A Prophylactic Human Cytomegalovirus (HCMV) Vaccine Designed to Prevent Congenital Infection Using Enveloped Virus-Like-Particles (eVLPs) by Inducing Potent Immunity Greater Than Natural Infection

This presentation contains forward-looking statements within the meaning of the provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are generally identifiable by the use of words like "may," "will," "should," "could," "expect," "anticipate," "estimate," "believe," "intend," or "project" or the negative of these words or other variations on these words or comparable terminology. The reader is cautioned not to put undue reliance on these forward-looking statements, as these statements are subject to numerous factors and uncertainties outside of our control that can make such statements untrue, including, but not limited to, inadequate capital, adverse economic conditions, intense competition, lack of meaningful research results, entry of new competitors and products, adverse federal, state and local government regulation, termination of contracts or agreements, technological obsolescence of our products, technical problems with our research and products, price increases for supplies and components, inability to carry out research, development and commercialization plans, loss or retirement of key executives and research scientists and other specific risks. We currently have no commercial products intended to diagnose, treat, prevent, or cure any disease. The statements contained in this presentation regarding our ongoing research and development and the results attained by us to-date have not been evaluated by the Food and Drug Administration. There can be no assurance that further research and development, and/or whether clinical trial results, if any, will validate and support the results of our preliminary research and studies. Further, there can be no assurance that the necessary regulatory approvals will be obtained or that we will be able to develop new products on the basis of our technologies. In addition, other factors that could cause actual results to differ materially are discussed in a Proxy Statement filed with the SEC on June 30th, 2014. Investors and security holders are urged to read these documents free of charge on the SEC's web site at www.sec.gov. We undertake no obligation to publicly update or revise our forward-looking statements as a result of new information, future events, or otherwise.
## Introduction

Virus-like particle (VLP) vaccines have evolved considerably since their introduction in the early 1990s.

### 1st Generation
- **Design:** Antigens are produced and self-assemble
- **Key Advantage:** Simple structures and repetitive pattern of antigenic epitopes
- **Key Limitation:** Only a very limited number of antigens spontaneously form orderly VLP structures; cannot be applied to all enveloped viruses
- **Examples:** Gardasil®, Cervarix®, Engerix-B®, and Recombivax HB®

### 2nd Generation
- **Design:** Antigens of interest are covalently attached to the surface of a backbone protein
- **Key Advantage:** Can be applied to multiple different target antigens; VLP structure is not limited to the properties of the antigen
- **Key Limitation:** Antigen of interest is artificially bound to the structural protein and not represented in a natural configuration
- **Example:** Qb VLP Platform

### 3rd Generation – VBI
- **Design:** Common protein backbone and a lipid membrane in which the antigen of interest can be expressed
- **Key Advantage:** Enables a more natural presentation of the target antigen within a membrane that more closely mimics a virus; can be used to express multiple target antigens in a single VLP
- **Limitation:** More effort required in purification to meet FDA/EMA standards
- **eVLP Ideal Candidates:** CMV, HCV, Dengue, RSV, and West Nile
eVLP Platform

eVLPs are a third-generation class of synthetic vaccines that closely resemble the structure of the virus they mimic.

eVLP PLATFORM HIGHLIGHTS

- Same size and structure as enveloped viruses
- Present antigens in their natural state (lipid bilayer) to provoke an optimal immune response
- In animal research, demonstrated ability to trigger strong, broadly neutralizing antibodies in multiple preclinical models (CMV, HCV, and Flu)
- Suitable to a wide array of viruses including CMV, HCV, Dengue, RSV, and West Nile
- Strong intellectual property estate

Top: eVLP Diagram – the foundation of the eVLP technology is a stable, protein-based core on which additional vaccine antigens of interest can be added; Bottom: Electron microscopy image of VBI’s CMV eVLP captured by Nanol Imaging Services.
Medical Need

Cytomegalovirus (CMV) is a common virus that can cause serious, life-threatening complications in persons with weakened immune systems.

PERSONS LIKELY TO DEVELOP CMV COMPLICATIONS

- **Congenital CMV:** Unborn babies whose mothers become infected with CMV during pregnancy are at high risk
  - Congenital CMV infection causes more long-term problems and childhood deaths than Down Syndrome or Fetal Alcohol Syndrome
  - In the U.S., congenital CMV causes one child to become disabled every hour

- **Immunocompromised:** A primary CMV infection can cause serious disease in organ and bone marrow transplant recipients, cancer patients, and patients receiving immunosuppressive drugs
Overview of eVLP Design and Production

- eVLPs are produced after transient transfection of cells (e.g. HEK 293, CHO, Vero) with plasmids encoding:
  - MLV Gag
  - Extracellular domain of gB protein fused with transmembrane (TM) domain of vesicular stomatitis virus G protein (VSV-G)

- Presence of VSV TM domain enhances targeting to cell membrane and optimal protein conformation (greater induction of neutralizing antibodies)

- MLV Gag expression induces “budding” of particles from lipid raft domain of transfected cells, with CMV gB protein incorporated into the final eVLP structures

- Formulation of eVLPs with alum phosphate (VBI-1501A) provides product stability in vitro and enhanced durability of immunity in vivo
VBI-1501A: Rapid, Potent, and Durable Immunity

- VBI-1501/A were produced using a GMP compliant HEK 293 cell line and purified to meet FDA standards.

- Pooled sera from vaccinated mice (n=8) were tested for the ability to neutralize CMV infection in both Fibroblast and Epithelial cells, two clinically relevant cell types susceptible to CMV infection.
Successful Optimization of Yield at GMP Manufacturer

- Optimization study improved gB yield ~4X while maintaining optimal gB/Gag ratio
Regulatory Compliant Purity Achieved

eVLP Purification Scheme

Centrifuge
Remove cells/debris

Tangential flow filtration
Purify eVLPs from soluble proteins

Benzonase/βPL Tx & diafiltration
Inactivate/remove residual DNA

Ultracentrifugation
Purify eVLPs from residual host cell proteins

Sterilize (filter)

SDS-PAGE of VBI 1501

Full length gB-G
N-terminus gB-G
High Molecular Weight Gag
High Molecular Weight Gag
Full Length Gag
Gag Cleavage
C-terminus gB-G
Gag Cleavage
CMV Program Summary

- Rapid, potent and durable immunity demonstrated with both drug substance (VBI-1501) and drug product (VBI-1501A)

- Pilot scale (10L) production of VBI-1501 meets Phase I release criteria
  - gB to Gag Ratio a key determinant of potency

- Purity:
  - Residual DNA: Target <10ng/dose Actual: 5.8ng/dose
  - Residual HCP: Target <500ng Actual: 5ng/dose

- Stability:
  - Confirmed in vivo stability of drug substance (VBI-1501) after 6 mo @ -20°C

- Planned IND submission / Phase I start in Q4 2015
Acknowledgements

- Catalina Soare
- Jasminka Bozic
- Barthelemy Ontsouka
- Tanvir Ahmed
- Abebaw Diress
- Melissa Lemieux
- Matthew Yorke

- Isabel Yang
- Diana Duque
- Adam Asselin
- Anne Catherine Fluckiger
- Marc Kirchmeier
- Scientific Advisory Board
VBI Vaccines, Inc.
222 Third Street, Suite 2241
Cambridge, MA 02142
(617) 830-3031
info@vbivaccines.com