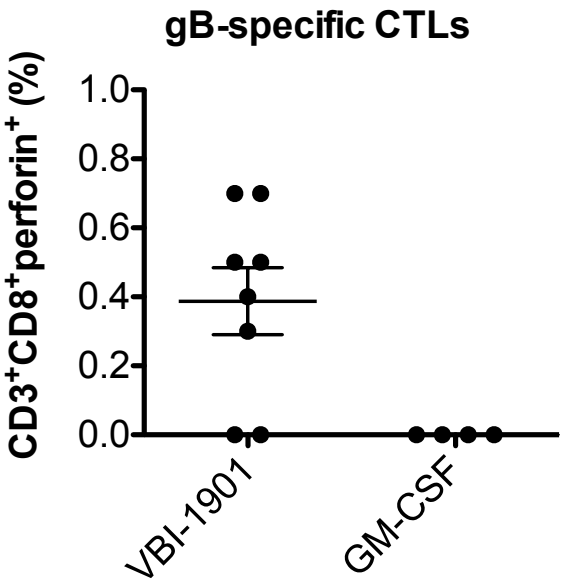
- ✓ Builds on body of evidence demonstrating CMV-immunity impacts survival
- ✓ pp65 DC vaccine analogous to eVLP (which are readily taken up by DCs in vivo)
- ✓ VBI-1901 offers potential to build on outcome with "Off-the-shelf" vaccine

