



FluBlok / PanBlok: An Influenza Virus Vaccine based on the Baculovirus - Insect Cell Expression System

Implications for Pandemic Preparedness

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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



Production of influenza vaccine

Characteristics

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

Production process:

Chicken Embryos



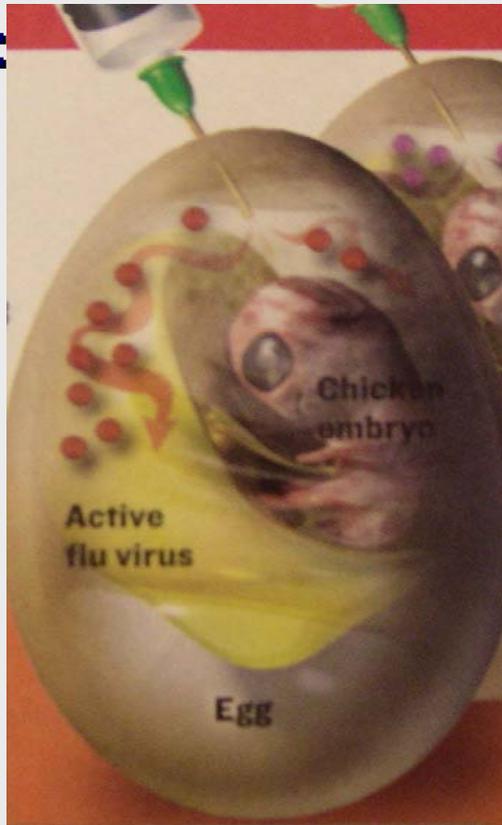
Isolation of Virus



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



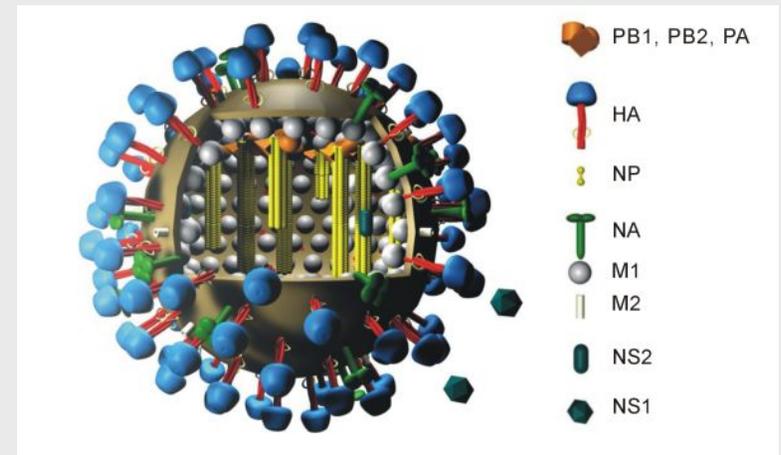
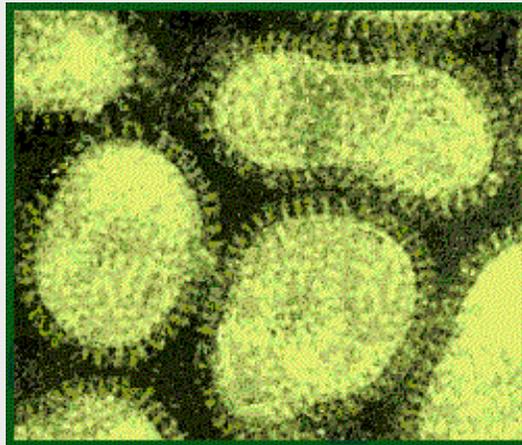
Major Influenza Surface Proteins

- **HA (*Hemagglutinin*):** Sixteen antigenic subtypes (H1-H16)
 - Mediates attachment of the virus to the host cell surface via binding to sialic acid residues.
 - Fusion capability that enables the viral envelope to integrate with the host cell membrane.
 - Each viral particle contains over 500 copies.
- **NA (*Neuraminidase*):** Nine antigenic subtypes (N1-N9)
 - Plays a role in penetration of the mucus layer that surrounds the target cell and in release of virus from the surface of the infected cell.
 - The active center that splits polysaccharides is almost identical in influenza viruses of classes A and B. It is here that NA inhibitors bind and exert their action.
 - Each viral particle contains 100 to 250 copies.



