

## HARNESSING FOREIGN VIRAL CMV ANTIGENS TO RESTIMULATE ANTI-TUMOR IMMUNITY WORLD VACCINE CONGRESS

NASDAQ: VBIV TSX: VBV

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

#### **Historic Context of Cancer Vaccines**

- Historically: weakly immunogenic "self" tumor associated antigens (TAA)
  - Naturally opposed by central tolerance
- PD-1 & CTLA-4 blockade success explained by mutation frequency – "NeoAntigens"
  - Occur in mutating/inflamed/"hot" tumors
  - Lead to potent "vaccine-like" immunity in the context of PD-1 or CTLA-4 blockade
  - 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 make an ideal antigenic target

#### Nature Review Article on "NeoAntigens": Schumacher & Schrieber, Science, April 2015



Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual turnors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different turnor 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.





## **Evidence for CMV as a Target Antigen in GBM**

## Multiple Independent Labs Have Confirmed the Presence of CMV 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**

#### Immuno-histochemical Staining of CMV in GBM Samples



C: negative control Ab

E: pp65 stained GBM sample

Lucas KG(2011)

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





## Clinical Evidence Supporting CMV as a Cancer Immunotherapeutic Target

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-loaded DC vaccine
  - Single immunization increased CMV pp65-specific CD8<sup>+</sup> T cells from 0.2% to 4.4%
  - IHC staining confirmed pp65 expression in the tumor tissue
- Crough T (2012)
  - Recurrent GBM patient received 4 infusions of *in vitro* expanded CMV-specific T cells
  - After 2<sup>nd</sup> infusion, 9% of CD8<sup>+</sup> T cells were specific to CMV
  - 1 month later, MRI revealed improvement with stable disease reported for 17 months
- Schuessler A (2014)
  - 10 recurrent GBM patients received 3-4 infusions of autologous CMV-specific T cells
  - Achieved median overall survival of 403 days and only minor adverse events
- Mitchell DA (2015)
  - 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



## CMV is Highly Expressed in Multiple Solid Tumors

#### Breast

- Taher C(2013) J Clin Virol 54, 240;
- Harkins LE (2010)
   Herpesviridae 1, 8

#### Neuroblastoma

• Wolmer-Solberg N (2013) Int J Cancer, 133, 2351-61

#### **Medullo-blastoma**

- Baryawno N(2011) J Clin Invest 121, 4043-4055;
- Libard S(2014) PLoS ONE
  9, e108861;

#### Meningioma

Libard S(2014) PLoS ONE
9, e108861;



## Leveraging CMV 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



1) Wolmer-Solberg N, et al.Int. J Cancer. Nov 15;133(10):2351-61, 2) Libard, et al. PLoS ONE 9, e108861

3) Cobbs CS(2013) Curr Opin Oncol 25, 682; 4) Baryawno N(2011) J Clin Invest 121, 4043-4055; 6) Taher C(2013) J Clin Virol 54, 240; 7) Harkins LE (2010) Herpesviridae 1, 8





## **VBI-1901:** *Construct Design & Rationale*



# Enveloped Virus-Like Particles (eVLPs) Enable 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
  - Envelope glycoproteins presented in lipid membrane as in nature
  - T-cell antigens can be delivered internally to promote cellular immunity
  - Particle structure & size promotes dendritic cell update and activation



#### VBI-1901: A Rationally Designed Therapeutic CMV Vaccine

#### **Highly Potent Antigens Delivered in a Next-generation VLP**

Vaccine Component	Immune Response	Scientific Support
CMV gB	Anti-gB Antibodies Anti-gB CD4+ T-helper ce	<ul> <li>#1 Antibody target for CMV (to stimulate ADCC)</li> <li>gB binding is known to potentiate tumor growth<sup>1</sup></li> <li>#1 CD4+ T-helper cell target</li> </ul>
CMV pp65	Polyvalent CD8+ T-cell Responses	<ul> <li>#1 CD8+ T-cell target</li> <li>Multivalent/multi-epitope design avoids tumor escape</li> <li>Clinical evidence of pp65-mediated survival<sup>2</sup></li> </ul>
eVLP formulation with GM-CSF	Stimulation of IFN-g and CCL3	<ul> <li>CCL3 and IFN-γ are key biomarkers of efficacious tumor immunity<sup>2,3</sup></li> </ul>
	gf Lipid bilayer Gag/pp65	expression on eVLP surface pp65 expression within particle