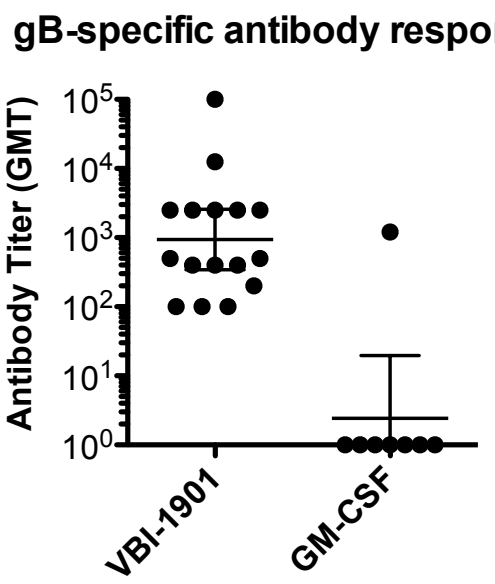
# VBI-1901 IND-Enabling Data

# VBI-1901: Elicits Balanced Cellular & Humoral Immunity

## Tumor Clearance by CTLs is Known to be Enhanced by CD4 & Antibody Responses



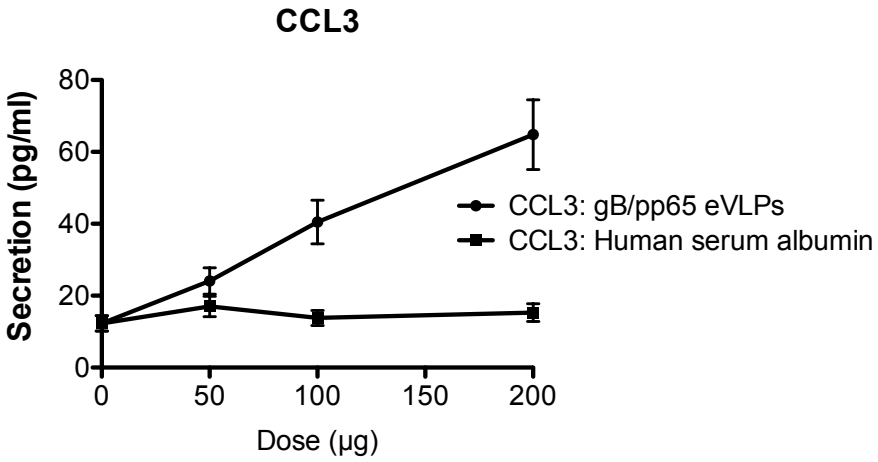



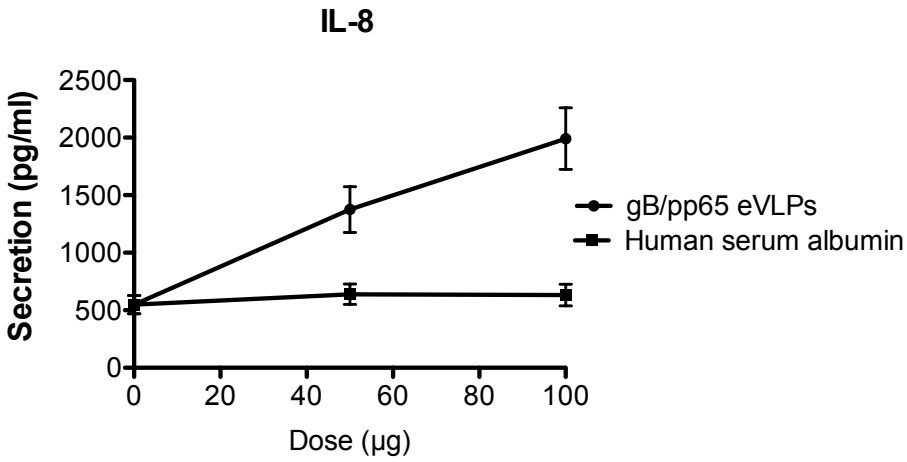




Naïve mice (n= 4 or 8/group) were immunized subcutaneously at 0 and 4 weeks, and splenocytes harvested 10 days later. Splenocytes from the above groups were stimulated with recombinant CMV gB or pp65 antigens; responses against empty eVLPs were subtracted from all responses. The endpoint titer (EPT)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

# VBI-1901: Potential "Off-the-Shelf" Dendritic Cell Vaccine

## VBI-1901 Recruits (CCL3) and Activates (IL-8) Dendritic Cells



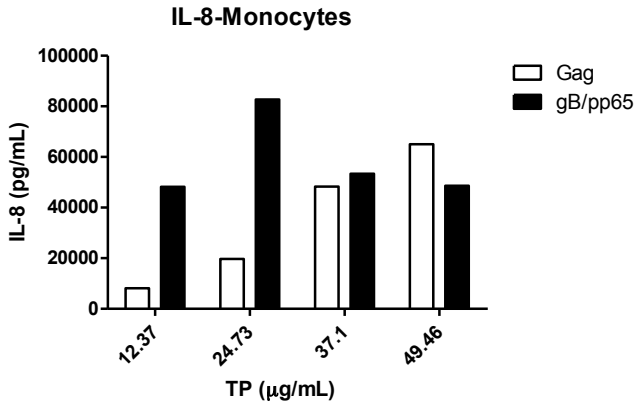

- Immature DCs generated by culture of MUTZ-3 myeloid cell line for 6 days in GM-CSF
- DCs exposed to eVLPs or control recombinant protein (human serum albumin) for 48 hours
- Induction of proinflammatory IL-8 cytokine and CCL3 chemokine determined by CBA assay with comparable results in repeat independent assays (n=3)

