



Preparing for the Next Pandemic: Rapid “Novel” Influenza Vaccine Product

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FluBlok[®]

- First recombinant influenza vaccine
- First cell-based influenza vaccine in U.S.
- FDA licensure in 2010?
 - *No additional safety or efficacy studies required – FDA letter 01/11/10*
- The pandemic solution
 - **Only pandemic vaccine that can be quickly manufactured and/or transferred to and manufactured in other countries**

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Topics

- Influenza Viruses and Vaccines
- BEVS Technology
- Insect Cells as Substrate for Vaccine Manufacturing
- Flublok: a Recombinant Influenza Vaccine
- Pandemic Influenza Vaccine: PanBlok
- Summary

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The Influenza Viruses

- Orthomyxoviruses (Greek, myxa=mucus)
- Three types of influenza virus (A, B, and C)
 - A viruses
 - Divided into subtypes based on genetic and antigenic differences among surface proteins (HA & NA)
 - Current subtypes found in people are A(H1N1) and A(H3N2)
 - B viruses
 - No subtypes
 - C viruses
 - Cause mild respiratory illness
- Antigenic “Drift” of A and B viruses leads to epidemics every winter
- Antigenic “Shift” of A viruses leads to pandemics
 - 3x in the past 100 years

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Production of influenza vaccine

Characteristics

- Trivalent vaccine: 2 A strains and 1 B strain
- Protection correlates with hemagglutinin (HA) antibodies

Production process:

Chicken Embryo's



Isolation of Virus



Kill Virus



Isolate virus proteins



Long production cycle

One egg = one dose

Production affected by Avian influenza outbreaks

Adaptation required

Adverse reactions

Less effective in the elderly

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BEVS Technology

“Enabling products where speed, cost and safety matter”

Baculovirus Expression Vector System (BEVS)



- Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)
- Baculoviruses highly specific to insect cells
- Powerful promoter generates high yield of protein of interest
- Culture expression of insect cells in a fermenter
- Infect cells with engineered virus
- Incubate infection for ~48 - 72 hours
- Protein forms rosettes
- Purify protein to > 90% into final product
- Formulate with PBS into vaccine

FluBlok® Approval → Validation

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BEVS Technology

“Enabling products where speed, cost and safety matter”

Key Advantages of BEVS Technology

- Versatility
 - Produced > 1,000 proteins
- Speed
 - Single serum-free cell line for all products
 - Cloning in weeks vs. months
- Low cost
 - High yields in a low-cost proprietary media
 - High-density fermentation
- Safety
- Reliable scale-up
 - Current scale 500L; others up to 5,000L



Insect Cell Substrate

Inherent Safety ?

■ Baculovirus

- Daily exposure - typical serving of coleslaw contains 112 million polyhedra (each polyhedron contains multiple baculoviruses)¹
- Limited Host Range (Lepidopteran Species of Insects)
- Do NOT Replicate in Mammalian Cells

■ Insect Cells

- Virtually No Known Adventitious Agents Can Replicate in both Insect Cells and Mammalian Cells
- Arboviruses are Rare Exceptions (West Nile Encephalitis)
- Derived from Non-biting Insects – Low Adverse Events

¹Heimpel et al (1973) Environmental Entomology, vol2 (1), pp. 72.



Insect Cell-Produced Products & Regulatory Approval Status

Cervarix – First insect cell product licensed by FDA

- Papillomavirus vaccine
- Oct. 19, 2009 - Approved in U.S
- 2007 - Approved in EU & Australia

Provenge® - Prostate cancer treatment

- First cancer immunotherapy to be approved by the Agency
- Approved May 2010
- Impact
 - Removes a “barrier” for insect cell-based production platform from regulatory viewpoint

Now Approved

Cervarix®
Human Papillomavirus Bivalent
(Types 16 and 18) Vaccine, Recombinant



Dendreon

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Insect Cell-Produced Products Approaching FDA Approval with PSC's Assistance



▪Glybera® - Lipoprotein Lipase Deficiency

- Recombinant Adeno-Associated Virus (rAAV) -based gene therapy
- Orphan disease indication
- BLA filed January 11, 2010



