Enveloped Virus Like Particles: Third-generation VLPs for the Development of a Broadly Neutralizing Hepatitis C Vaccine

World Vaccine Congress Asia – June 2015

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Platform Technologies

Two complementary vaccine platform technologies.

Enveloped Virus-Like Particle ("eVLP") Platform

- "Third-generation" virus-like particle vaccines that closely mimic the structure of target viruses.
- Possible utility in both prophylactic and therapeutic vaccine applications.
- Lead program is developing a prophylactic cytomegalovirus ("CMV") vaccine ("VBI-1501A") with strong preclinical proof of concept.[1]
  - CMV market could exceed $1B annually.[2,3]
  - Toxicology expected to begin in Q2 2015.
  - Phase I start anticipated in Q1 2016.
- Exploring other eVLP vaccine candidates for internal development.

Liquid Particle Vaccine ("LPV™") Platform

- Enables the development of vaccines that can withstand storage or shipment at elevated or constantly fluctuating temperatures.[4]
- Entered into an agreement (April 2015) with Sanofi Pasteur to use LPV™ formulation technology to further the development of a key Sanofi Pasteur vaccine candidate
- Pursuing additional partnerships, all of which are expected to be self funding.
  - Currently, more than 90% of all vaccines require "cold chain" shipment at 4°C.[5]
- Extensive LPV™ intellectual property extending to 2030.

Experienced Leadership

Vaccine development, commercialization, and financing expertise.

DR. STEVE GILLIS, CHAIRMAN OF THE BOARD

- Immunologist and investor with track record of blockbuster drugs and visionary corporate development success.
- Founder of Immunex, the developer of Enbrel, a $7B/year landmark innovation.
- Managing director at Arch Venture Partners, a biotech VC with $1.9B under management.

ARCH Venture Partners

immunex

JEFF BAXTER, PRESIDENT & CEO

- A history of focused value creation, company building, and strategic management.
- Former Senior Vice President, R&D Finance and Operations at GlaxoSmithKline (“GSK”) during a period of tremendous corporate growth and shareholder returns.
- Managing Partner at The Column Group, a VC fund, responsible for start-ups and successful exits.

gsk GlaxoSmithKline

THE COLUMN GROUP

DR. FLORIAN SCHODEL, SAB CHAIR

- Clinical vaccinologist with extensive drug development experience.
- Former VP Vaccines Clinical Development at Merck.
- Led development of multiple complex global licensures for Measles, Mumps, and Rubella (“MMR”) and Rotavirus, each billion dollar products.

MERCK *Be well*

eVLP Platform

Virus-like Particle Vaccine Evolution

Virus-like particle 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®, 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

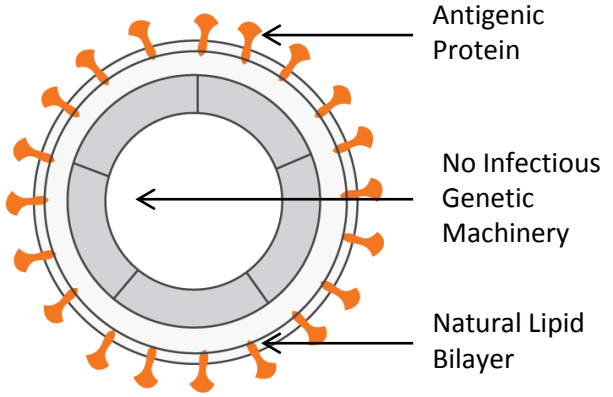
- Design: Common protein backbone and lipid membrane in which the antigen of interest can be expressed.
- Key Advantage: Enables more natural presentation of target antigen within a membrane that more closely mimics a virus; can express multiple target antigens in a single VLP.
- Limitation: More effort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

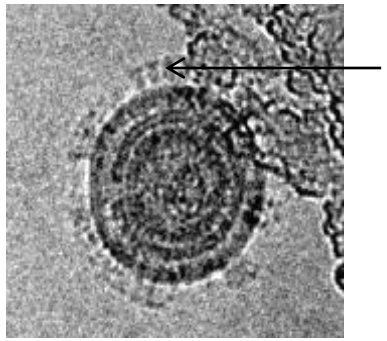
eVLP Platform Overview

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 for an improved immune response.
- Demonstrated ability to trigger strong, broadly neutralizing antibodies in multiple preclinical models (CMV, HCV, Flu and West Nile).
- Suitable to a wide array of viruses such as RSV and Dengue.
- Strong intellectual property estate.