Major Influenza Surface Protein

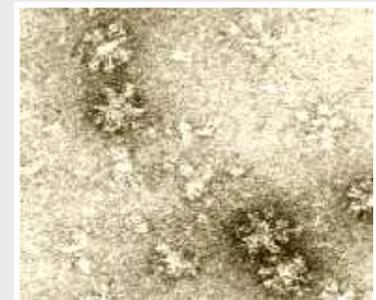
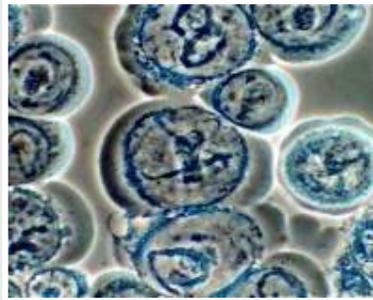
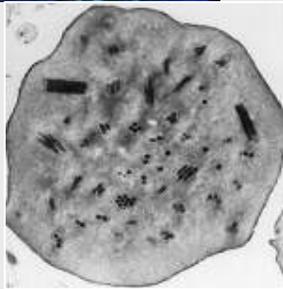
- **HA (*Hemagglutinin*):**
Coat of the influenza virus
Antibodies against HA protect against influenza
Changes in HA require annual update of vaccine





rHA produced in insect cells

Baculovirus Expression Vector System (BEVS)

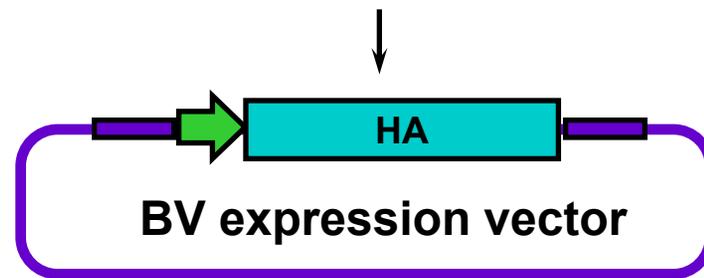
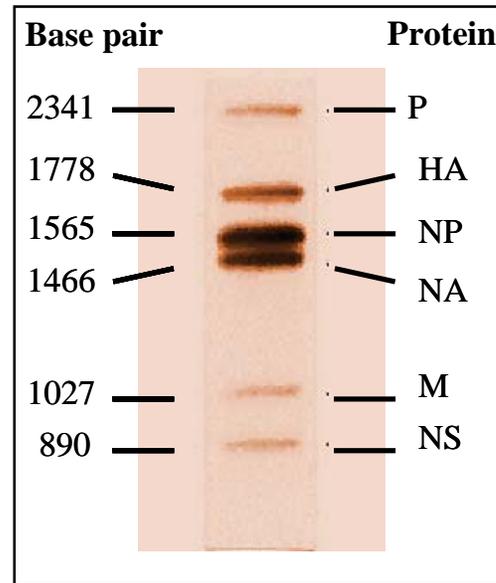


- Engineer baculovirus with the gene of interest (e.g. Hemagglutinin)
- Baculoviruses highly specific to insect cells
- Powerful promoter generates high yield of protein of interest
- Culture expression of insect cells in a fermenter
- Infect cells with engineered virus
- Incubate infection for ~48 -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

