

Novel Vaccine Candidates through Natural Presentation of Antigens in Enveloped Virus-like Particles

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Company Overview



VBI VACCINES INC. (NASDAQ: VBIV) IS DEVELOPING NOVEL TECHNOLOGIES THAT SEEK TO EXPAND VACCINE PROTECTION IN SIGNIFICANT MARKETS OF UNMET MEDICAL NEED

- VBI is developing two complementary vaccine platform technologies:
 - Enveloped Virus-like Particle ("eVLP") Platform: "Third-generation" VLP vaccines mimic enveloped viruses and present target antigen in natural conformation
 - Prophylactic CMV Vaccine (Lead Candidate)
 - GBM Immunotherapy
 - Prophylactic RSV Vaccine
 - Lipid Particle Vaccine ("LPV") Platform: Proprietary formulation technology enables development of vaccines with preserved stability and potency
 - Broad LPV research collaboration with Sanofi Pasteur executed April 2015
- Headquartered in Cambridge, MA with its main research site in Ottawa, Canada



VBI Vaccines Pipeline

Multiple opportunities in infectious disease and oncology.

	Research	Lead	Preclinical	Phase I	Phase II	Phase III
Infectious Disease						
CMV (VBI-1501A)				Expected Ph I Start H1 2016		
HCV						
RSV						
Immuno-Oncology						
GBM						
Undisclosed						
Thermostable LPV						
Undisclosed		SANOFI				



Improved Antigen Expression with eVLP Platform



Virus-like Particle Vaccine Innovation

CONSIDERABLE EVOLUTION IN VLPS SINCE EARLY 1990s



eVLP Production: Two Genes and Cell Line Create Natural Viral Mimic

Key structural elements of enveloped viruses represented



- "e" VLP Key Attributes
 - Antigen presented in Virus-like Structure (common to all VLPs)
 - MLV capsid protein creates viral structure (*unique*)
 - Lipid membrane derived from production cell line (*unique*)
 - Multiple cell lines can be used, HEK offers 'human' glycosylation patterns (as virus does)
 - Envelope glycoproteins presented in lipid membrane as in nature (unique)
 - May allow unique "conformation" benefits



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Not All Antibodies to Envelope Glycoproteins are Equal

Multiple CMV gB Epitopes Identified with Distinct Neutralizing Properties



- AD-1 Immuno-dominant Epitope⁴
 - Predominant: 38% of B cell, IgG close bind AD-1
 - Weakly neutralizing: only 2% are neutralizing
- AD-2 Linear Epitope⁵
 - Infrequent but highly potent neutralization
- AD-4 Epitope⁴
 - Very rare: only 5.9% of b-cell clones
 - Strongly neutralizing
- AD-5 Epitope⁴
 - Very rare: only 5.9% of b-cell clones
 - Strongly neutralizing
 - 4) Potzsch S (2011) PLoS Pathlog 7, e1002172
 - 5) Ohlin M (2014) Mol Immunol 60, 95-102



Distinct Envelope Glycoprotein Conformations Expose Different Epitopes - Influences Potency



gB-G Antigen in eVLP Promotes Cell Fusion: Suggests Altered, Biologically Relevant Conformation versus Recombinant gB



Native gB Antigen

Optimized gB-G Antigen

(VSV –G protein transmembrane domain induces altered conformation that drives significant cell fusion)

eVLP Presentation Improves Potency of gB Antigen

Presentation of gB antigen in an eVLP improves relevant functional CMV neutralizing responses relative to recombinant gB protein.¹

PRECLINICAL RESULTS

- gB in eVLP generates higher levels of CMV nAbs than recombinant (gB)
- Modification of transmembrane domain further improves eVLP potency
- No adjuvant included
- For more details see: <u>Kirchmeier et</u> al, <u>Clinical Vaccine Immunol.</u> 2014, 21(2):174.⁶





VBI RSV Discovery Program

GRANT SPONSORED PROGRAM HIGHLIGHTS

- Unmet Medical Need: RSV accounts for 6.7% of deaths among infants under one year old, more than any other pathogen except malaria
- **Objective 1:** Leverage eVLP platform for RSV-F vaccine with improved conformation
- Objective 2: Confirm potency of eVLP RSF-F vaccine candidate(s) in preclinical animal models



NRC Industrial Research Programme d'aide à la Assistance Program recherche industrielle du CNRC

- VBI awarded \$350,000 CAD grant by the National Research Council-Industrial Research Assistance Program ("NRC-IRAP")
 - NRC-IRAP supports innovative technologies developed in Canada



Preliminary evidence of pre-fusion RSV F protein on surface of cells secreting RSV F eVLPs



HEK 293 cells were transfected with an eVLP RSV F plasmid. Surface staining was performed with a pre-fusion RSV F protein mAb (5C4) at 2µg/mL. No staining was observed in mock transfected cells (no DNA).