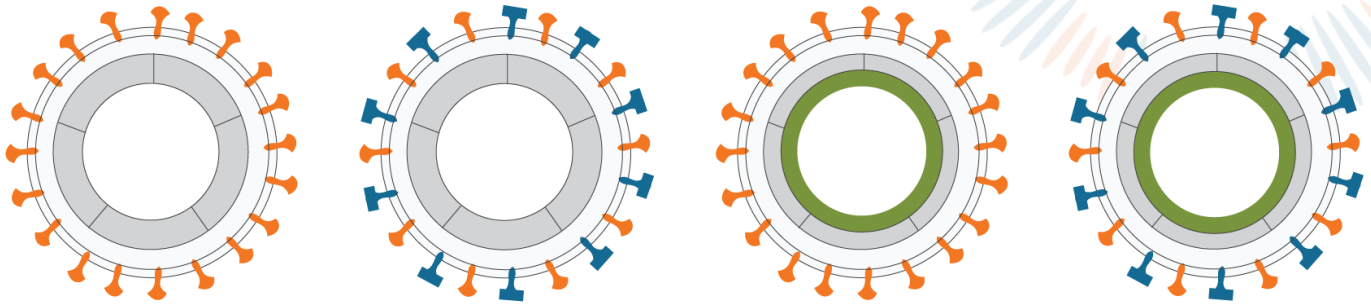




Top: eVLP Diagram – the foundation of the eVLP technology is a stable, protein-based core on which additional vaccine antigens of interest can be added; Bottom: Electron Microscopy image of VBI's CMV eVLP captured at Sripps Institute.

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	+	+	+++	+++

eVLP Platform Characteristics

eVLP Platform provides VBI with a novel technology designed to address unmet vaccine needs.

KEY CHARACTERISTICS

- **Highly Immunogenic:** eVLP immune responses comparable to or better than natural infection by closely mimicking structure of target virus.
- **Customizable:** eVLPs provide ability to rationally design a vaccine by including different antigens and controlling their relative expression.
- **Safe:** Unlike live-attenuated vaccines, eVLPs cannot revert back to an infectious state.
- **Commercially Viable:** Manufactured and purified using scalable methods; demonstrated high yields and purity.

VBI's Ottawa, Canada-based research facility.

Therapeutic HCV eVLP Vaccine Candidate

Therapeutic HCV Vaccine Opportunity

HCV market analysis: critical numbers infected in many established & growing economies

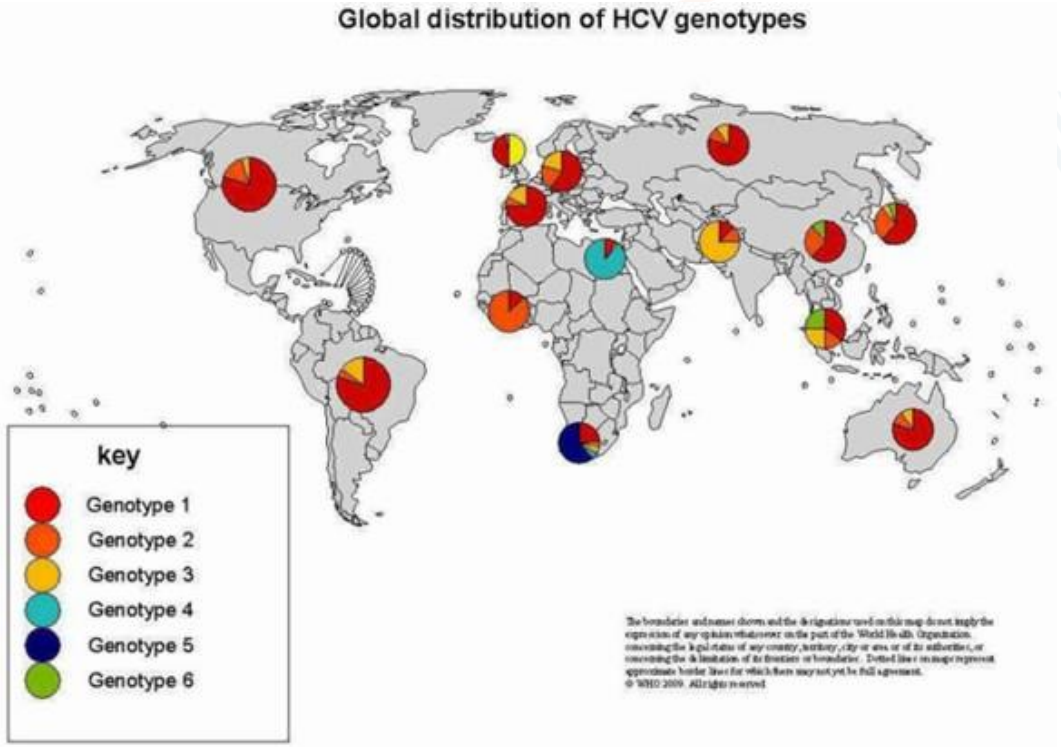
Region	Example Countries	Total Infected[1]	GDP/Capita[2]	Infection Rate[1]
China & Southeast Asia	China	20,000,000	$8,862	1.50%
	Vietnam	2,600,000	$3,503	2.90%
	Thailand	1,900,000	$9,371	2.80%
	Taiwan	1,000,000	$30,874	4.40%
	Korea	635,000	$19,890	1.30%
Middle East & India	Egypt	10,700,000	$4,753	14.90%
	India	9,500,000	$1,330	1.50%
	Pakistan	8,800,000	$2,976	4.70%
Russia & Eastern Europe	Russia	4,252,500	$9,900	3.00%
	Romania	770,000	$9,446	3.50%
North America & Europe	Italy	3,400,000	$30,791	5.50%
	USA	2,500,000	$45,218	1.00%
	Spain	1,200,000	$28,810	2.60%