▪Diamyd® – Type I Diabetes Vaccine

- Phase III studies ongoing in U.S. and Europe
- Preservation of insulin secretion
- Major partnership deal with J&J



▪FluBlok - Influenza Vaccine

- First non egg-based flu vaccine in U.S.
- Under final review at FDA

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Examples of Vaccines that are being Produced in Insect Cells

- **Human therapeutic & prophylactic vaccines**
 - SARS – Spike – entering Phase I
 - HIV
 - Norovirus – Phase I
 - Hepatitis B, C and E
 - West Nile
 - Malaria
 - Dengue
 - Marburg, Ebola
- **Veterinary vaccines**
 - PCV
 - Influenza (avian; porcine; horse)

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SARS Vaccine S = Major Surface Antigen

Coronaviruses are large enveloped RNA viruses that infect mammals and birds

Target for vaccine: S - Spike glycoprotein (surface protein) = major antigen

Rationale:

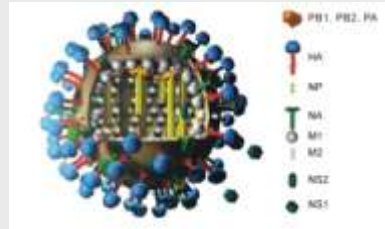
- Veterinary vaccine development
- Key to Infection - ACE2 receptor binding
- Antibodies to S-Protein identified from SARS survivors neutralized the virus





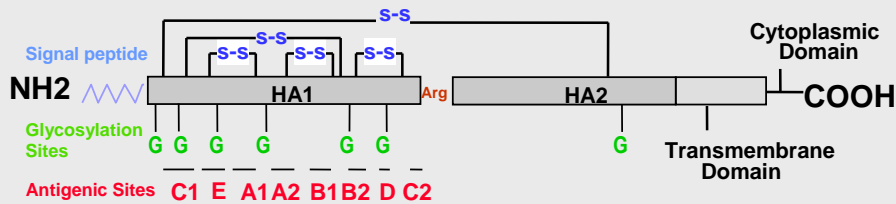
Major Influenza Surface Protein

- **HA (Hemagglutinin):**
 - Coat of the influenza virus
 - Antibodies against HA protect against influenza
 - Changes in HA require annual update of vaccine



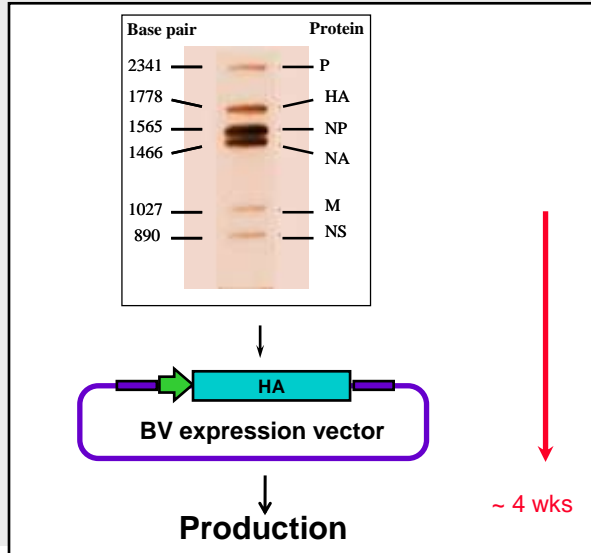
Hemagglutinin properties

- Trimeric integral membrane protein
- Cleavage of HA with host protease into HA1 and HA2 needed for fusion activity
- HA1 and HA2 linked by disulfide bonds
- Contains four antigenic sites (A, B, C, and D)
- Contains many glycosylation sites
- Hydrophobic transmembrane domain