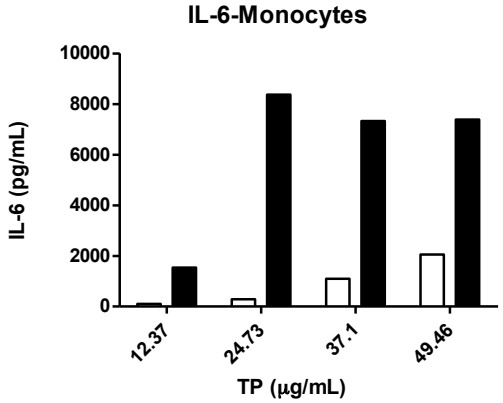
# VBI-1901: Stimulates Innate Immunity

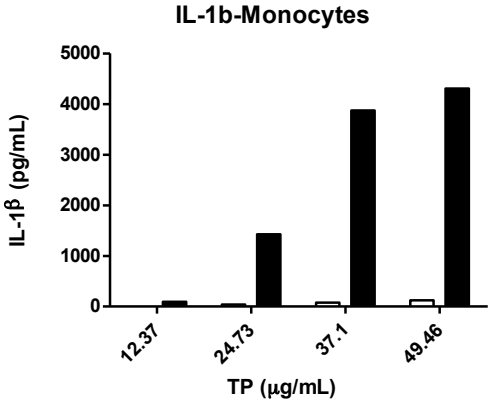
## eVLP particles stimulate IL-8 (independent of antigen)

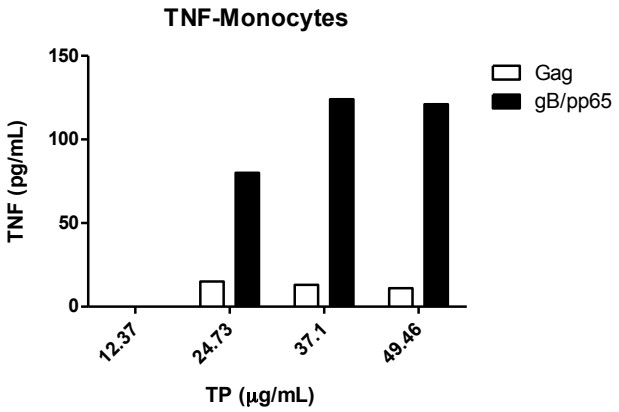
## Inclusion of gB/pp65 antigens stimulates additional pro-inflammatory cytokines

**Note:** Human monocytes were purified by negative selection to >90% purity and stimulated with increasing concentrations of eVLPs. Cytokines were measured by CBA.