Therapeutic vaccination is a cost effective alternative to expensive antivirals

1) *Liver International, v31 suppl 2, July 2011; IMF WEO Online Database*

Global Distribution of HCV Genotypes – One Solution for All?

- Viral resistance and genotype distribution requires a broadly active solution
- Example: Southeast Asia experiencing a dramatic rise in Genotype 6[1]



1) Yan, et al. Changing Pattern of Clinical Epidemiology on Hepatitis C Virus Infection in Southwest China. Hepatitis Monthly 12(3) 196-204, 2012

Current Interferon-based HCV Therapy is Associated with Significant Toxicity & Side Effects

- **Fatigue**
- **Flu like symptoms**
- **Rash**
- **Anemia**
- **Depression**

Therapeutic Vaccine Rationale: Eliminate use of interferon while effectively managing viral load (and transmission)

HCV Market Dynamics – Cost of New Therapies is a Critical Barrier to Addressing Unmet Medical Need

LATE 90's	RECENT PAST	PRESENT

U.S. & EU Markets

Ribavirin + Interferon

- Viral suppression
- Highly toxic – compliance issues

→

2nd Gen Small Molecules + Interferon

- Viral clearance in certain populations
- Very expensive
- Tox issues remain
- Anti-viral resistance

→

3rd Gen Oral Small Molecules

- Promising efficacy without interferon/toxicity
- Oral administration

BRICM & Growing Economies

Few treatment options

→

Ribavirin & Interferon now available

- As above, tox issues & compliance are issues
- Viral resistance
- **Expensive 2nd Gen small molecules may not be an efficient use of Public Healthcare dollars**

→

Ribavirin + Therapeutic Vaccine

- Reduced toxicity (interferon-free)
- Multi-genotype efficacy
- Clear health economic benefits

Is a Therapeutic Vaccine for HCV Possible and How Would it be Evaluated?

