VBI VACCINES

# eVLPs as an Antigen Delivery & Immunomodulatory Platform in Cancer

*World Vaccine Congress Europe 2019*

NASDAQ: VBIV

OCTOBER 29 2019

# Forward-Looking Statements

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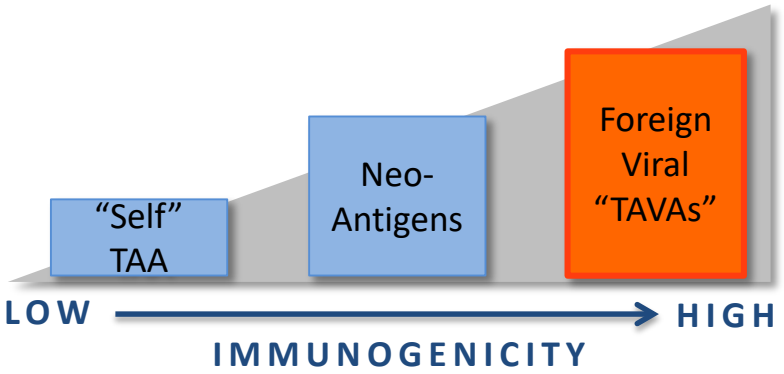
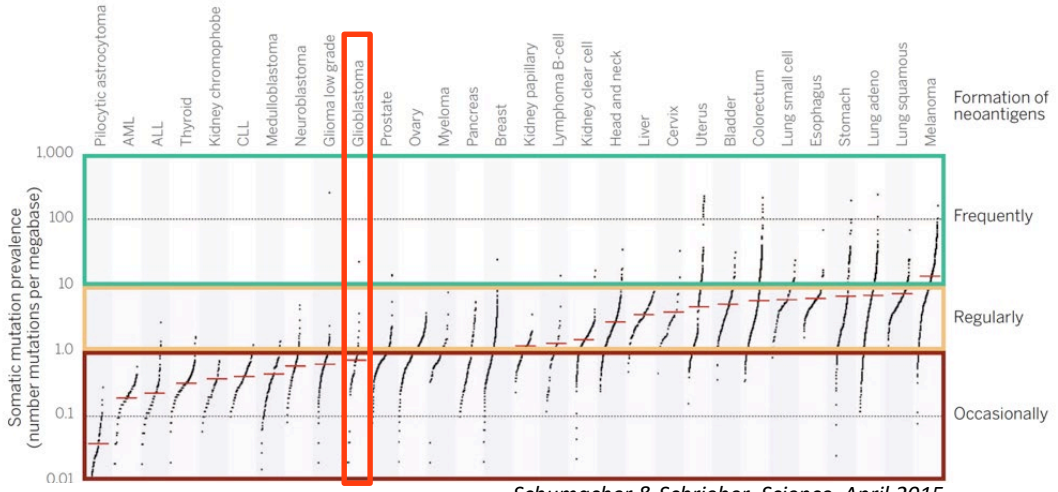
# Therapeutic Vaccination & Immuno-Oncology

# The Immuno-Oncology Renaissance Depends on an Ability to Activate Anti-Tumor Immunity via Appropriate Antigen Selection

## Historic Context of Cancer Vaccines

- Historically, cancer vaccines have consisted of weakly immunogenic "self" tumor associated antigens (TAA)
  - Central tolerance naturally limits potent responses to "self" TAA
- PD-1 & CTLA-4 blockade success explained by mutation frequency – "neoantigens"
  - Occur in frequently mutating/inflamed/"hot" tumors
  - Enhance immunogenicity in the context of PD-1 or CTLA-4 mAb blockade
- Foreign viral antigens are inherently immunogenic
  - Our body has large repertoires of pre-existing anti-viral T cells (e.g. against CMV, EBV)
  - Opportunity for off-the-shelf therapy
- ***Tumor-associated viral antigens ("TAVA") make an ideal antigenic target***




*Schumacher & Schrieber, Science, April 2015*

# Evidence for Cytomegalovirus (CMV) as a Target Antigen in GBM (1)

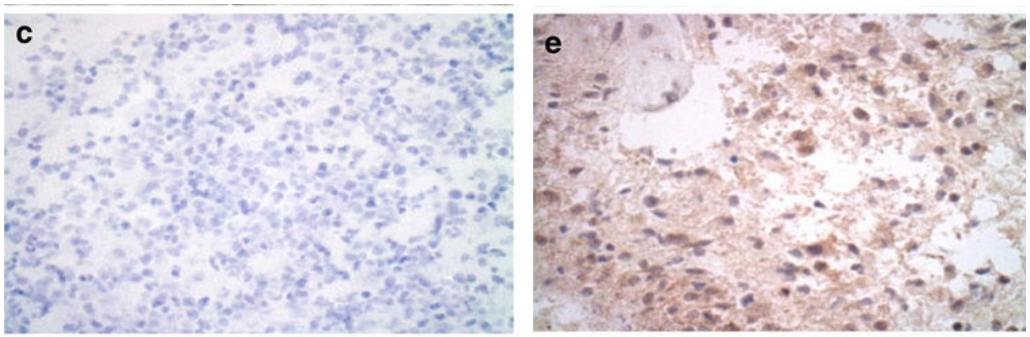
## Multiple labs have confirmed presence of CMV antigens in GBM tumor samples but NOT in adjacent healthy tissue

- **Cobbs CS (2002)**
  - Immunohistochemical (IHC) staining with CMV pp65 antibody confirmed expression in 22/22 GBM tumor samples
  - No CMV expression in normal brain tissue (n=5), stroke tissue (n=4), and brain tissue from Alzheimer's subjects (n=3)
  - *In situ* hybridization (ISH) with CMV-specific probes confirmed reactivity in 8/8 GBM samples but no reactivity in normal brain tissue (n=4), stroke tissue (n=1) or Alzheimer's brain tissue (n=2)

- **Mitchell DA (2007)**
  - IHC staining with CMV IE-1 antibody confirmed expression in 42/45 GBM tumor samples with no expression in surrounding non-tumor brain tissue
  - IHC staining with CMV pp65 antibody confirmed expression in 30/33 GBM tumor samples but no adjacent areas of normal brain
  - ISH with CMV IE1 probe confirmed reactivity in 16/16 GBM samples but not to blood vessels or normal brain

# Evidence for CMV as a Target Antigen in GBM (2)

## Immuno-histochemical Staining of CMV in GBM Samples

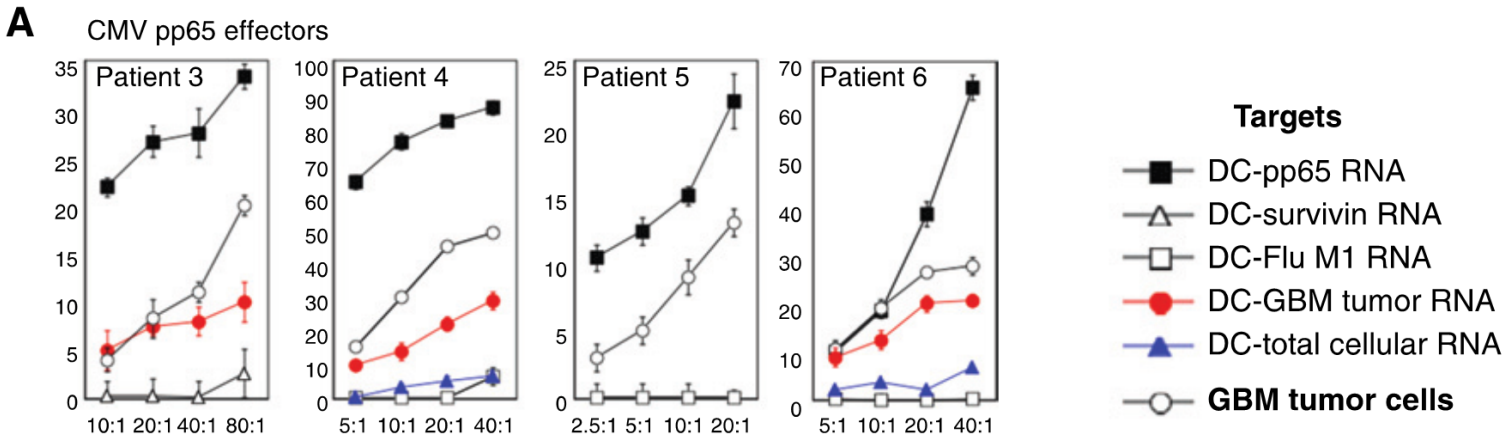



Lucas KG(2011)

C: negative control Ab

E: pp65 stained GBM sample

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




Nair SK(2014)