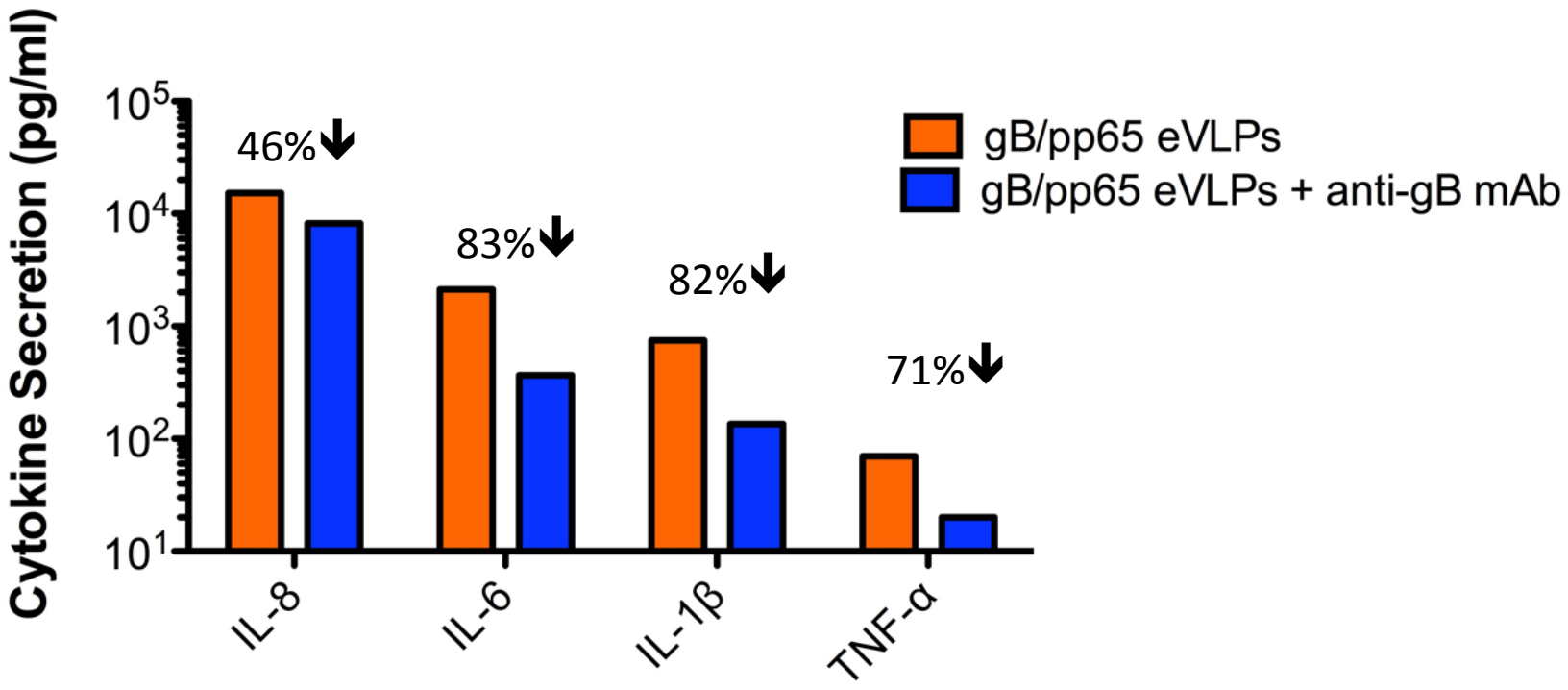



# VBI-1901: Stimulates Innate Immunity

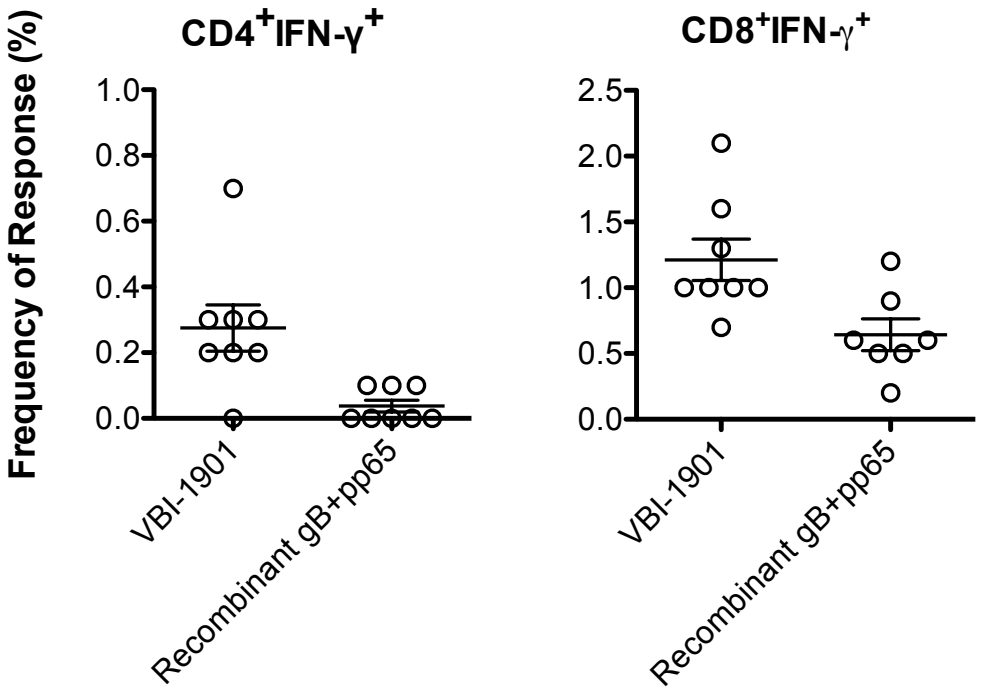
## Antigen specific upregulation of pro-inflammatory cytokines is driven by CMV-gB