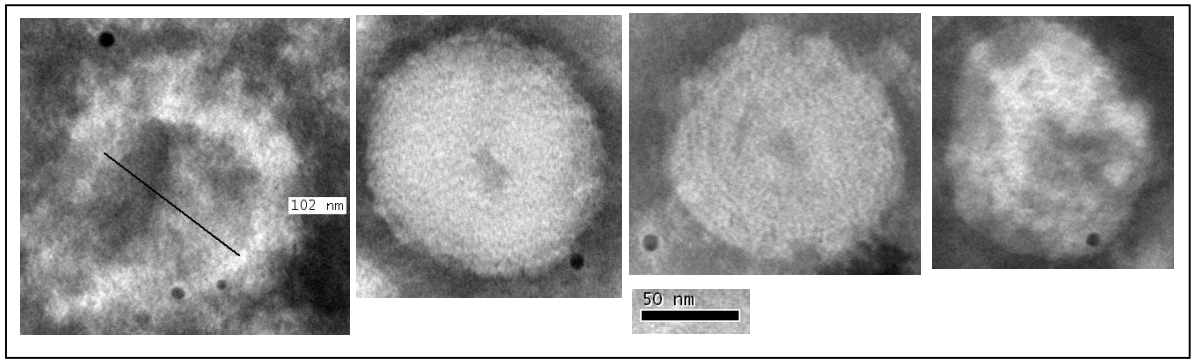
- **There is significant evidence that immune control and clearance of HCV is possible**
  - Approximately 25% of those infected can "spontaneously" clear the virus[1]
  - Virus-specific neutralizing antibodies contribute to clearance
  - Genotype of HCV influences spontaneous viral clearance
- **Concepts for clinical development**
  - Phase I trial designed to compare standard antiviral therapy (ribavirin + interferon) vs Tx vaccine + ribavirin
    - Demonstrate non-inferiority in terms of virus control with reduced toxicity/greater compliance
  - Experimental groups will be removed from traditional therapy following Tx vaccination
  - Inclusion criteria: patients early in onset of infection, with controlled viremia

1) Grebely et al., Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infectious Disease* vol12: 408-414, 2012

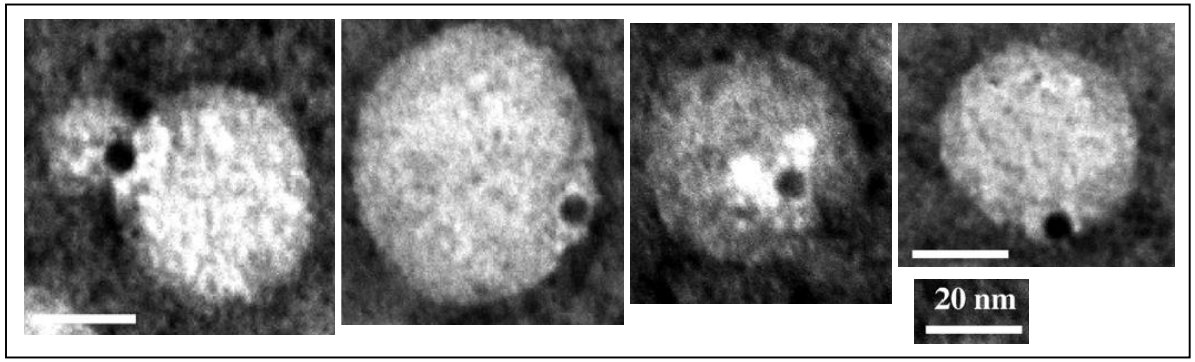
Therapeutic HCV Vaccine Target Product Profile

	Target Profile
Indication	Therapeutic use in patients infected with HCV (any genotype) to eliminate use of interferon
Regions	Vietnam/Southeast Asia where a therapeutic vaccine has clear health economic benefit
Ages/classes	Seropositive adults
Regimen	6 monthly immunizations + ribavirin (improvement from current daily regimens given up to 48 weeks)
Efficacy	Non-inferior to current standard of care (interferon + ribavirin), improved efficacy against non-genotype 1 or drug-resistant HCV
Safety	Significantly reduced toxicity due to lack of interferon

HCV Imaging: Detection of Envelope Glycoprotein on HCV eVLPs vs. Virions Using Immunogold EM Staining



