eVLPs as an Antigen Delivery & Immunomodulatory Platform in Cancer

World Vaccine Congress Europe 2019
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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

C: negative control Ab
E: pp65 stained GBM sample

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

A

CMV pp65 effectors

Patient 3

Patient 4

Patient 5

Patient 6

Targets
- DC-pp65 RNA
- DC-survivin RNA
- DC-Flu M1 RNA
- DC-GBM tumor RNA
- DC-total cellular RNA
- GBM tumor 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:
  - Lucas KG 2011
  - Nair SK 2014
  - Batick K 2017
  - Penas-Prado 2018

**Breast Cancer**
- Expressed on over 90% and may modulate tumor macrophages
- Key references:
  - Herbein (2014) Frontiers Oncol
  - 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

**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**

<table>
<thead>
<tr>
<th></th>
<th># Tumor Recurrences</th>
<th>Median Age</th>
<th>Baseline Tumor Size</th>
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<tbody>
<tr>
<td>Part A</td>
<td>1.83</td>
<td>52</td>
<td>921mm² (mean)</td>
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<tr>
<td>Part B</td>
<td>1</td>
<td>TBD</td>
<td>Limit to 400mm²</td>
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</table>
GBM, Ki-67 and CD3 Stained, 100x
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

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

N=6
Enrollment completed September 2018

**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

**Study Arm 2:**
10.0µg + GSK's AS01B adjuvant system

N=10
Enrollment expected to initiate Q4 2019

New arm added to Part B of study

**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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior Recurrences</th>
<th>Age / Sex / KPS</th>
<th>Vaccine-Induced Response</th>
<th>Tumor Response</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CMV gB ELISPOT</td>
<td>CMV pp65 ELISPOT</td>
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<tr>
<td>LOW DOSE COHORT - 0.4µg of pp65</td>
<td></td>
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<tr>
<td>01-003</td>
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<td>Yes</td>
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<td>01-005</td>
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<td>HIGH DOSE COHORT - 10.0µg of pp65</td>
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<td>56 / F / 70</td>
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</table>
Impact of Vaccination on CMV-Specific Immunity in Part

A  Vaccine Responders

Patient 01-003

Patient 03-003

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

**Vaccine Responders**

**Vaccine Non-Responder**

- **pp65-specific**
- **gB-specific**
VBI-1901 Expands gB-Specific CD8⁺ T Cells in Vaccine Responders

CMV⁺ Healthy Subject

- Unstimulated
- gB stimulation
- pp65 stimulation
- PMA/iono

Ki67⁺

Proliferating Ki67⁺ CD8⁺ T cell (%)

Time (months)

03-004
03-006
01-013
Progression-Free Survival Among Vaccine Responders & Non-Responders

DATA FROM ASCO 2019 POSTER PRESENTATION

Individual Patients in Part A

Progression Free Survival (weeks)

- Vaccine Non-Responders
- Vaccine Responders
Summary of Vaccine Responses vs. Tumor Responses

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

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 400mm² at baseline (including resection of 1st recurrent tumors)**
  - The mean area of tumor in Part A was 921mm² (186mm²-1980mm²)
  - Baseline tumors in 4 patients with SD for 3 months or longer were 186mm², 237mm², 544mm², and 955mm²

- 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

<table>
<thead>
<tr>
<th>Infectious Disease</th>
<th>Immuno-Oncology</th>
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<tbody>
<tr>
<td>Prophylactic CMV (VBI-1501)</td>
<td>Prophylactic Zika (VBI-2501)</td>
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<table>
<thead>
<tr>
<th>Schematic</th>
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<td><img src="image4" alt="Schematic" /></td>
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<table>
<thead>
<tr>
<th>Construct Design</th>
<th>Monovalent: Modified gB-G</th>
<th>Bivalent: Modified-E / NS1</th>
<th>Bivalent: gB / pp65 (major CD4, CD8 &amp; Ab epitopes)</th>
<th>Bivalent with Immuno-modulatory protein</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Alum</th>
<th>Alum</th>
<th>GM-CSF</th>
<th>Self Adjuvanted</th>
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<tr>
<th>Most Advanced Development Stage</th>
<th>Ph I complete</th>
<th>Preclinical</th>
<th>Ph I/II ongoing</th>
<th>Preclinical</th>
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<tr>
<th>Key Features</th>
<th>Modified gB elicits fibroblast &amp; epithelial cell neutralization</th>
<th>Modified-E enhances neutralizing responses</th>
<th>Internal antigen expression elicits T cell immunity</th>
<th>Immunomodulatory proteins can enhance antigen-specific Th1 immunity</th>
</tr>
</thead>
</table>

- Modified gB-G
- Modified-E
- NS1
- Bivalent with Immuno-modulatory protein
- Alum
- GM-CSF
- Ph I complete
- Preclinical
- Preclinical
- Modified gB elicits fibroblast & epithelial cell neutralization
- Modified-E enhances neutralizing responses
- Internal antigen expression elicits T cell 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

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