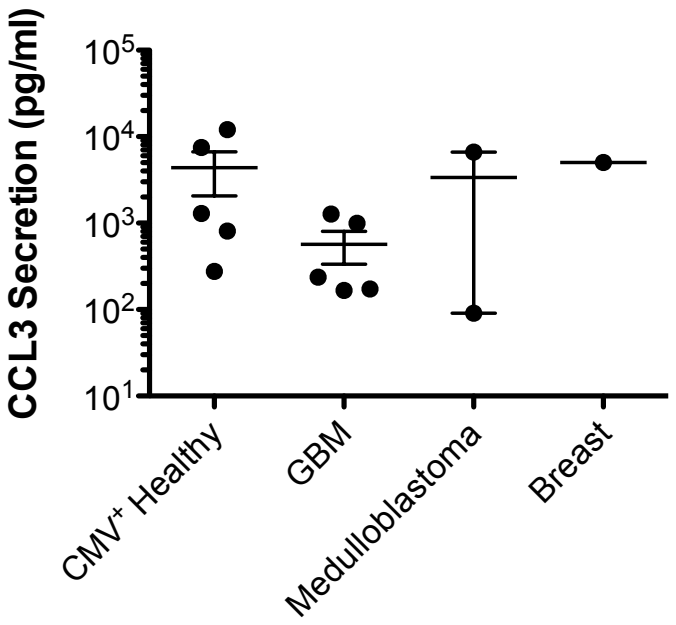

## gB Monoclonal Can Neutralize Stimulation of Innate Cytokine Profile

# VBI-1901: Re-stimulates CMV-specific Immunity in Human *Ex Vivo* Samples

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




**Stimulation of CCL3 in CMV+ Tumors – Correlated to >O.S. by Mitchell et al (2015)**

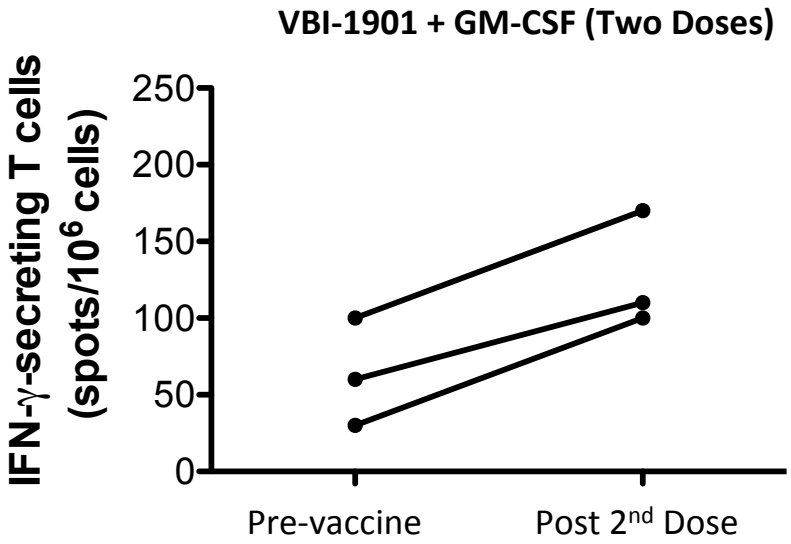



- VBI-1901 stimulates key biomarkers of effective CMV-specific anti-tumor immunity
- Delivery of CMV pp65 & gB in eVLP enhances potency relative to recombinant protein