488nm

light

Construct Screening by ELISA Indicates that Purified RSV F eVLPs Express both Pre and Post Fusion RSV-F Protein

Natural Display of Pre and Post Fusion RSV-F in Enveloped Virus-like Particle ("eVLP")



Sandwich ELISAs using the 131 and 5C4 mAbs detect post- vs. pre-fusion conformations of the RSV F protein, respectively. Inactivated RSV or eVLPs expressing RSV-F were purified by sucrose gradient purification



eVLP Platform: Multiple Infectious Disease and Immuno-Oncology Candidates

eVLP DESIGN CAN BE TAILORED FOR DESIRED IMMUNE RESPONSE





CMV Program Update



CMV Vaccine Unmet Medical Need: Durable, broadly neutralizing antibody responses

- **Congenital CMV:** Transmission from mother to child during pregnancy
 - Congenital CMV infection causes more long-term problems and childhood deaths than Down Syndrome or Fetal Alcohol Syndrome
 - In the EU, congenital CMV is the leading cause of neurological disabilities, affecting ~1/200 newborns⁶
- Vaccine Development: Landmark Phase II CMV vaccine study achieved projected 50% efficacy (Pass⁷), but plenty of room for improvement:
 - Key Goal 1 Improved potency vs natural immunity:
 - Ab induced by previous vaccines were 10X lower than natural immunity (Cui⁸)
 - Key Goal 2 Improved breadth of immunity:
 - Previous vaccine approaches could neutralize CMV in fibroblasts, but not epithelial cells (Cui⁸)
 - Key Goal 3 Improved durability of immunity:
 - Efficacy appeared to wane quickly after 1st year (Lilja⁹)

⁶⁾ Ludwig, Hengel, Eurosurveillance, Vol14, Issue 9, Mar 2009; ⁷⁾Pass RF (2009) N Eng J Med 360, 1191-1199; ⁸⁾Cui X (2008) Vaccine 26, 5760-5766; ⁹⁾Lilja AE (2013) Vaccine 30, 6980-6990



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VBI 1501A Induces Neutralizing Antibody Titers in Rabbits Equivalent to or Exceeding Natural Infection

Key Achievement 1:

 Vaccine induced neutralization matches (or exceeds) natural immunity

Key Achievement 2:

 CMV neutralization effective in both
Fibroblasts AND
Epithelial Cells

The endpoint neutralization titer of individual rabbit sera (n=5/group) collected **28 days after a 2nd immunization** are shown against CMV infection of fibroblast and epithelial cells. The neutralizing activity of CMV⁺ human sera were also evaluated.



Potent Durability of nAb Responses in Rabbits Vaccinated with Planned Human Doses of CMV Vaccine Candidate

Key Achievement 3:

- Durable immunity persists 4 months between immunizations in rabbits
- ✓ No signs of fall off following 3rd immunization
- ✓ In mice (not shown), durability persisted for 6 mos following 2 immunizations





Overview of VBI-1501 Purification Process

Process Optimized to Preserve Particle Integrity and Meet FDA Standards



Total particle count (~5x10¹²) remains constant through process



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CMV eVLP Platform Development Summary

Bulk Drug Substance



Adsorbed on Alum



Key Achievements

- Consistent, high yield production achieved in HEK (~150 purified doses/L)
- Exceptional purity achieved for GLP tox batch:
 - Residual host cell DNA: 0.2 ng/dose
 - Total nucleic acid: 26.2 ng/dose
 - Residual host cell protein: 12.1 ng/dose
- Qualitative & quantitative release criteria established
- Applicable to multiple cell lines (HEK, CHO, Sf2)



Completed CMV Milestones

ACHIEVED RISK MITIGATION

- ✓ **Q1 2015:** CMV vaccine candidate manufactured at 50L production-scale
- ✓ **Q2 2015:** Verified stability of CMV vaccine candidate
- ✓ **Q2 2015:** Demonstrated batch to batch consistency
- ✓ Q2 2015: Start formal toxicology studies for CMV vaccine candidate
- ✓ **Q2 2015:** Confirmed potency of clinical formulations in 2nd animal model
- ✓ Q3 2015: GMP clinical batch started
- ✓ **Q4 2015:** Finalize clinical protocol & Investigators Brochure
- ✓ **Q4 2015:** Conclude toxicology trial

REMAINING MILESTONES TO PH I START

H1 2016: File CTA & Initiate Phase I Clinical Trial



Summary

CMV PROGRAM

- Continued pre-clinical progress toward IND submission
- Acceptable yield and purification achieved with bulk clinical batch
- Strong potency in preclinical animal models

eVLP PLATFORM

- Unique VLP platform, specialized for enveloped viruses
- Presents antigen in biologically relevant structure and conformation
- Expanding program to additional targets including RSV and GBM
- Open to potential partnerships: i) new programs ii) novel antigens

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