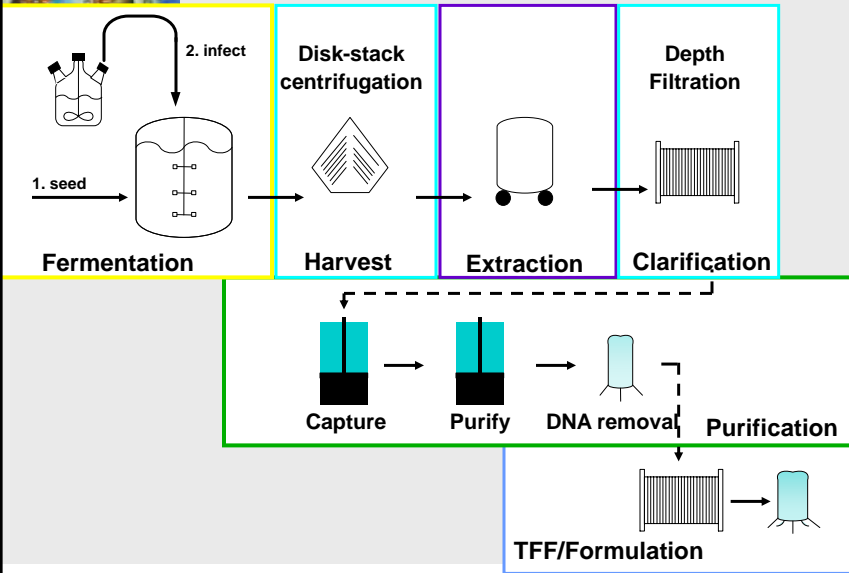




Cloning of influenza HA gene



Downstream Process





Safety & Immunogenicity of FluBlok Potential Benefits (3x45µg rHA)

- Influenza rHA antigens are produced in insect cells – protein based vaccine with low endotoxin content
- rHA protein is highly purified and does not contain egg protein or other contaminants from eggs
- Selection or adaptation of influenza virus strains that produce at high levels in eggs is not required =>the best genetic match
- Cloning, expression and manufacture of FluBlok within 2 months
- FluBlok does not require any embryonated chicken eggs
- Manufacturing of FluBlok does not require biocontainment facilities
- Manufacture of rHA does not include formalin inactivation or organic extraction procedures

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PanBlok: Pandemic Flu Vaccine based on rHA

1997 Hong Kong “bird flu”	<ul style="list-style-type: none"> ▪ 8 weeks from development to product ▪ FDA authorized immediate use ▪ 200 healthcare workers & researchers vaccinated
Safety During Production	<ul style="list-style-type: none"> ▪ No need to grow or handle a live virus
Authenticity of Antigens	<ul style="list-style-type: none"> ▪ Antigen is exact match to natural H5N1 (or any other) virus ▪ No induced structural changes as occurs with reverse genetics
Manufacturing	<ul style="list-style-type: none"> ▪ Any monoclonal antibody facility ▪ More than adequate existing capacity

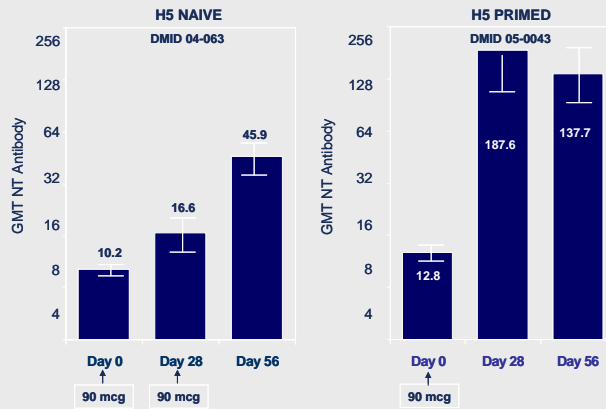
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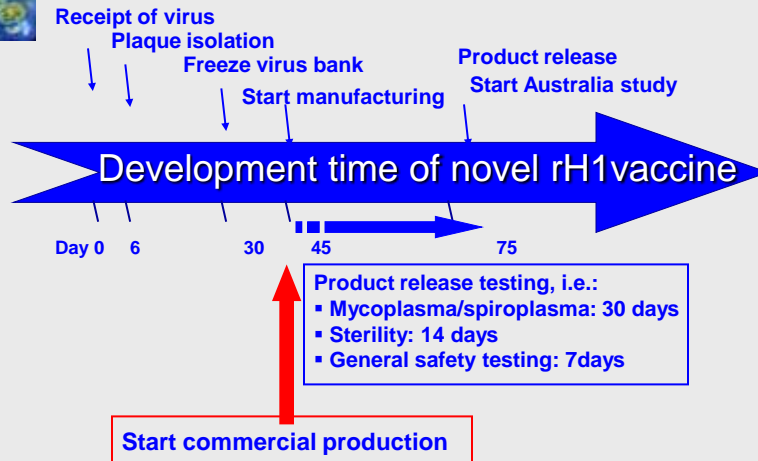
NIAID-Sponsored Study by Drs. Topham & Treanor at University of Rochester

