Optimization of the Process for Making Clinical Supplies of an Enveloped Virus-like Particle for Cytomegalovirus

Modern Vaccine Adjuvants & Delivery Systems
Leiden, Netherlands

May 18th, 2015
Forward-Looking Statement Disclaimer

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 our Annual Report on Form 10-K for the year ended December 31, 2014 filed with the SEC on March 20, 2015. 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. NO OFFER; NO RELIANCE. This presentation does not constitute an offer to sell, or a solicitation of an offer to buy, any security and may not be relied upon in connection with the purchase or sale of any security. Any such offer would only be made by means of formal documents, the terms of which would govern in all respects. You should not rely on this presentation as the basis upon which to make any investment decision.
Key Messages

- VBI has an innovative virus like particle platform, but one that carries unique challenges
  - Unique viral mimic with core protein structure & lipid membrane
  - Allows the expression of membrane viral proteins in natural conformation

- Complexity of the eVLP required careful design of upstream & downstream processes
  - Upstream – a critical variable for final purity
  - Downstream – a kinder, gentler purification scheme

- The challenges are worthwhile
  - High potency
  - High, predictable yields
  - Unique & meaningful attributes in antigen conformation

- eVLPs represent a step forward in viral mimicry and can be manufactured at commercially viable yields and purity
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
- Presents 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)
- Excellent expression system for viral fusion proteins from a wide array of viruses including CMV, HCV, RSV, Dengue, and West Nile
- Strong intellectual property estate

Top: Electron microscopy image of VBI’s CMV eVLP captured by NanoImaging Services. Image shows stable, protein-based core with gB on surface.

Bottom: Proposed structure of CMV gB from E. Heldwein.

HCMV gB shares structural and functional properties with gB proteins from other herpesviruses, Sapna Sharma, Todd W. Wisner, David C. Johnson, Ekaterina E. Heldwein, Virology 435 (2013) 239–249
### eVLP Platform Cont.

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

<table>
<thead>
<tr>
<th>1&lt;sup&gt;ST&lt;/sup&gt; Generation</th>
<th>2&lt;sup&gt;ND&lt;/sup&gt; Generation</th>
<th>3&lt;sup&gt;RD&lt;/sup&gt; Generation (VBI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design: Antigens are produced and self-assemble.</td>
<td>Design: Antigens of interest are covalently attached to the surface of a backbone protein.</td>
<td>Design: Common protein backbone and a lipid membrane in which the antigen of interest can be expressed.</td>
</tr>
<tr>
<td>Key Advantage: Simple structures and repetitive pattern of antigenic epitopes.</td>
<td>Key Advantage: Can be applied to multiple different target antigens; VLP structure is not limited to the properties of the antigen.</td>
<td>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.</td>
</tr>
<tr>
<td>Key Limitation: Only a very limited number of antigens spontaneously form orderly VLP structures; cannot be applied to all enveloped viruses.</td>
<td>Key Limitation: Antigen of interest is artificially bound to the structural protein and not represented in a natural configuration.</td>
<td>Limitation: More effort required in purification to meet FDA/EMA standards.</td>
</tr>
</tbody>
</table>

3<sup>RD</sup> Generation (VBI)
What’s Different about eVLPs?

Example of First Generation VLP, Protein-based: Gardasil®

Disassembly and reassembly of human papillomavirus virus-like particles produces more virion-like antibody reactivity

- **Purification of soluble L1 protein:** very low impurity profile
- Disassemble/reassemble
- 50 nm, protein-based

Third Generation VLP, enveloped VLP: VBI-1501

- Structurally more complex, multiple proteins, lipid bilayer
- **Purification of intact particle:** Must have strategy for dealing with adventious and host cell impurities
- 120 nm, Lipid bilayer with embedded glycoproteins
Overview of eVLP Platform

- eVLPs are produced after transient transfection of cells (e.g. HEK 293, CHO, Vero, Sf9) with plasmids encoding: MLV Gag and Glycoprotein of interest

- MLV Gag expression induces “budding” of particles from membrane of transfected cells, glycoprotein is incorporated into outer envelop during budding process.

- eVLPs are purified using simple, mostly disposable, platform process yielding material which meets todays regulatory expectations for residual host cell impurities

• For VBI’s first clinical candidate (VBI-1501A) contains CMV, glycoprotein B

• VBI’s final drug product, (VBI-1501A) is formulated with alum phosphate which provides product stability in vitro and enhanced durability of immunity in vivo
CMV eVLP Manufacturing Summary

- Rapid, potent and durable immunity demonstrated with both drug substance (VBI-1501) and drug product (VBI-1501A)
- Batch consistency demonstrated using *in vivo* potency release assay
- eVLPs expected to meet Phase I release criteria:
  - **Toxicology batch (50L production scale)**
  - Purity (based on 1 µg gB, anticipated human dose):
    - Residual host cell DNA: qPCR 0.2ng/dose
    - Residual nucleic acid: Picrogreen: 26.2 ng/dose
    - Residual host cell protein: HEK 293 ELISA 12.1 ng/dose
  - Current Yield: ~150 doses/L purified drug substance
    - Over 500 doses/L prior to final 0.2 µm sterilizing filtration
- Opportunity to begin new eVLP vaccine candidates (e.g. RSV, Dengue) internally and with partners
**eVLP Platform Overview**

CUSTOMIZED DELIVERY OF ANTIGENS IN THEIR NATURAL STATE TO TAILOR IMMUNE RESPONSE

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Monovalent</th>
<th>Bivalent – Multiple Surface proteins</th>
<th>Bivalent – Internal Protein</th>
<th>Trivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present antigen in natural conformation</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Broadly Reactive Neutralizing Antibodies</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Polyvalent Immune Response</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Potent Cellular Immunity for Therapeutic Applications</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Acknowledgements

VBI Vaccines
Abebaw Diress
Tanvir Ahmed
Catalina Soare
Jasminka Bozic
Barthelemy Ontsouka
Anne Catherine Fluckiger
Melissa Lemieux
Matthew Yorke
Isabel Yang
Diana Duque
Adam Asselin
Dave Anderson