# Broad Clinical Evidence Supports CMV as an Immunotherapeutic Target in GBM

- **Prins RM (2008)** – Autologous, GBM tumor lysate DC vaccine
  - Single immunization 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
- **Batich K (2017)** – CMV-specific DC vaccine with GM-CSF & Temozolomide
  - OS increased (>41.1 months) vs historic control
  - **Survival correlated with CMV-pp65-specific INF-γ T-cells**

# While NOT Causative, CMV is Highly Associated with Multiple Solid Tumors

### Glioblastoma

- Over 95% CMV+ and clinical evidence of targeting CMV
- Key references:
  - *Cobbs 2002, 2013*
  - *Lucas KG 2011*
  - *Nair SK 2014*
  - *Batich K 2017*
  - *Penas-Prado 2018*

### Breast Cancer

- Expressed on over 90% and may modulate tumor macrophages
- Key references:
  - *Pasquereau (2017) Open J Virol*
  - *Herbein (2014) Frontiers Oncol*
  - *Taher C (2013) J Clin Virol*
  - *B Cox (2010) BJC*
  - *Harkins LE (2010) Herpesviridae*

### Other Brain Tumors

- Key references:
  - *Wolmer-Solberg N (2013) Int J Cancer*
  - *Baryawno N (2011) J Clin Invest*
  - *Libard S (2014) PLoS ONE*

### Others Requiring Analysis

- CRC, Liver, Prostate
- Prevalence typically ~50% (higher than a standard TAA)

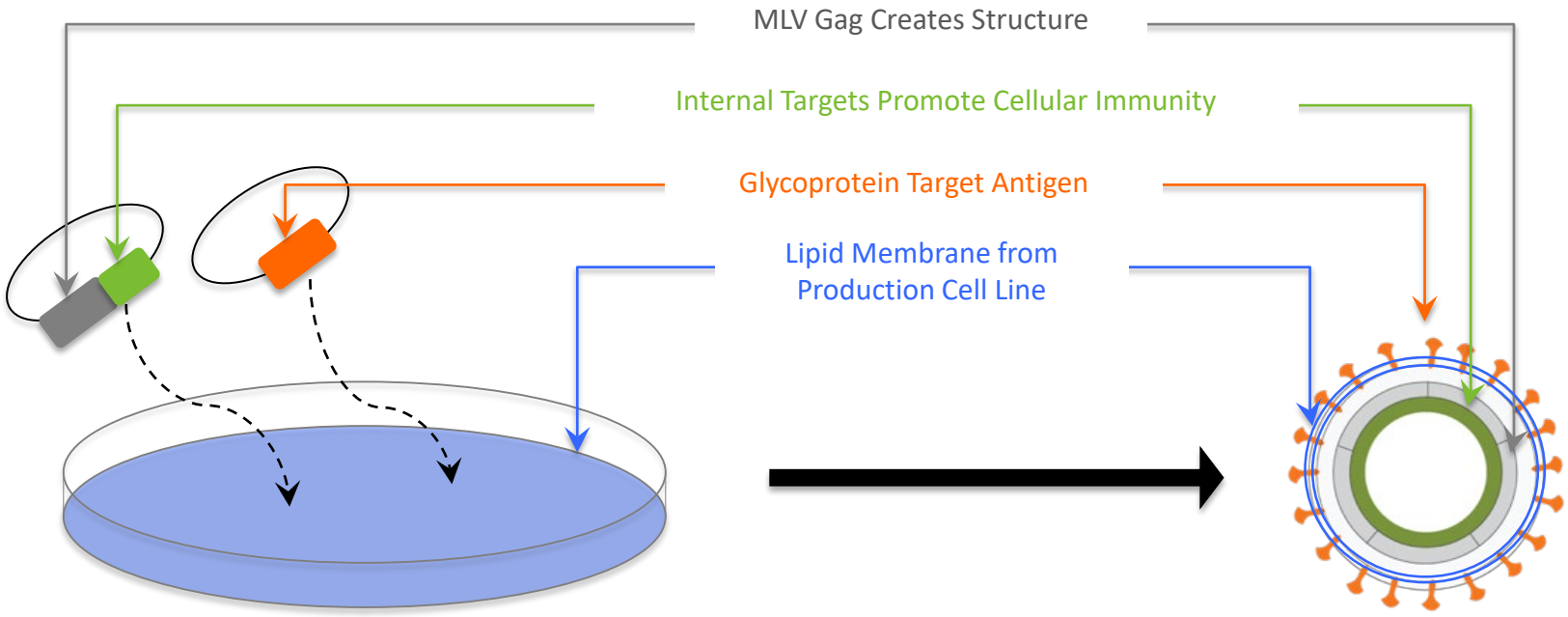
**Potential Application to Multiple Cancers**

**VBI-1901**

# Enveloped Virus-like Particles (eVLPs)

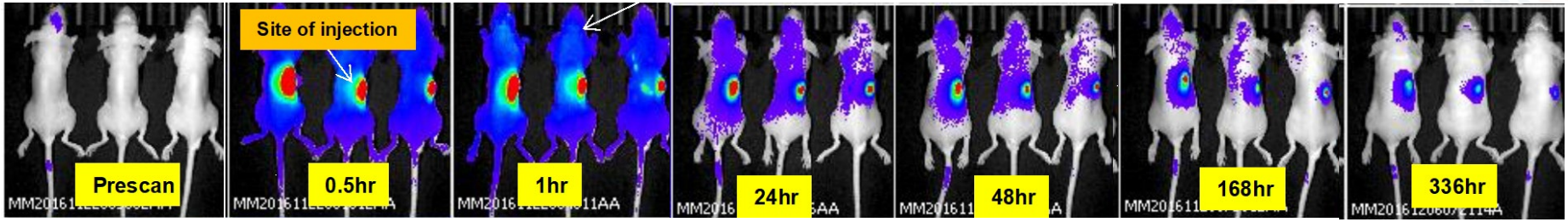
# eVLP Platform : Enveloped Virus-Like Particles (eVLPs) Enable Potent Delivery of Tumor Antigens in an Effective Viral Mimic

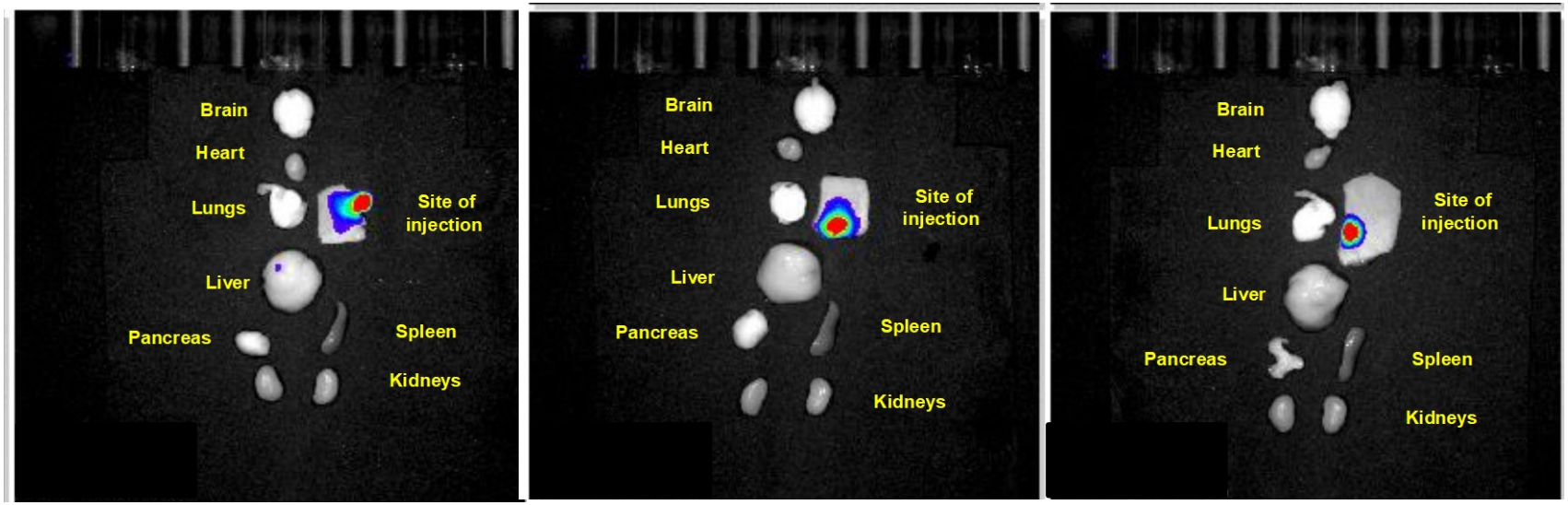
## Flexible, customized antigen delivery in a biologically relevant construct