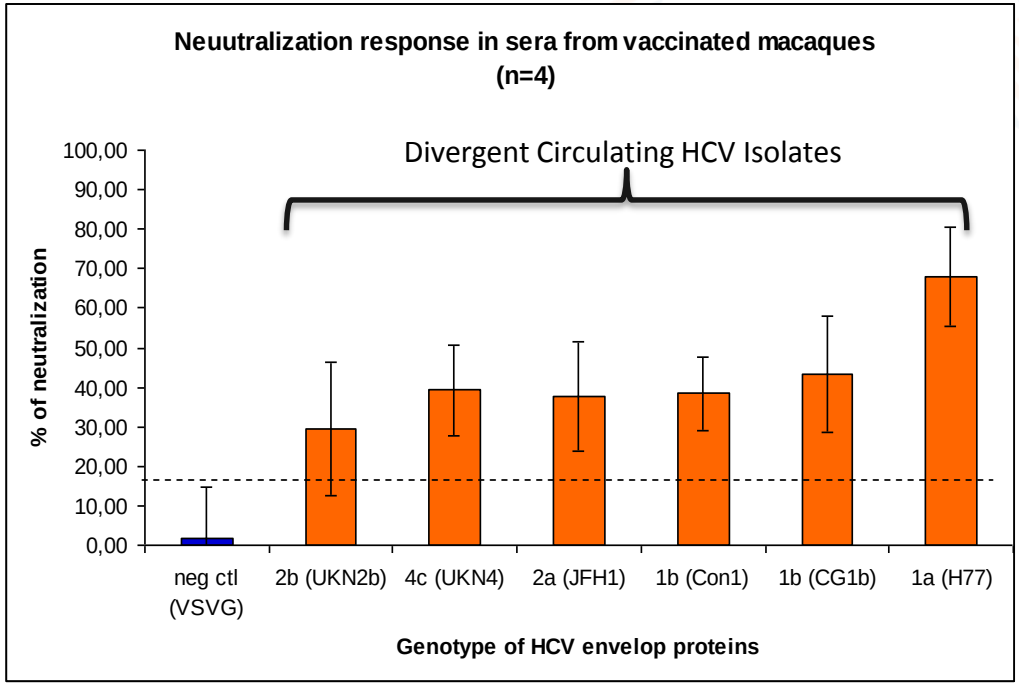
HCV eVLP
(Garrone et al., Science Translation Medicine 2011)



HCV virions isolated from patients
(Petit et al. Virology 2005)

HCV eVLP Induction of Broadly Reactive Neutralizing Antibodies in Non-human Primates

- Macaques primed with adenoviral vector to induce suboptimal HCV immunity (no induction of nAbs) that mimics infected individuals
- Strong cross-reactive neutralizing antibody responses against divergent genotypes of HCV
  - Neutralizing Ab titers measured at week 12 after 1st eVLP immunization



P. Garrone, et al Sci. Transl Med 3, 94ra71 (2011)
Internal Reference: VAC0805 CrossNeutral

eVLP Vaccines : Scalable manufacturing process established with exceptional purity

eVLP PURIFICATION SCHEME

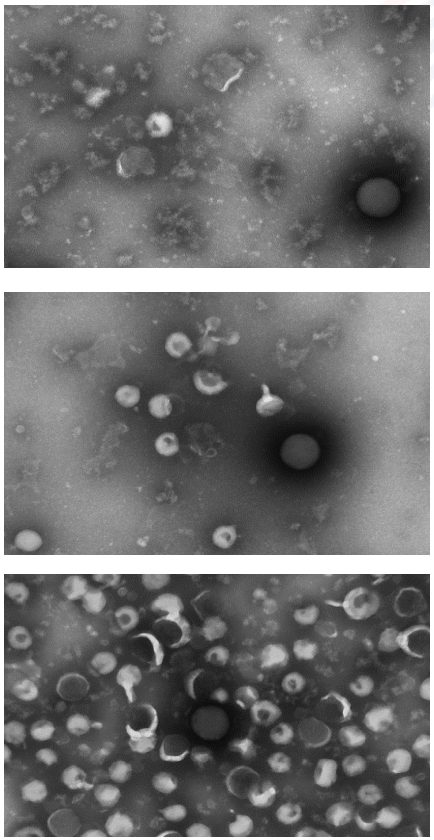
Clarification
(Depth filtration)

Concentrate particles
(Tangential flow filtration)

Inactivate residual host DNA and adventicious virus
(Benzonase/βPL Tx & diafiltration)

Wash and Concentrate
(Diafiltration & ultracentrifugation)

Sterilize (filter)



eVLP density = 9.60×10^6 particles/mL

TFF & BZ Tx

1.44×10^{12} particles/mL

Diafiltration & UC

1.15×10^{10} particles/mL

Current Scale with Lead Program: 50L

Current Yield – Lead Program: ~150 purified doses / liter

HCV eVLP Program Summary

- HCV eVLP proof-of-concept (Garrone et al. 2011)
  - Strong induction of neutralizing antibody responses in monkeys
  - Broadly reactive against multiple HCV genotypes

- eVLP production and purification development
  - Substantial knowledge & expertise gained from CMV eVLP program
  - VBI has licensed a GMP-compliant HEK 293 cell line (serum-free, cell suspension growth)
  - VBI has developed a scalable, cost-effective purification process that provides:
    - High yields
    - High purity (residual DNA and host cell protein content meet regulatory targets)

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