VDI

## 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<sup>1</sup> •
- Standard of care is Temodar + surgery •
- ~90% of patients will experience recurrent GBM<sup>2</sup> •
- Market is predicted to grow to \$623M by 2020<sup>2</sup> •

#### Multiple Brain Cancers<sup>3</sup>

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

#### **Breast Cancer**

- 12% of women will experience breast cancer, with an incidence of 71.2/100,000<sup>5</sup> •
- Despite advances in therapeutics, metastatic breast cancer still carries a 24.3% 5 year survival<sup>6</sup> •
- Market (7MM) is predicted to grow to \$13.1 billion by 2020<sup>7</sup> •
  - 1. http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html

2. GBI Research: Glioblastoma Multiforme Therapeutics in Major Developed Markets to 2020 3.

- http://www.abta.org/brain-tumor-information/types-of-tumors/medulloblastoma.html
- http://www.cancer.org/cancer/neuroblastoma/ 4.
- 5. Youlden et al., 2012
- 6. National Cancer Institute Report, 2013
- 7. GBI Research: Breast Cancer Therapeutics Maj Mkts to 2020





## **VBI-1901:** Proof of Concept Data



## VBI-1901: Restimulates 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

Frequency of Response (%)

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





# VBI-1901 eVLPs Stimulate CCL3 when Expressing CMV gB and pp65 Antigens

Stimulation of CCL3 biomarker correlated with improved clinical outcome after CMV pp65 DC vaccination of patients with GBM (Mitchell et al, 2015)





## VBI-1901 Induction of CCL3 in *ex vivo* PBMCs from CMV-Positive Healthy Subjects and Patients with Solid Tumors

Stimulation of CCL3 biomarker correlated with improved clinical outcome after CMV pp65 DC vaccination of patients with GBM (Mitchell et al, 2015)



## Balanced Cellular & Humoral Immunity in Mice Immunized with VBI-1901





## GM-CSF Improves the Potency of gB/pp65 eVLPs After Intradermal Vaccination of Rabbits





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

## gB/pp65 eVLPs Recruit (CCL3) and Activate (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:** Scalable Manufacturing with Exceptional Purity

#### SDS-PAGE Analysis of VBI-1901 eVLP Purity During Downstream Processing



#### **Samples**

(3µg total protein, reducing/denaturing conditions) Lane 1: Ladder (Precision Plus Protein Standard) Lane 2: Harvest Lane 3: Clarification: Supernatant Lane 4: Clarification: Filtrate Lane 5: **TFF:** Permeate Lane 6: TFF: Retentate Lane 7: BZ-treated TFF Retentate Lane 8: Diafiltration: Permeate Lane 9: Diafiltration: Retentate Lane 10: Ultracentrifugation: Supernatant Lane 11: Ultracentrifugation: Pellet Lane 12: Sterile filtered product = impurities = Gag/pp65 fusion protein



## **Biodistribution Study: Intradermal Injection of VBI-1901**



#### eVLP particles persistent at the injection site for at least 14 days



#### eVLP particles do not accumulate in major organs



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## **Analysis of eVLP Biodistribution**



eVLP particles persist at the injection site but not within the brain





eVLP particles are present in draining lymph nodes within 1 hour

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

**Next Generation Cancer Vaccine Leverages Natural Anti-Viral Immunity** 

- Tumor-associated viral CMV antigens represent a unique "off-the-shelf" vaccination opportunity relevant to multiple solid tumors
- CMV is highly immunogenic and expressed by over 90% of:
  - Glioblastomas (GBM)
  - Brain Cancers
  - Breast Cancer
- VBI-1901 benefits from rational design & potent antigen delivery platform
  - eVLP presentation natively stimulates all arms of immunity (Antibody, T-helper & CTL)
  - 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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