# eVLP Platform : eVLPs Persist at Injection Site After Intradermal Administration

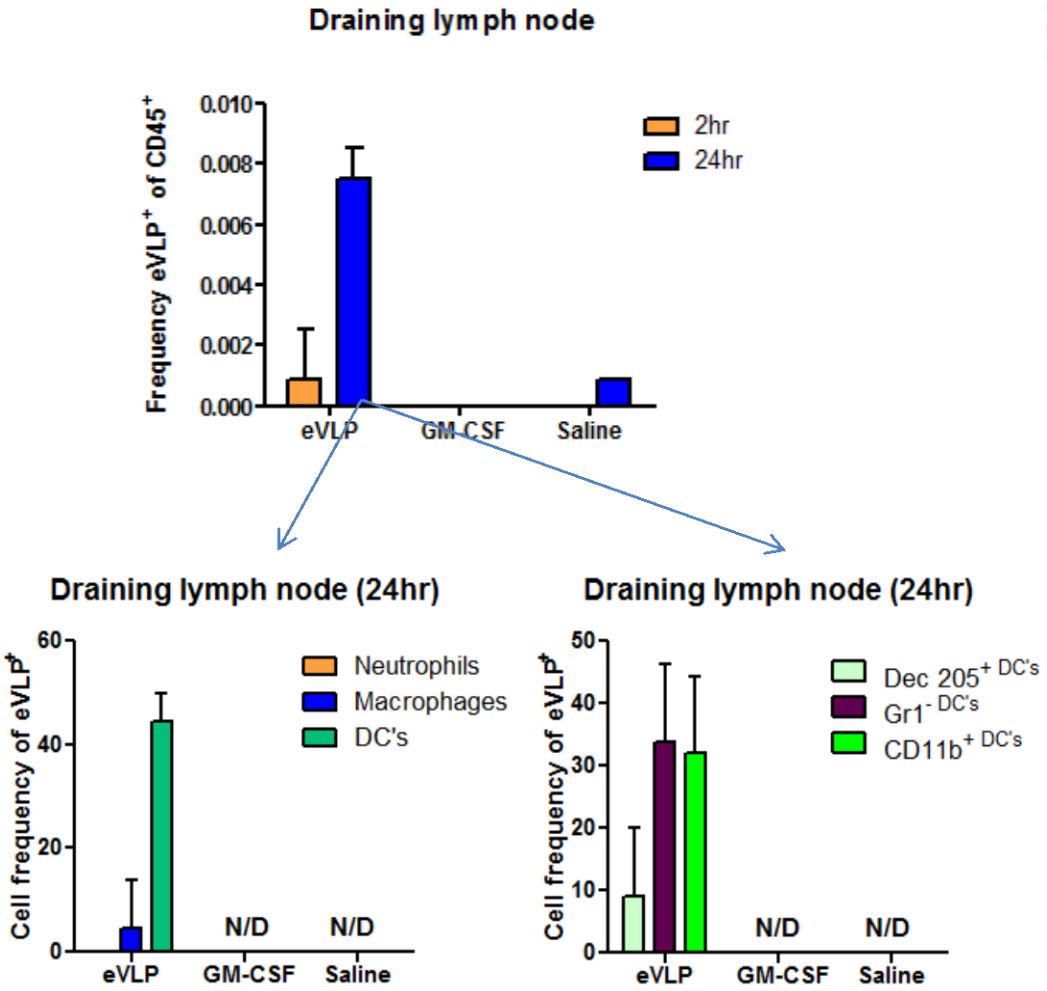
## Biodistribution study demonstrates eVLP persistence at injection site after 14 days with no accumulation in major organs



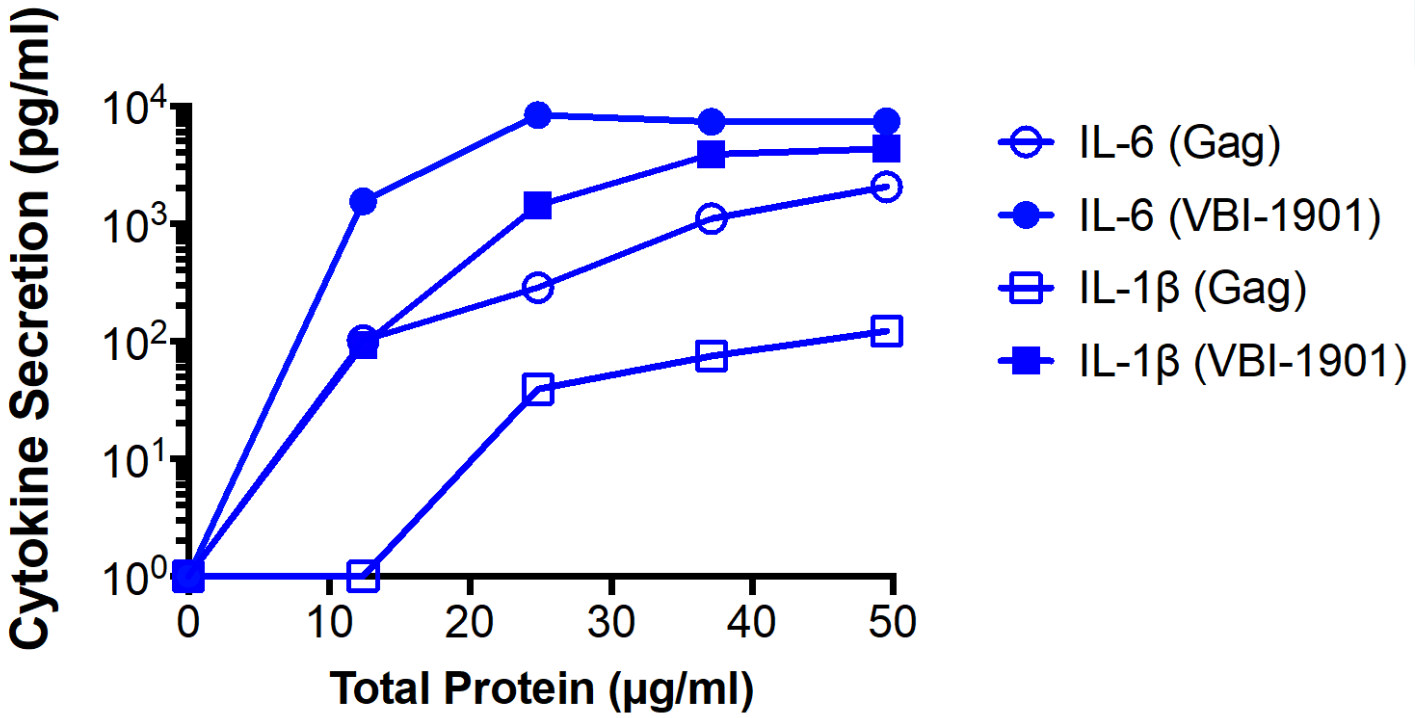
# eVLP Platform : eVLPs Appear Within Hours of Injection in Draining Lymph Nodes

## eVLP uptake is predominantly by dendritic cells



# eVLP Platform : eVLP Particles Stimulate Innate Immunity

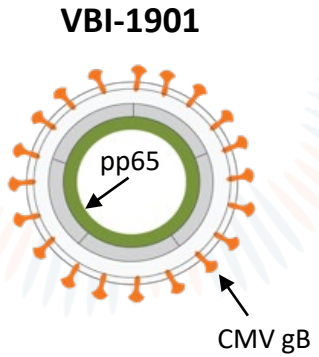
## eVLP particles stimulate pro-inflammatory cytokines – enhanced by inclusion of CMV gB antigen




**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 :
# On-going Phase I/IIa Trial in rGBM

# VBI's Cancer Vaccine Approach is Differentiated from Past Attempts




## *Weaknesses of Past Cancer Vaccines*

**Lack of Inherent Potency**
*Targeting self (or near self) tumor antigens limits potency due to central tolerance*

**Lack of Balanced Immunity**
*The importance of CD4 T-cell immunity was poorly understood*

**Lack of Breadth**
*Typically short peptide antigens – often limited to single epitopes – HLA restricted*

**Poorly Immunogenic Delivery**
*Peptides in emulsions & DNA delivery are poorly immunogenic*

## *The VBI Approach*

Target CMV+ tumors, where 'anti-viral' immunogenicity dwarfs 'anti-self'

VBI induces both CD4+ and CD8+ immunity

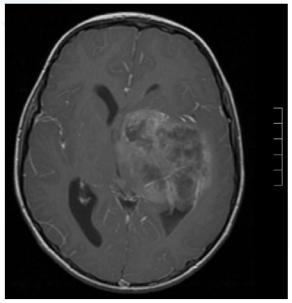
Both gB & pp65 are "full length" to provide multiplicity of epitopes

eVLPs are naturally presented to DCs and stimulate innate & adaptive immunity

# Glioblastoma (GBM) Study Population

## Aggressive disease with decreasing prognosis each successive recurrence

### Glioblastoma Treatment Paradigm



- **Primary GBM**
  - *Standard of Care :* Surgical resection + radiotherapy + chemotherapy
  - *Median Overall Survival :* ~ 16 months
  - Stable disease is transient, recurrence inevitable

