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

Modern Vaccine Adjuvants & Delivery Systems

Leiden, Netherlands

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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

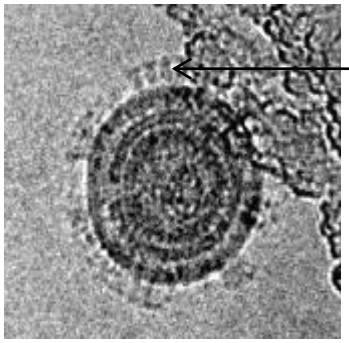
- eVLPs represent a step forward in viral mimicry and can be manufactured at commercially viable yields and purity

eVLP Platform

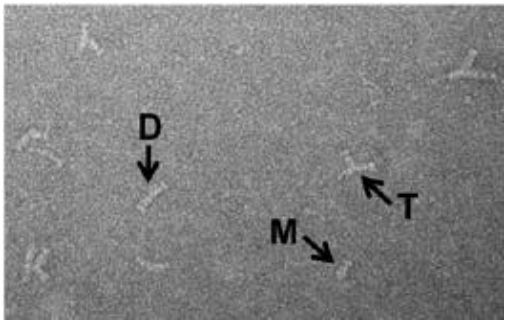
eVLPs are a third-generation class of synthetic vaccines that closely resemble the structure of the virus they mimic

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



Antigenic protein retains natural conformation in the Lipid Bilayer



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

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.

eVLP Platform Cont.

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

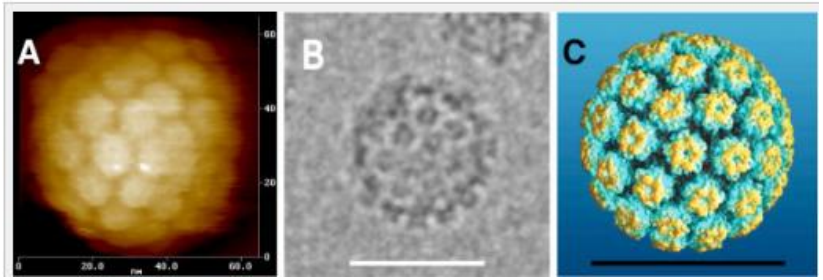
- Design: Antigens of interest are covalently attached to the surface of a backbone protein.
- Key Advantage: Can be applied to multiple different target antigens; VLP structure is not limited to the properties of the antigen.
- Key Limitation: Antigen of interest is artificially bound to the structural 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.

What's Different about eVLPs?

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

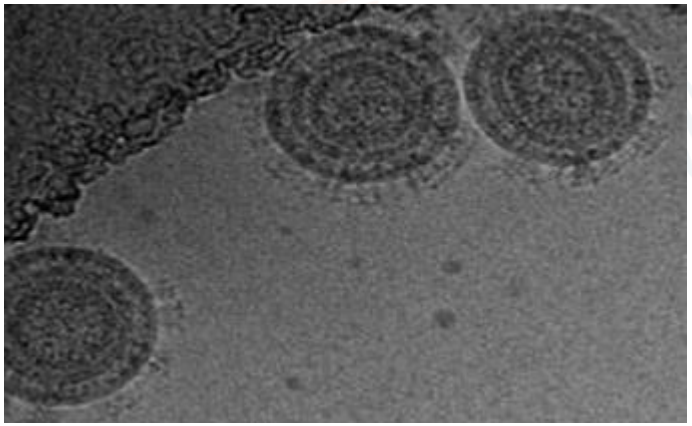


http://openi.nlm.nih.gov/detailedresult.php?img=3308208_1743-422X-9-52-6&req=4#

Disassembly and reassembly of human papillomavirus virus-like particles produces more virion-like antibody reactivity
Zhao Q, Modis Y, High K, Towne V, Meng Y, Wang Y, Alexandroff J, Brown M, Carragher B, Potter CS, Abraham D, Wohlpart D, Kosinski M, Washabaugh MW, Sitrin RD - (2012)

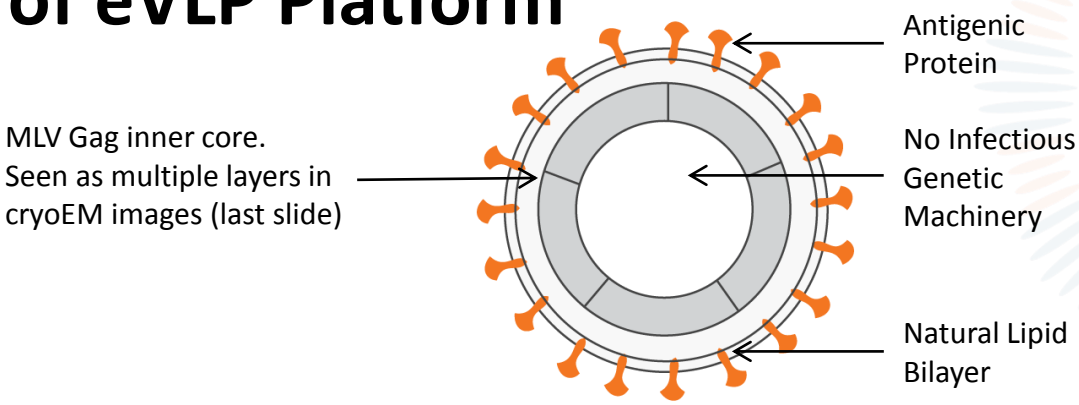
- **Purification of soluble L1 protein:** very low impurity profile
- Disassemble/reassemble
- 50 nm, protein-based

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

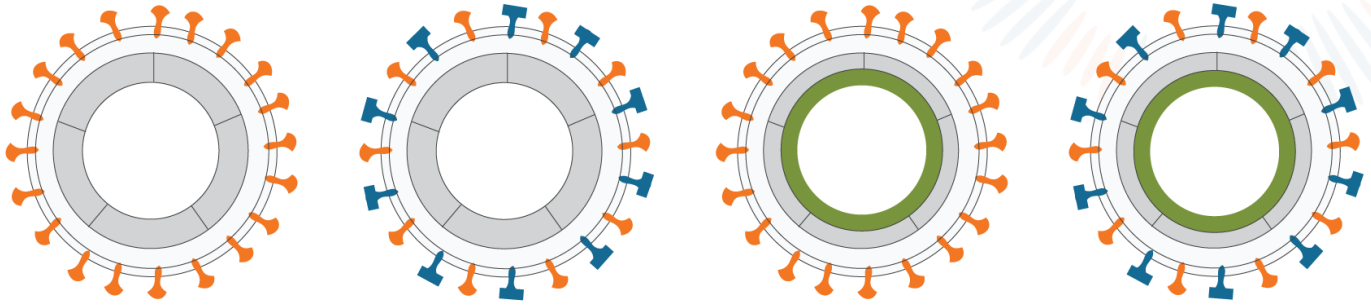
- **For VBI's first clinical candidate (VBI-1501A) contains CMV, glycoprotein B**
  - **VBI's final drug product, (VBI-1501A) is formulated with alum phosphate which provides product stability *in vitro* and enhanced durability of immunity *in vivo***

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



Attributes	Monovalent	Bivalent – Multiple Surface proteins	Bivalent – Internal Protein	Trivalent
Present antigen in natural conformation	+++	+++	+++	+++
Broadly Reactive Neutralizing Antibodies	+++	+++	+++	+++
Polyvalent Immune Response		++	++	+++
Potent Cellular Immunity for Therapeutic Applications	+	+	+++	+++

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