IMMUNO-ONCOLOGY SUMMIT

eVLP DELIVERY OF NOVEL FOREIGN ANTIGENS ELICITS POLYVALENT ANTI-TUMOR IMMUNITY
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Leading Vaccine & Immunology Innovation in Significant Markets with High Unmet Need

**TECHNOLOGY PLATFORMS**

- Enveloped Virus-Like Particle ("eVLP") platform closely mimics viruses and induces potent and durable immune responses
- Thermostable Lipid Particle Vaccine ("LPV™") platform enables thermostable delivery, and increased access, safety, and efficacy

**PIPELINE**

- **Hepatitis B Vaccine**: 3rd generation vaccine targeting non-responders to Standard of Care
- **Congenital CMV Vaccine**: Target young women to prevent a leading cause of birth defects
  - **GBM Therapeutic**: Therapeutic vaccine for most common brain tumor type
  - **Zika Vaccine**: Prevent birth defects caused by congenital Zika infection

**LPV™ COLLABORATIONS**

- Broad research collaborations to confer thermostability and enhance stability of key vaccine programs with:
  - Sanofi Pasteur
  - GSK

**MANAGEMENT**

- **World-class leadership**: Dr. Steve Gillis, Steve Rubin, Jeff Baxter, Dr. Michel De Wilde, and Dr. David Anderson
- **Scientific Advisory Board**: Dr. Florian Schödel and Dr. Stanley Plotkin
About VBI Vaccines

FINANCIAL OVERVIEW (as at close 8/18/2016)
- Traded on Nasdaq (VBIV) and TSX (VBV.TO)
- Current Nasdaq share price: $3.88
- Market Cap: $140MM
- 3 Month Average Volume: 71,714 shares

HEADQUARTERS – CAMBRIDGE, MA
- CEO, CSO, CTO, CFO + 4 FTEs
- Central location in biotechnology hub

RESEARCH OPERATIONS – OTTAWA, CANADA
- CMO + ~25 FTEs
- World-class R&D team and facility

MANUFACTURING FACILITY – REHOVOT, ISRAEL
- ~50 FTEs
- GMP manufacturing facility for the production of Sci-B-Vac™ and for contract services
## VBI Vaccines Pipeline

### Multiple Opportunities in Infectious Disease and Oncology

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<thead>
<tr>
<th>Platform</th>
<th>Lead</th>
<th>Preclinical</th>
<th>Phase I</th>
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<td><strong>Thermostable LPV™ Platform</strong></td>
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Overview

VBI-1901 provides an off-the-shelf, highly potent, immuno-oncology vaccine capable of addressing multiple solid tumors

- Breakthrough immuno-oncology therapy depends on appropriate antigen selection
  - Past cancer vaccines focused on weakly immunogenic “self” antigens (TAA)
  - Success of PD-1/PD-L1 therapy is built on a tapestry of “not-quite-self” neoantigens
  - Like neo-antigens, foreign viral antigens are inherently more immunogenic than TAA

- CMV provides ideal target antigens suitable for multiple solid tumors:
  - CMV is highly immunogenic
  - CMV is expressed on over 95% of glioblastomas, breast cancer & medulloblastoma tumors

- Presentation matters, eVLP technology allows:
  - Customized presentation of multiple antigens in a highly potent virus like particle
  - eVLP particles recruit & activate dendritic cells

- VBI-1901 utilizes highly potent CMV antigens for an “off-the-shelf” cancer vaccine
  - Currently in late stage preclinical development, with pre-IND meeting completed
  - Builds on VBI’s lead prophylactic CMV vaccine (VBI-1501a), now in Ph I development
Antigen Selection:
Breakthrough Immunotherapy Depends on Appropriate Antigens to Target Anti-Tumor Immunity
The Immuno-Oncology Renaissance Depends on an Ability to Direct 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 opposes potent responses to “self” TAA
- Recently, PD-1 & CTLA-4 success explained by mutation frequency – “NeoAntigens”
  - Occur in frequently mutating/inflamed/“hot” tumors
  - Lead to potent “vaccine-like” immunity in the context of PD-1 or CTLA-4
  - Must be personalized, time consuming, cancer doesn’t wait
- Foreign viral antigens are inherently “hot”
  - Our body has vigorous anti-viral immunity
  - Opportunity for off the shelf therapy
- **Tumor-associated viral antigens (“TAVA”) make an ideal antigenic target**
Ideal Features of CMV as a “TAVA” in GBM & Beyond