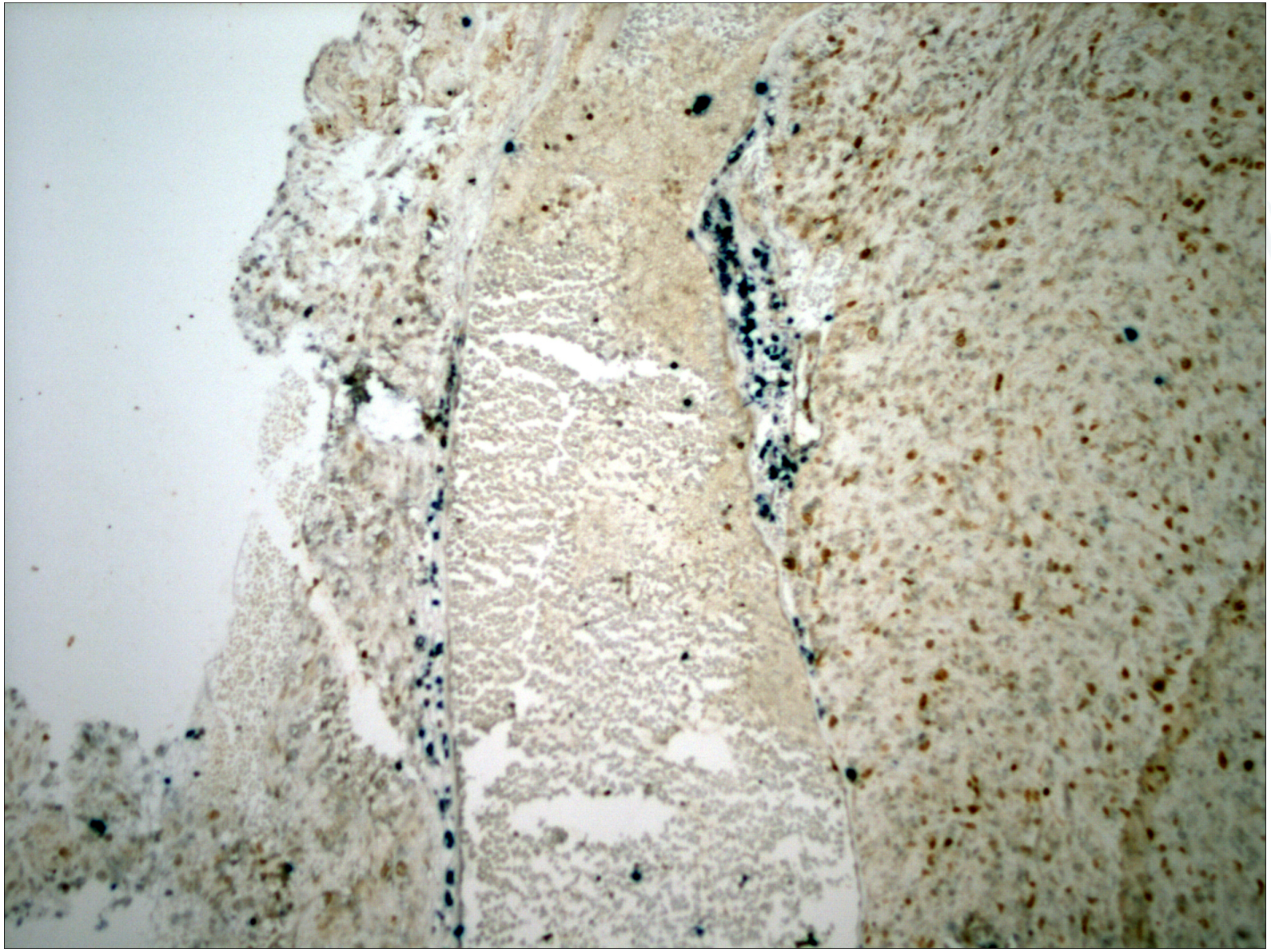
- **Recurrent GBM (1st recurrence)**
  - *Standard of Care :* Repeat rounds of chemotherapy, re-op surgery in limited cases
  - *Median Overall Survival :* ~8 months, ~30% achieve 12-months OS
  - Stable disease is rare, tumors tend to double in size between MRIs during progressive disease

- **Multiple recurrent GBM**
  - *Standard of Care :* None, typically hospice care or clinical trials
  - Profound, rapid growth of tumor leading to death

### VBI-1901 Trial Population

| | # Tumor Recurrences | Median Age | Baseline Tumor Size |
|---|---|---|---|
| **Part A** | 1.83 | 52 | 921mm$^2$ (mean) |
| **Part B** | 1 | TBD | Limit to 400mm$^2$ |

# GBM, Ki-67 and CD3 Stained, 100x



# GBM Phase I/IIa Clinical Study Design

## Two-part, multi-center, open-label, dose-escalation study of VBI-1901 in patients with recurrent glioblastoma (GBM)

### PART A : Dose-Escalation Phase

*Patient population :*

Recurrent GBM (any # of recurrences)

*Study Arm 3:*
**High Dose – 10.0µg + GM-CSF**

*N=6*
*Enrollment completed December 2018*

**VS.**

*Study Arm 2:*
**Intermediate Dose – 2.0µg + GM-CSF**

*N=6*
*Enrollment completed September 2018*

**VS.**

*Study Arm 1:*
**Low Dose – 0.4µg + GM-CSF**

*N=6*
*Enrollment completed April 2018*

### PART B : Extension Phase

*Patient population :*

First Recurrent GBM

*Study Arm 1:*
**10.0µg + GM-CSF**

*N=10*
*Enrollment initiated July 2019*

**VS.**

*Study Arm 2:*
**10.0µg + GSK's AS01$_B$ adjuvant system**

***New arm added to Part B of study***

*N=10*
*Enrollment expected to initiate Q4 2019*

### Outcome Measures : Part A & B

- *Safety*
- *Immunogenicity :* (1) T-cell immunity (gB, pp65), (2) serum anti-gB antibody titers, (3) other immune correlates and biomarkers
- *Tumor and clinical responses :* Based on MRIs and survival data
- *Quality of life :* Change from baseline

# Overview of Immunologic and Tumor Responses in Part A

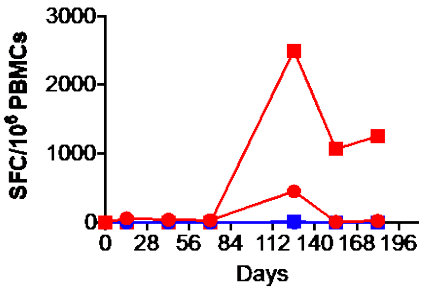
## DATA FROM ASCO 2019 POSTER PRESENTATION

| Patient | Prior Recurrences | Age / Sex / KPS | Vaccine-Induced Response CMV gB ELISPOT | CMV pp65 ELISPOT | Tumor Response |
|---|---|---|---|---|---|
| **LOW DOSE COHORT - 0.4µg of pp65** | | | | | |
| 01-003 | 2 | 64 / F / 70 | Yes | Yes | SD → SD → SD+ |
| 01-005 | 2 | 39 / M / 90 | No | No | ? → ? → PD |
| 01-004 | 2 | 58 / M / 80 | No | No | PD |
| 01-006 | 2 | 66 / F / 80 | No | No | PD |
| 01-007 | 2 | 44 / M / 80 | Yes | Yes | PD |
| 01-009 | 6 | 57 / M / 70 | No | No | PD |
| **INTERMEDIATE DOSE COHORT - 2.0µg of pp65** | | | | | |
| 01-012 | 1 | 59 / M / 80 | Yes | Yes | SD → PD |
| 01-013 | 2 | 45 / F / 70 | No | No | PD |
| 01-015 | 1 | 39 / M / 70 | Data not available | | PD |
| 01-016 | 3 | 53 / M / 90 | No | No | SD → PD |
| 03-001 | 1 | 54 / F / 70 | No | No | SD → † |
| 03-002 | 1 | 43 / M / 70 | Data not available | | PD |
| **HIGH DOSE COHORT - 10.0µg of pp65** | | | | | |
| 01-017 | 2 | 47 / M / 90 | No | No | PD |
| 03-003 | 1 | 43 / M / 80 | Yes | Yes | SD → ? → SD |
| 01-018 | 2 | 65 / M / 90 | No | No | PD |
| 03-004 | 1 | 53 / M / 90 | Yes | Yes | SD → SD |
| 01-020 | 1 | 54 / F / 70 | Data not available | | PD |
| 03-006 | 1 | 56 / F / 70 | Yes | No | SD → SD → SD |