# VBI-1901: Boosts CMV pp65-specific IFN-γ T cell Responses in Macaques

## Batich et al (2017) Observed CD8 T-cell Immunity after 3-doses & Improved Overall Survival

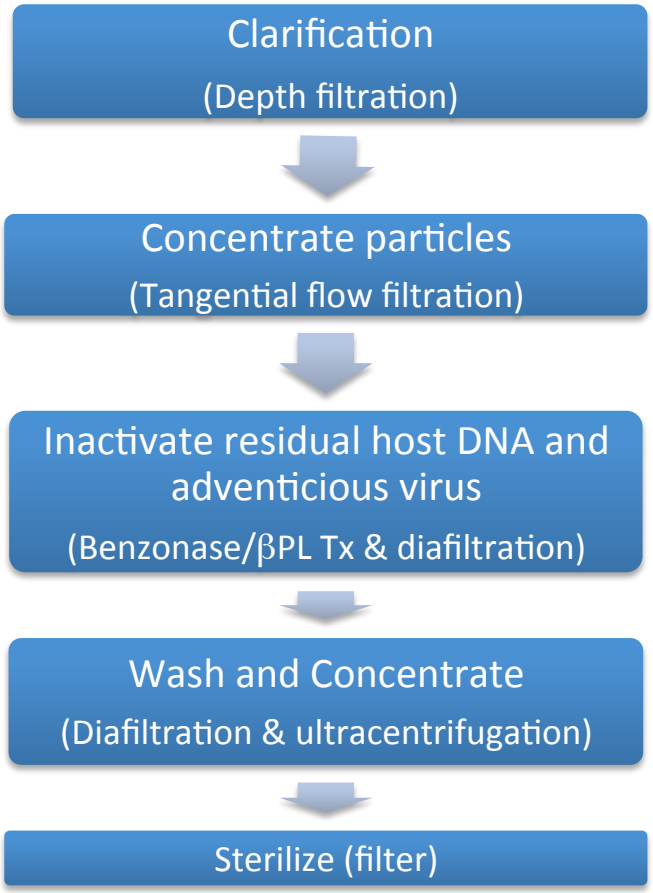
## VBI-1901 Restimulates CD8 Immunity in CMV+ Monkeys – Basis for Clinical Evaluation




**VBI:** CMV+ Rhesus macaque-matched CMV pp65 ELISPOTS before and after 2 vaccinations with VBI-1901 + GM-CSF. ELISPOT tested for IFN-γ using overlapping pp65 peptide pools.

# VBI-1901: Overview of CMC Process

## Process optimized to preserve particle integrity & meet FDA standards

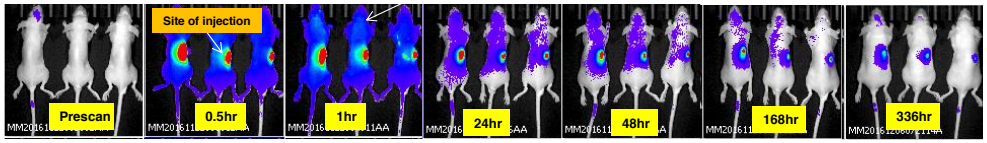



| Assay Description | Test Result |
|---|---|
| Residual host cell DNA (quantitative PCR) | 1.4 ng/µg pp65 |
| Residual host cell protein (ELISA) | 4 ng/µg pp65 |
| Particle count (nsEM) | $5.3x10^{10}$/ml |

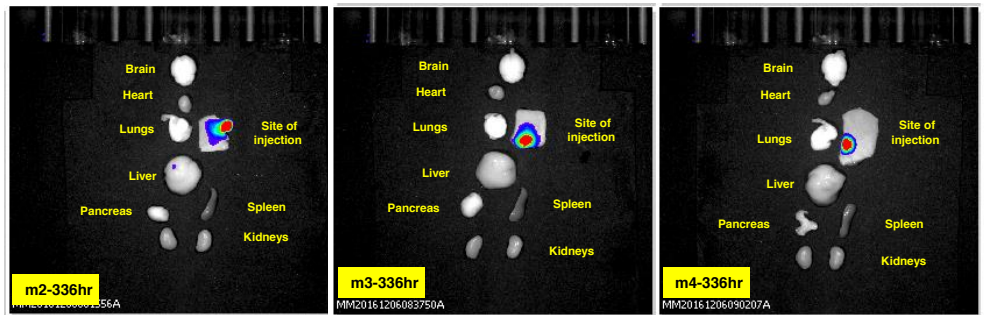
# VBI-1901: IND Enabling Tox & Safety

- Standard Toxicology
  - ✓ No adverse events seen with VBI-1901
  - ✓ eVLPs already safely evaluated in Ph I