CMV is Highly Immunogenic

- CMV stimulates powerful immunity – 1-2% of circulating T-cells in infected individuals
- CMV – gB: Predominant antibody & CD4+ T-cell target on CMV
- CMV – pp65: Highly immunogenic CD8+ T-cell target

CMV is Highly Expressed in Multiple Solid Tumors

- CMV is highly expressed (> 90%) on multiple solid tumors:
  - Glioblastoma (GBM)
  - Medulloblastoma
  - Meningioma
  - Neuroblastoma
  - Breast cancer

Leveraging CMV Tumor Associated Viral Antigens Provides Opportunity to Attack Tumors NOT Predicted to be Susceptible to PD-1/CTLA-4 Alone

PD-1/CTLA-4 Success Rate is Dependent on Availability of Suitable Antigens

>90% CMV Positive\(^1,2,3,4,5\):
Great potential for VBI-1901

Success with PD-1

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VBI-1901:
Unmet Medical Need & Construct Design
VBI – 1901: Addresses Multiple Unmet Medical Needs

Glioblastoma (GBM)

• GBM is the most aggressive form of brain cancer
• Median overall survival is 14.6 months, only 30% will live two years\(^1\)
• Standard of care is Temodar + surgery
• ~90% of patients will experience recurrent GBM\(^2\)
• Market is predicted to grow to $623M by 2020\(^2\)

Multiple Brain Cancers\(^3\)

• Medullo-blastoma is a common pediatric brain cancer, representing 18% of all diagnosis\(^3\)
• Meningioma: represent one third of all primary brain tumors
• Neuroblastoma: accounts for 6% of all cancers in children\(^4\)

Breast Cancer

• 12% of women will experience breast cancer, with an incidence of 71.2/100,000\(^5\)
• Despite advances in therapeutics, metastatic breast cancer still carries a 24.3% 5 year survival\(^6\)
• Market (7MM) is predicted to grow to $13.1 billion by 2020\(^7\)

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2. GBI Research: Glioblastoma Multiforme Therapeutics in Major Developed Markets to 2020
5. Youlden et al., 2012
7. GBI Research: Breast Cancer Therapeutics Maj Mkts to 2020
VBI-1901: A Rationally Designed Therapeutic CMV Vaccine

**Highly potent antigens delivered in a next-generation VLP**

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<tr>
<th>Vaccine Component</th>
<th>Immune Response</th>
<th>Scientific Support</th>
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| CMV gB            | Anti-gB Antibodies Anti-gB CD4+ T-helper cells | • #1 Antibody target for CMV (to stimulate ADCC)  
• gB binding is known to potentiate tumor growth\(^1\)  
• #1 CD4+ T-helper cell target |
| CMV pp65          | Polyvalent CD8+ T-cell Responses | • #1 CD8+ T-cell target  
• Multivalent/multi-epitope design avoids tumor escape  
• Clinical evidence of pp65-mediated survival\(^2\) |
| eVLP formulation with GM-CSF | Stimulation of IFN-g and CCL3 | • IFN-g and CCL3 are key biomarkers of efficacious tumor immunity\(^2, 3\) |


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**Diagram:**
- Lipid bilayer
- Gag/pp65 expression on eVLP surface
- pp65 expression within particle
Enveloped Virus Like Particle (eVLP) Enables Potent Delivery of Vaccine Antigens in an Effective Viral Mimic

Flexible, Customized Antigen Delivery in a Biologically Relevant Construct

• “e” VLP Key Attributes
  - MLV capsid protein creates “enveloped” virus like structure (*unique*)
  - Envelope glycoproteins presented in lipid membrane as in nature (*unique*)
  - T-cell antigens can be delivered internally to promote cellular immunity (*unique*)
  - Particle structure & size promotes dendritic cell update and activation (*unique*)
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

1) Antigen Presentation (or Steering)

Examples:
Positive: Viral & Neo-antigens
Negative: “self” TAAs

3) Trafficking & Immunosuppressive Microenvironment

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

4) Recognition & Killing (Checkpoints = Brakes):