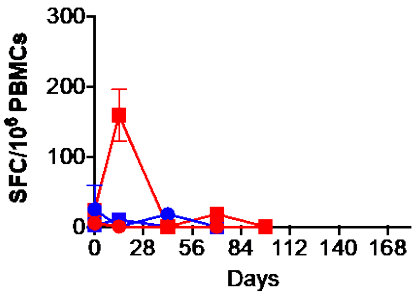
# Impact of Vaccination on CMV-Specific Immunity in Part A

## *Vaccine Responders*

**Patient 01-003**




**Patient 03-003**

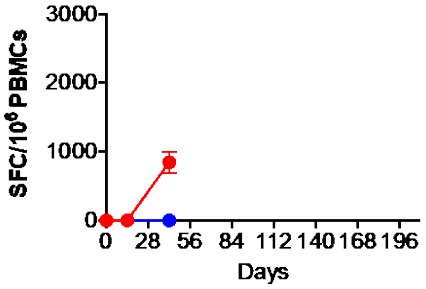



gB peptide pool (IFN-γ) — pp65 peptide pool (IFN-γ)
gB peptide pool (IL-5) — pp65 peptide pool (IL-5)

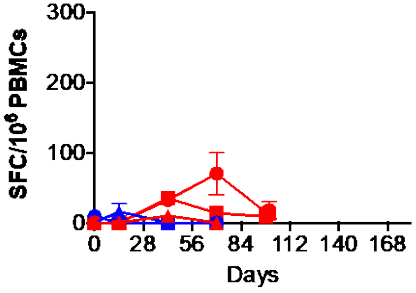
## *Vaccine Non-Responders*

*Examples illustrative of all non-responders*

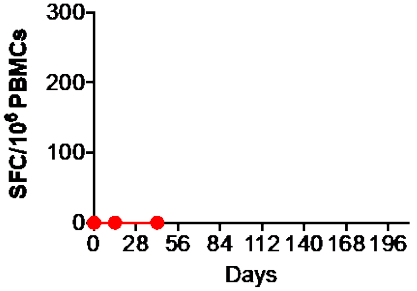
**Patient 01-007**



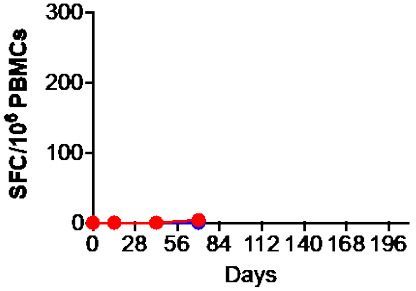

**Patient 03-004**



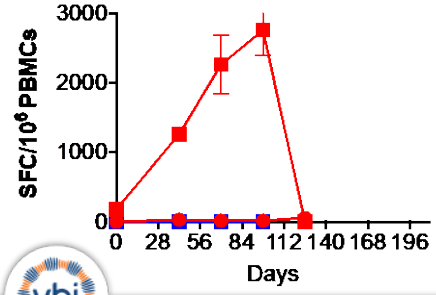

**Patient 01-006**



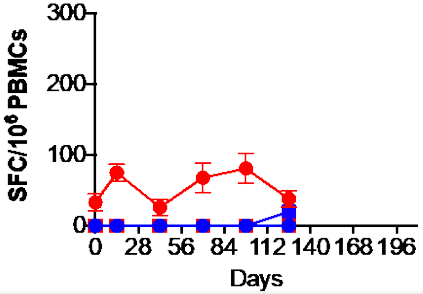

**Patient 01-013**



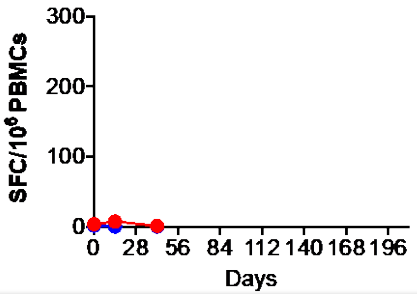

**Patient 01-012**



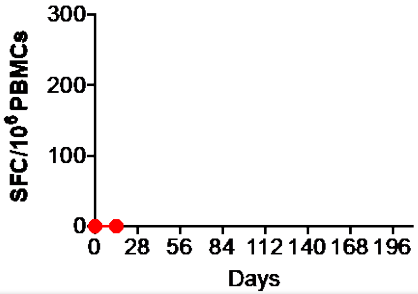

**Patient 03-006**




**Patient 01-009**




**Patient 01-018**

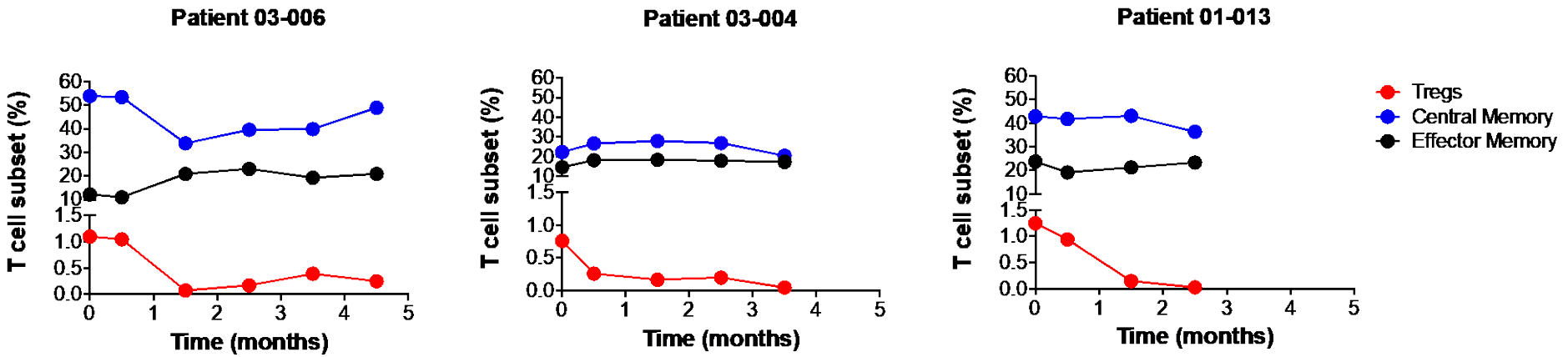


# Circulating Immunosuppressive Tregs Decline After VBI-1901 Vaccination

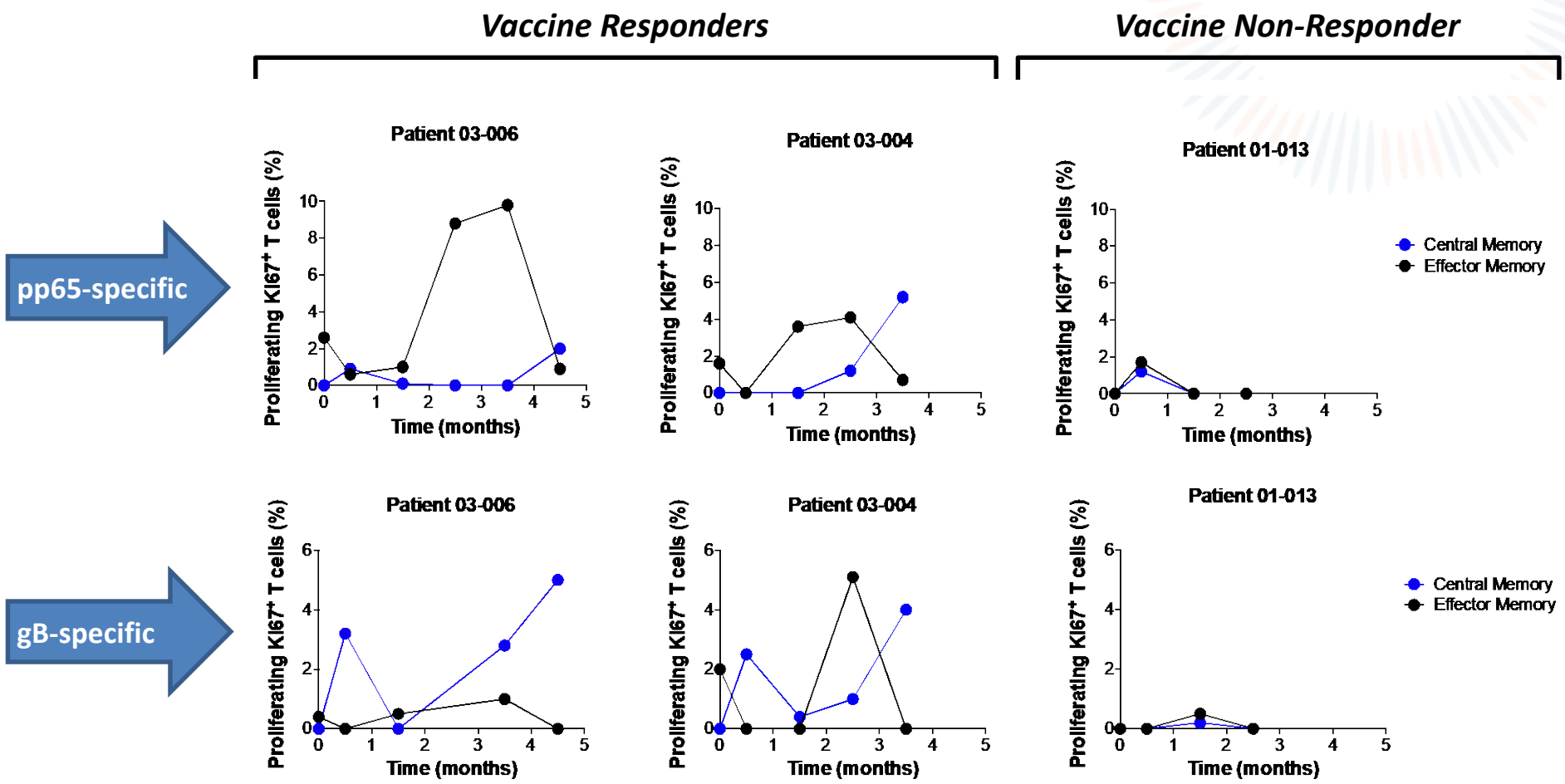
## An increased frequency of Tregs circulating in GBM patients suppresses anti-tumor immunity (Fecci PE, 2006)