Serum Neutralizing (NT) Antibody Responses Following One or Two Doses of H5 Vaccine in Naïve Subjects or Following a Single Dose in H5 Vaccine-Primed Subjects

- Determine the ability of a clade 3 H5 Protein Sciences recombinant vaccine administered in 1998 to prime for immune responses to a subsequent clade 1 H5 subvirion vaccine in healthy adults
- Comparison of responses in H5 primed subjects to those of H5 naïve subjects

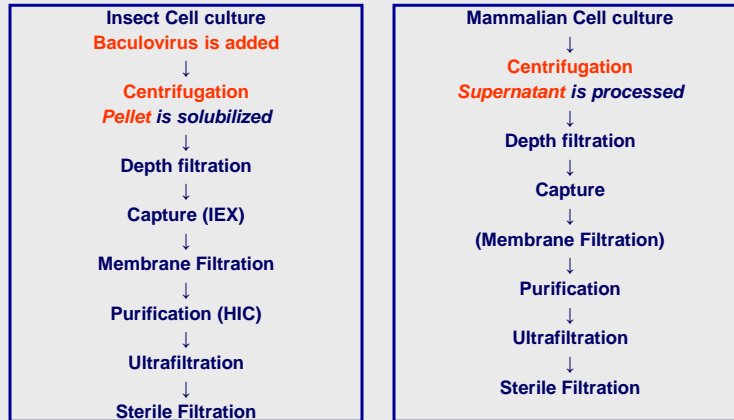


Time-line for Vaccine Development Novel rH1 Vaccine





Pandemic Vaccine Production



Shortage of vaccine is unnecessary as there is adequate cell culture capacity available worldwide.

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PanBlok: Clinical Studies (H5)

- Studies in Japan by UMN
(Japanese Partner)
 - Phase 1/2 study: Completed
 - A/Vietnam w/o Alum
 - Conclusion: Alum offered no benefit
 - Phase 2 study: Ongoing
 - Two doses of A/Vietnam, followed by booster dose with A/Indo/H5
 - Two doses of unadjuvanted 135mcg meet EMEA license criteria

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PanBlok: Clinical Studies H5 (2)

- Clinical study ongoing in the U.S. by PSC with BARDA support (Contract # HHS0100200900106C)
- Phase 1/2 study: Test H5 in combination with adjuvant (GLA/SE)
- Data expected: by end 2010

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Summary

- FluBlok was tested in >3000 Subjects
- FluBlok can be produced much faster than the egg-based vaccine
- FluBlok may provide better protection against influenza for adults ≥ 65 yr (specifically ≥ 75 yr)
- FluBlok may be approved in the U.S. in 2010
- PanBlok would address the need for large quantities of vaccine within short time.
- Next Steps
 - Scale-up manufacturing
 - Test vaccine in children
 - Alternative formulations (patch?)

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Cell Substrate Issues

- **Develop screens for (un)known viruses**

CODEHOP PCRs developed for the following virus families:

- Ascoviridae
- Iridoviridae
- Densoviridae A, B, C *and Penaeus merguensis* densovirus
- Nodaviridae (TNCL Virus)
- Tetraviridae

Master, Working and End of Production cells were screened.

- **RT Activity of insect cell substrate**

Co-cultivation assays, EM screening of (un) stressed cells, viral clearance studies, multiple PERT assays with variable results

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FluBlok Outlook – 2010 and beyond

- **FluBlok to market**

- **Large scale manufacturing deal**
- **Address remaining FDA cell substrate questions**
- **FDA approval under traditional approval regulations expected in 2010**
- **Filing for market authorization in EU and Australia in 2010**
- **Licensing of FluBlok/PanBlok**

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