Examples:
Positive: IFN-y
Negative: PD1

Image: Chen & Mellman (2013), Immunity v39 pp1-10 (image adapted at Gene.com)
VBI-1901 Therapeutic Concept for Glioblastoma:

Direct Activity on Three Quadrants of Effective Tumor Immunity

2) Priming & Activation
(or GAS)
Examples:
Positive: GM-CSF
Negative: CTLA-4

1) Antigen Presentation
(or Steering)
Examples:
Positive: CMV gB & pp65 in an eVLP
Negative: "self" TAAs

3) Trafficking & Immunosuppressive
Microenvironment
Examples:
Positive: TILs
Negative: T-regs, MDSC

Relief via Tumor “Debulking” Surgery

4) Recognition & Killing
(Checkpoints = Brakes):
Examples:
Positive: IFN-y
Negative: PD1

Image: Chen & Mellman (2013), Immunity v39 pp1-10 (image adapted at Gene.com)
VBI-1901: Proof of Concept Data
Rationale for VBI-1901 in GBM

VBI-1901 Builds on Data in the Field – Designed to Stimulate Balanced Anti-CMV Immunity for Therapeutic Benefit

1. 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
   - *Survival was correlated with increased levels of CCL3*

2. Evidence Supporting the Need for Balanced Anti-Tumor Immunity
   A. Cellular Immunity: CD8 Role Appreciated, but CD4+ responses play a critical role
      - CD4 T-cell responses are critical for sustained CD8+ T-cell activity\(^3\)
      - CD4 T-cell based CAR-T provides clinical responses in solid tumors\(^2\)
   B. Humoral Immunity
      - mAbs against EGFRvIII mutants on GBM can stimulate potent ADCC activity\(^4\)
      - B-cells are critical to tumor regression in murine model of GBM\(^5\)
      - Approved mAbs (Herceptin, Rituximab) elicit activity through antibody (FcR) mediated cytotoxicity\(^6\)

6. Clynes RA, Nature Medicine, v6, April 2000
VBI-1901: Re-stimulates CD4+ and CD8+ T-cell Responses in CMV-positive Human Subjects *Ex Vivo*

- Fresh PBMCs stimulated with VBI-1901 vs recombinant antigens
- eVLPs rapidly restimulate both CD4+ & CD8+ T-cell responses
- eVLP presentation enhances stimulation relative to matched recombinant antigen
VBI-1901: Specific *Ex-Vivo* Re-stimulation of CCL3 (biomarker of clinical success) in CMV-positive GBM Patient Samples

Stimulation of CCL3 Biomarker, Predictive of Clinical Efficacy of Analogous DC Vaccine

VBI-1901 Provides an Opportunity for an Off-the-Shelf Glioblastoma Immunotherapy with Excellent Clinical Promise

- PBMCs (n=4) from GBM patients were stimulated for 36 hours with the indicated eVLPs, at which time CCL3 production was measured
- gB/pp65 eVLP-induced responses were compared to stimulation of all T cells (PHA stimulation) to estimate the strength of the vaccine-induced response
VBI-1901 eVLPs recruit (CCL3) and Activate (IL-8) Dendritic Cells

VBI-1901: An “Off-the-Shelf” Dendritic Cell Vaccine

- Immature DCs generated by culture of MUTZ-3 myeloid cell line for 6 days in GM-CSF
- DCs exposed to IFN-γ, eVLPs, or control recombinant protein (HSA) for 48 hours
- Induction of proinflammatory IL-8 cytokine and CCL3 chemokine determined by CBA assay
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).
VBI-1901

Summary
VBI-1901: Targeting Solid Tumors Through Innovative Use of Foreign Viral Antigens

Next Generation Cancer Vaccines Leverages Natural Anti-Viral Immunity

• Tumor Associated Viral Antigens represent a unique “off the shelf” vaccination opportunity relevant to multiple solid tumors

• CMV is highly immunogenic and expressed by over 90% of:
  o Glioblastomas (GBM)
  o Brain Cancers
  o Breast Cancer

• VBI-1901 benefits from rational design & potent antigen delivery platform
  o eVLP presentation natively stimulates all arms of immunity (Antibody, T-helper & CTL)
  o eVLP particulate structure directly stimulates dendritic cell recruitment & activation

• **VBI is advancing VBI-1901 into Ph I clinical development & is exploring options for synergistic combinations in other cancers, including breast**
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