*Vaccine Responders*

*Vaccine Non-Responder*

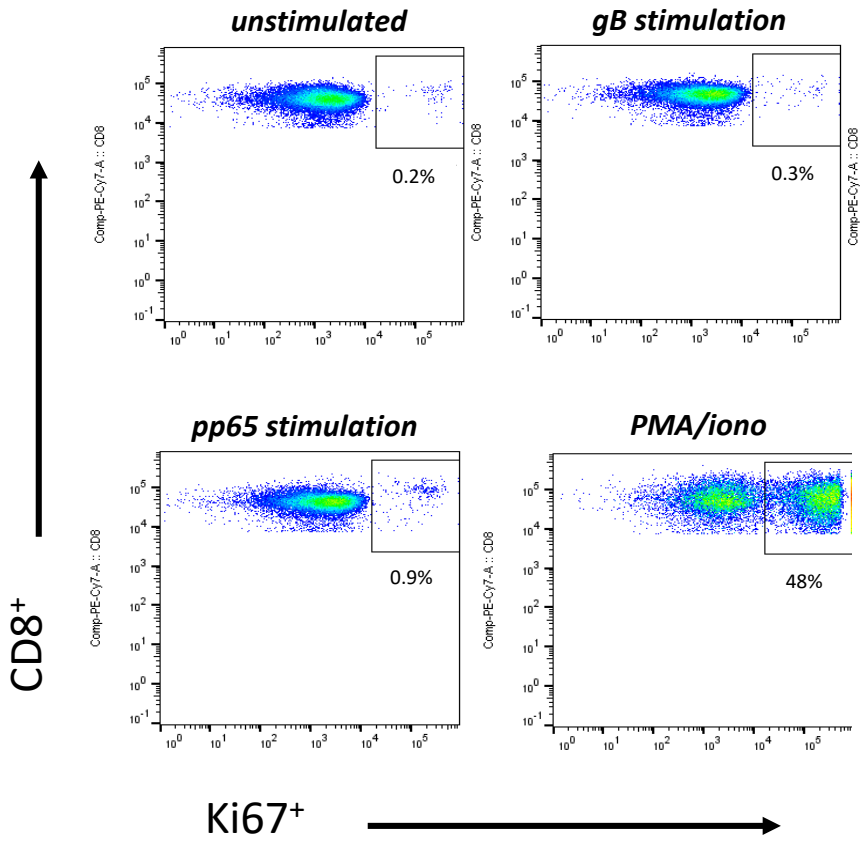


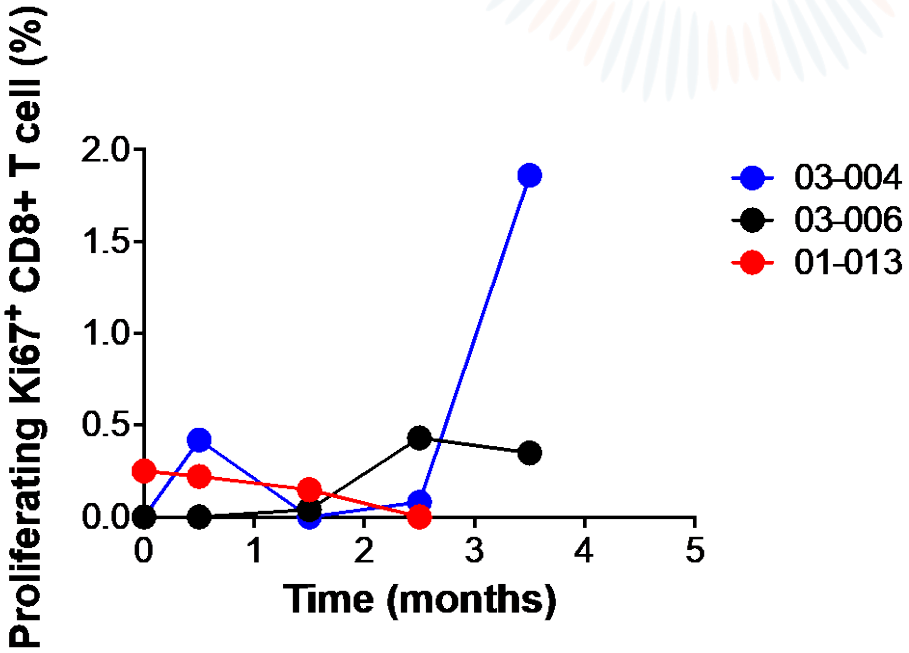
# VBI-1901 Expands CD4+ T Cells Against Both gB and pp65 Antigens