- Biodistribution Study
  - ✓ Vaccine observed at injection site for up to 14 days (depot effect)
  - ✓ No accumulation in major organs



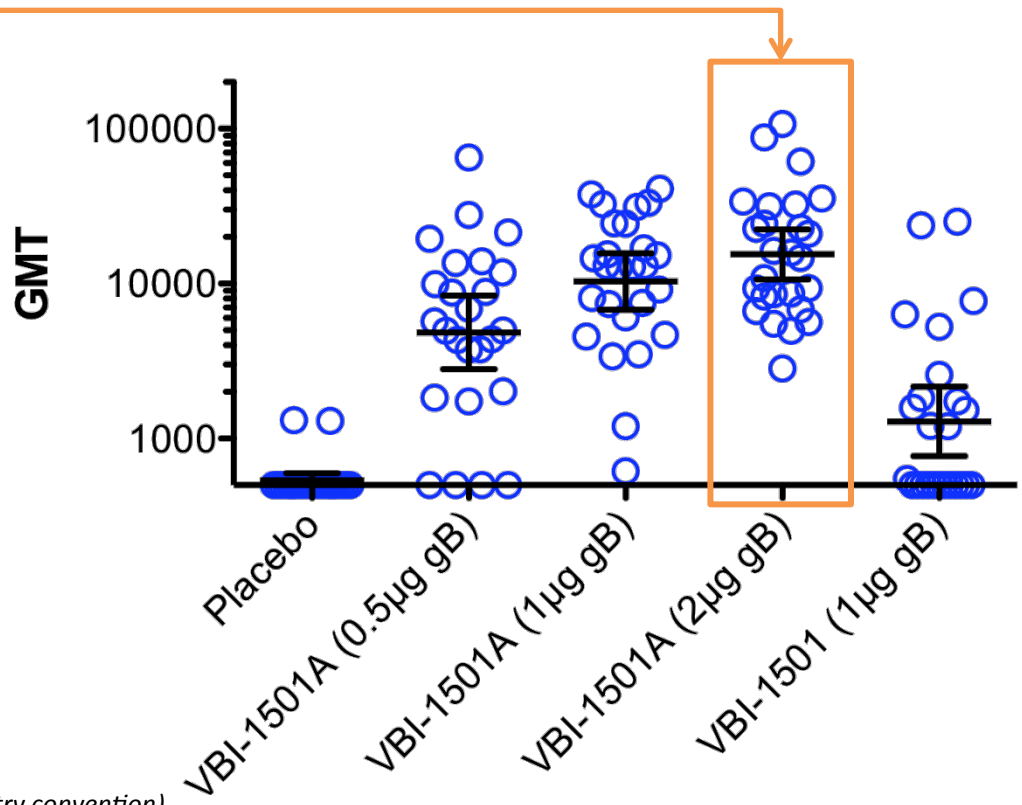

- Off-target Toxicology
  - ✓ Available literature satisfied FDA that off-target CMV toxicity was unlikely (given predominance of CMV in tumor vs healthy tissue and history of clinical safety)



# VBI's prophylactic CMV vaccine (similar design to 1901) achieved dose-dependent immune responses against CMV (interim Ph1 data)