# VBI-1901 Expands gB-Specific CD8+ T Cells in Vaccine Responders

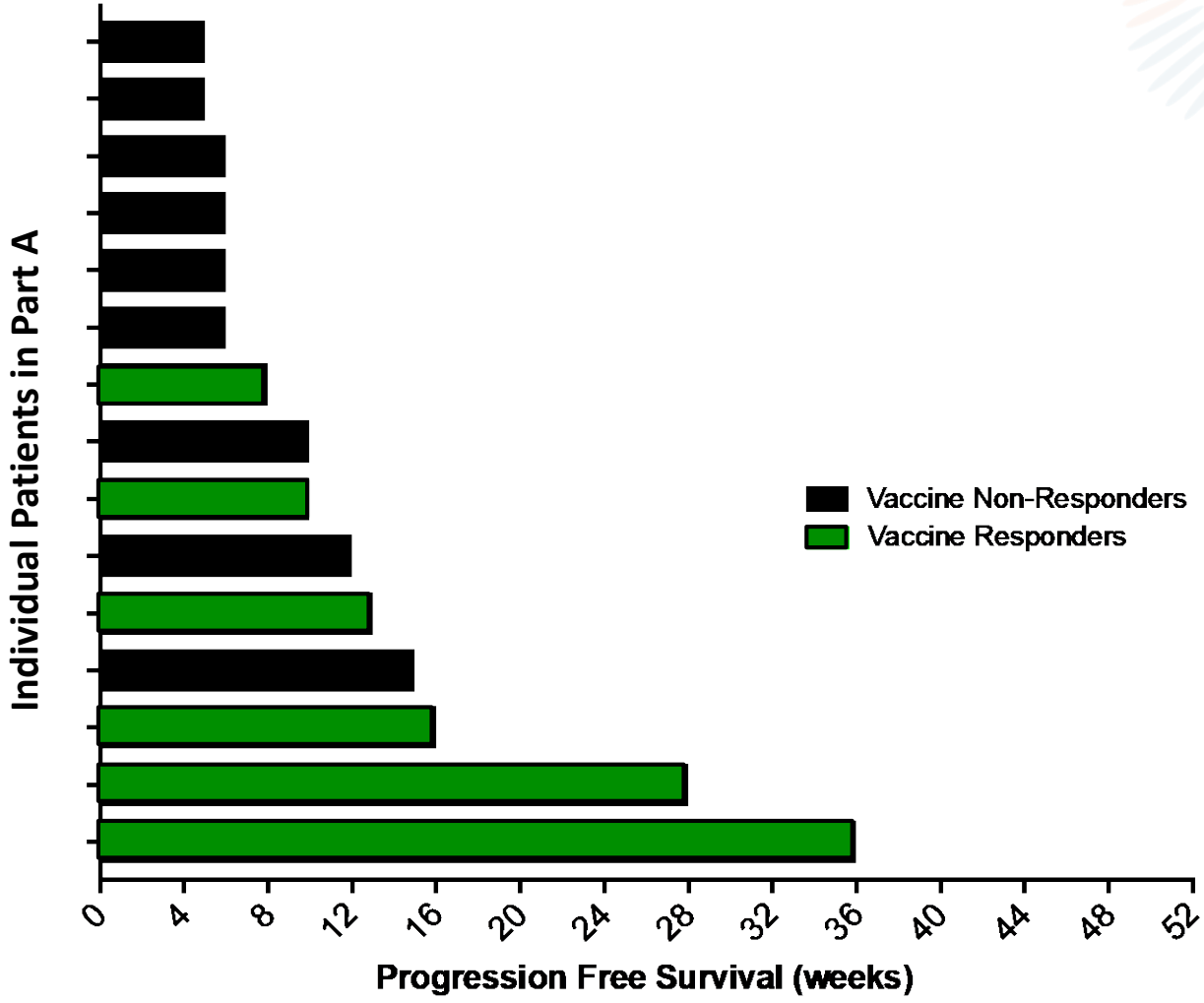
## CMV+ Healthy Subject



# Progression-Free Survival Among Vaccine Responders & Non-Responders

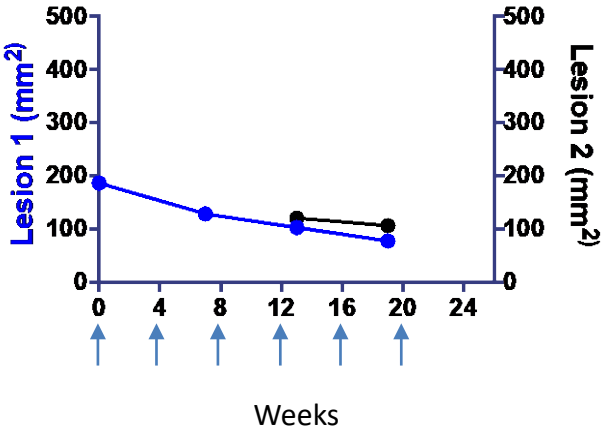
## DATA FROM ASCO 2019 POSTER PRESENTATION



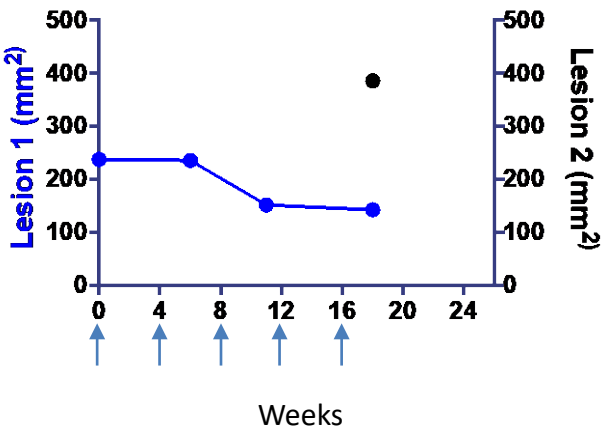
# Summary of Vaccine Responses vs. Tumor Responses

## Tumor responses in 3 patients in High Dose Cohort that responded to vaccination

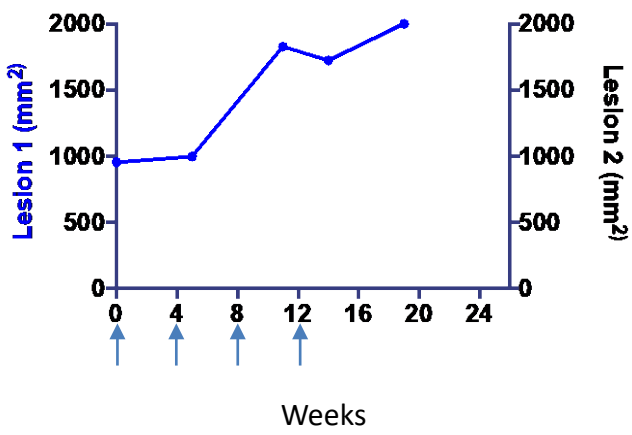
**Patient 03-006**




**Patient 03-004**




**Patient 03-003**




***Radiotherapy was completed > 6 months prior to Tx with VBI-1901***

# Part A Summary

## VBI-1901 Demonstrated Excellent Safety & Promising Immunogenicity & Tumor Impact

- **Vaccine Safe & Well Tolerated**
  - No vaccine-associated SAEs
  - No evidence for vaccine-induced cerebral edema

- **Vaccine Response Impacted Tumor Response**
  - 4 of 6 vaccine responders had MRI confirmed Stable Disease > 12 weeks (vs 0 of 9 evaluable non-responders)
  - Median PFS is significantly longer among vaccine responders vs. non-responders (14.5 weeks vs. 6 weeks, respectively)

- **High Dose Selected for Part B**
  - 3/6 patients in the high dose cohort had evidence of stable disease by MRI compared to 1/6 and 0/6 patients in the low and intermediate dose cohorts

# Part B Extension Phase of Trial – 1st Patient Dosed in July

## Part A has informed protocol changes that may enhance ability to observe efficacy signals in Part B

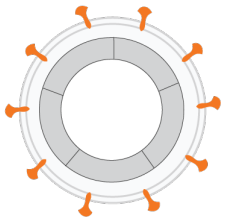
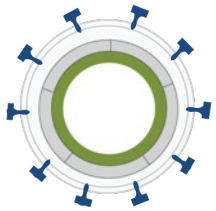
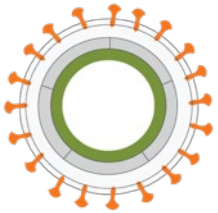
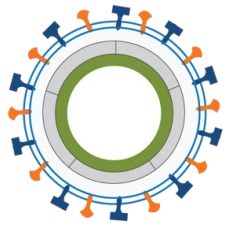
### PART B

- **Only patients with 1st tumor recurrence will be enrolled**
  - Recurrent patients will be healthier than those in Part A of the trial with more intact immune systems
  - 10 subjects in Part A of trial had 2 or more prior recurrences
  - 3/4 subjects with SD for 3 months or longer had single recurrence
- **Tumor area no greater than 400mm$^2$ at baseline (including resection of 1st recurrent tumors)**
  - The mean area of tumor in Part A was 921mm$^2$ (186mm$^2$-1980mm$^2$)
  - Baseline tumors in 4 patients with SD for 3 months or longer were 186mm$^2$, 237mm$^2$, 544mm$^2$, and 955mm$^2$
- **All patients in Part B of trial will receive the optimal (10µg pp65) dose of VBI-1901**
  - The highest dose of VBI-1901 induced SD for 3 months (2 MRI scans) in 3/6 subjects
- **All patients will remain on protocol until clinical (rather than MRI) progression**
  - Greater opportunity for repeat dosing/benefit from vaccine response

# eVLP Expression of Immuno-Modulatory Molecules

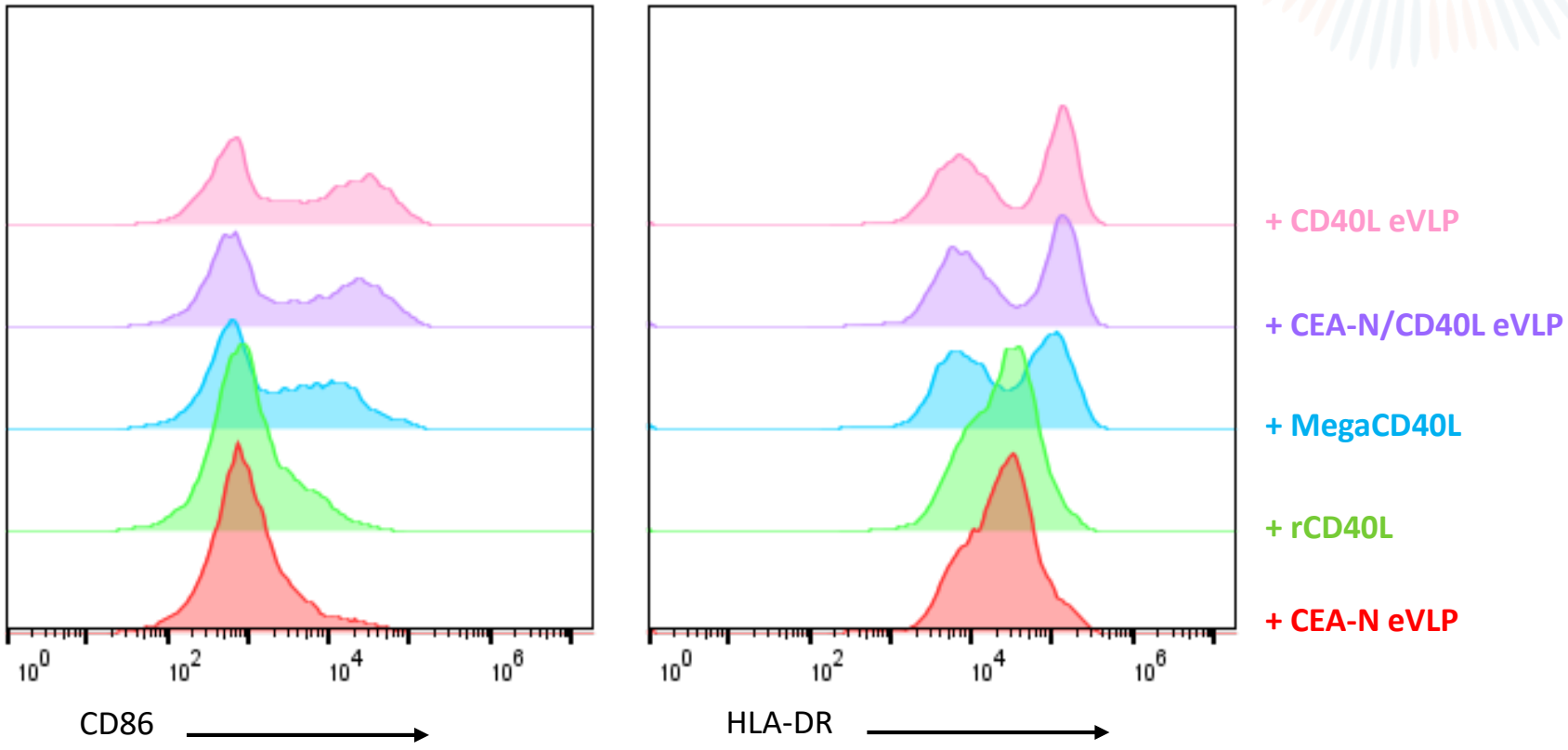
# Further Expansion of the eVLP Platform into Immuno-Oncology

## Multiple Exemplars of eVLP Constructs have Clinical & Preclinical Proof of Concept

| | *Infectious Disease* | | *Immuno-Oncology* | |
|---|---|---|---|---|
| | **Prophylactic CMV (VBI-1501)** | **Prophylactic Zika (VBI-2501)** | **Therapeutic CMV+ Tumors (VBI-1901)** | **Immuno-Oncology (VBI-2701)** |
| **Schematic** |  |  |  |  |
| **Construct Design** | *Monovalent:* Modified gB-G | *Bivalent:* Modified-E / NS1 | *Bivalent:* gB / pp65 (major CD4, CD8 & Ab epitopes) | *Bivalent* with Immuno-modulatory protein |
| **Adjuvant** | Alum | Alum | GM-CSF | Self Adjuvanted |
| **Most Advanced Development Stage** | Ph I complete | Preclinical | Ph I/II ongoing | Preclinical |
| **Key Features** | • Modified gB elicits fibroblast & epithelial cell neutralization<br>• Qualitatively enhanced neutralizing response | • Modified-E enhances neutralizing responses<br>• NS1 T cell response enhances antibody response & protection | • Internal antigen expression elicits T cell immunity<br>• Stimulates innate immunity | • Immunomodulatory proteins can enhance antigen-specific Th1 immunity |

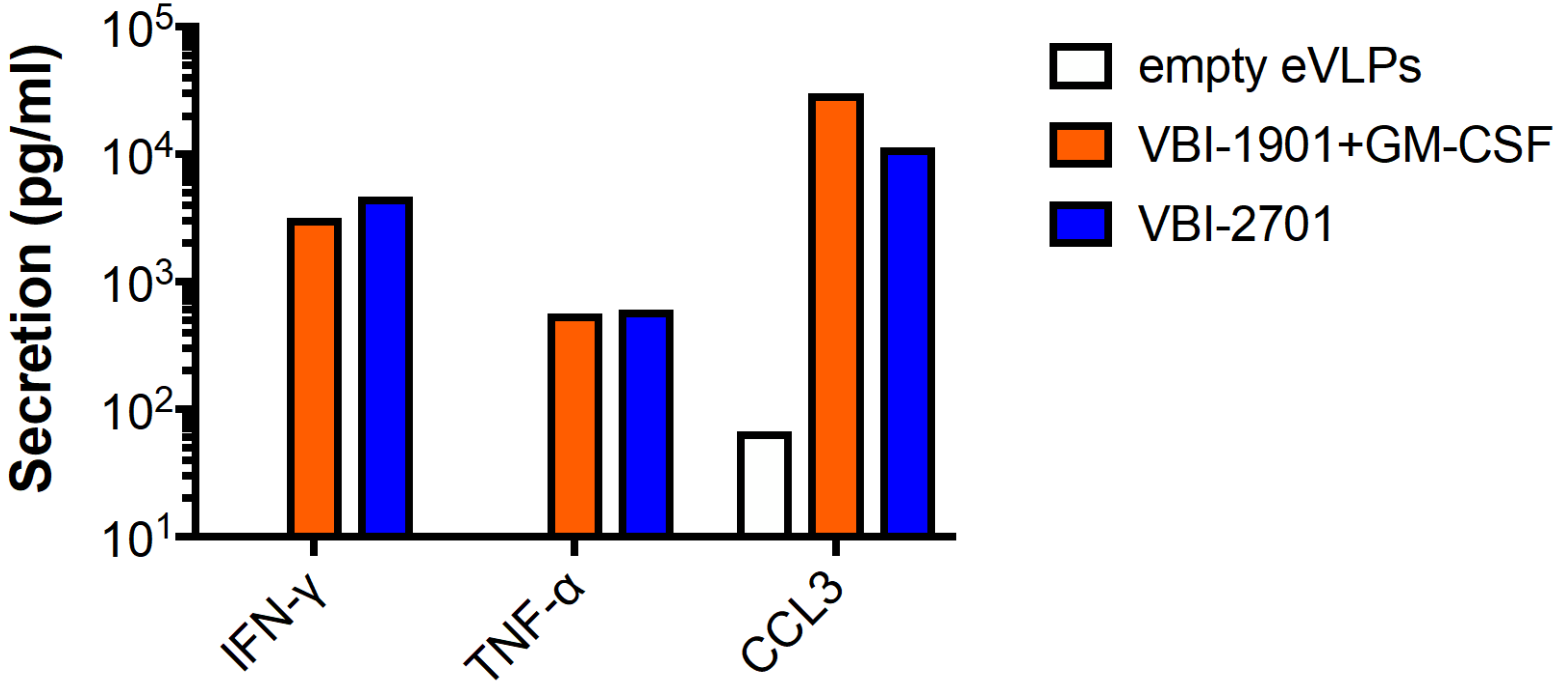
# Lipid Bilayer Surrounding eVLPs Enables CD40L Trimerization and Function

## B cells up-regulate HLA-DR & CD86 in response to trimeric CD40L



# VBI-2701 is Comparable to VBI-1901 + GM-CSF in Terms of T Cell Activation

**Intratumoral injection of eVLPs expressing immunomodulatory molecules may be used to inflame "cold" tumors and synergize with systemic vaccination**



# Potential 'Off-the-Shelf' Vaccines for CMV+ Solid Tumors

| | |
|---|---|
| ***Off-the-Shelf Design*** | • Leverages potency of foreign viral antigens to restimulate pre-existing immunity<br>• CMV is a highly immunogenic viral target<br>• Easily manufacturable and scalable |
| ***Broad Potential in CMV+ Tumors*** | • Over 95% of glioblastomas, medulloblastomas, & breast cancers are CMV+<br>• Harness & restimulate pre-existing anti-viral immunity to clear antigen+ tumors |
| ***CMV an Attractive Target w/ Clinical Proof-of-Concept*** | Numerous CMV-targeting therapies have achieved encouraging clinical activity in GBM |
| ***VBI-1901: Strong Clinical Rationale & Positive Early Data*** | • Clean safety profile through DSMB review of three dose cohorts from Part A of trial<br>• Phase I data indicate productive restimulation of CMV immunity with VBI-1901<br>• Anti-CMV responses correlating with tumor response & PFS |
| ***eVLP Platform & IO*** | • Flexible, engineered antigen delivery capable of potent antibody & T cell responses in humans<br>• Immunomodulatory molecules that activate APCs and/or T cells may be used to inflame "cold" tumors and enhance therapeutic vaccination |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