***After only two vaccinations @ 2.0ug, 100% of subjects seroconvert - Exceptionally immunogenic vaccine platform***

- Seroconversion* in 100% of subjects
- eVLPs highly immunogenic platform: 2.0ug dose is 10 - 50X lower than recently approved & late-stage VLP products
- Adjuvant (alum) enhances immunogenicity




**Seroconversion defined as 4x-fold above baseline titer (industry convention)*

# Opportunity & Clinical Development Plan

# Initial Clinical Development of VBI-1901 Will Focus on GBM – A Profound Unmet Medical Need

- ✓ GBM is the most aggressive form of brain cancer
- ✓ No standard of care options after initial surgery/radiation/chemotherapy
- ✓ Invasive primary tumor margins and secondary tumors are interspersed among healthy glial tissue and cannot be safely operated on
- ✓ Estimated incidence varies by country
  - ✓ US: 3.2/100,000[1]
  - ✓ France: 4.96/100,000[2]
  - ✓ UK: 3.43/100,000[3]
- ✓ 42.4% survive 6 months
- ✓ ~90% of patients will experience recurrent GBM[4]


1. Ostrum et al, CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009–2013 – Available at: https://doi.org/10.1093/neuonc/now207
2. Baldi (2010): http://www.ncbi.nlm.nih.gov/pubmed/20869733
3. www.ncin.org.uk/view?rid=2662
4. GBI Research: Glioblastoma Multiforme Therapeutics in Major Developed Markets to 2020

# VBI-1901 Comparison to Recent Clinical IO Advances in GBM

## Breadth of Reactivity may be an Important Parameter for Efficacy

| Company/Inst. | Approach | Key Finding | Take-Away |
|---|---|---|---|
| Novartis – CTL019 | EGFRvIII specific CAR-T | EGFRvIII CAR-T can traffic to brain and exert anti-tumor effect, tumor selected to escape | Targeting multiple epitopes & proteins may be required |
| BMS – Checkmate 143<br>Merck – Keynote 028 | PD1, PDL1 | Opdivo-alone not sufficient. Keytruda trial ongoing | Few neo-antigens typical of GBM may limit efficacy |
| Duke – Batich (et al) | pp65 loaded autologous DCs | Improved overall survival to 41 months with high-dose TMZ | Multi-epitope approach can lead to improved survival |
| VBI Vaccines | Off-the-shelf gB & pp65 eVLP that targets DCs | ***Clinical Study Thesis:*** Multiple full length proteins covering the major CD8, CD4 and ADCC epitopes, presented by virus like particle will stimulate broad immunity with an off-the-shelf approach | |

# VBI-1901: Potential 'Off-the-Shelf' Vaccine for CMV+ Solid Tumors

| | |
|---|---|
| **Off-The-Shelf Design** | • Leverages inherent immunogenicity of CMV to target CMV-positive tumors<br>• Easily manufactured and scalable |
| **Broad Potential in CMV+ Tumors** | • CMV is expressed in over 90% of Glioblastoma (GBM), Breast, Colorectal & other solid tumors<br>• High unmet need in ~18,000 recurrent GBM patients |
| **Strong Preclinical Data Package** | • Restimulation of CD4 and CD8 T-cell responses in CMV+ human subjects *ex vivo* & in CMV+ Rhesus Macaques<br>• Demonstrated safety and tolerability, ready for the clinic |
| **Clinical Rationale** | • Existing CMV-targeting dendritic cell vaccines have achieved a > 2X increase in overall survival in glioblastoma<br>• VBI's prophylactic CMV vaccine (also using eVLPs ) was well-tolerated and immunogenic after just two of three scheduled doses (interim Ph1 data) |
| **Milestones** | • VBI Vaccines has an accepted IND for VBI-1901<br>• Clinical studies in recurrent GBM are expected to begin H2 2017 |


**VBI Vaccines, Inc.**
222 Third Street, Suite 2241
Cambridge, MA 02142
(617) 830-3031

info@vbivaccines.com