FluBlok[®] Approval → Validation

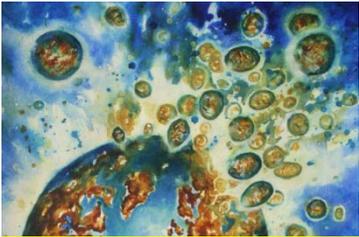


Cloning of influenza HA gene

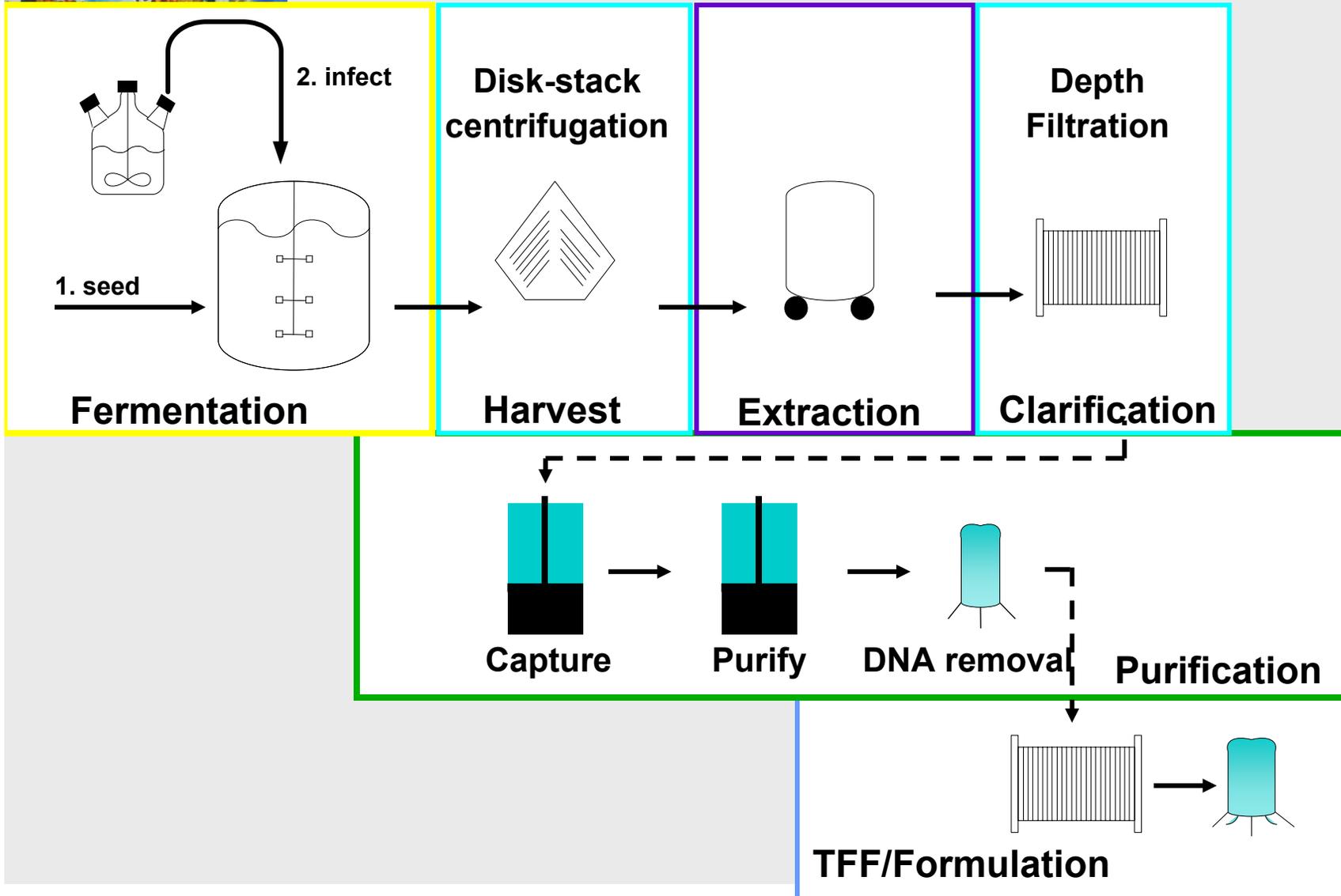


↓
Production

↓
~ 4 wks



Downstream Process



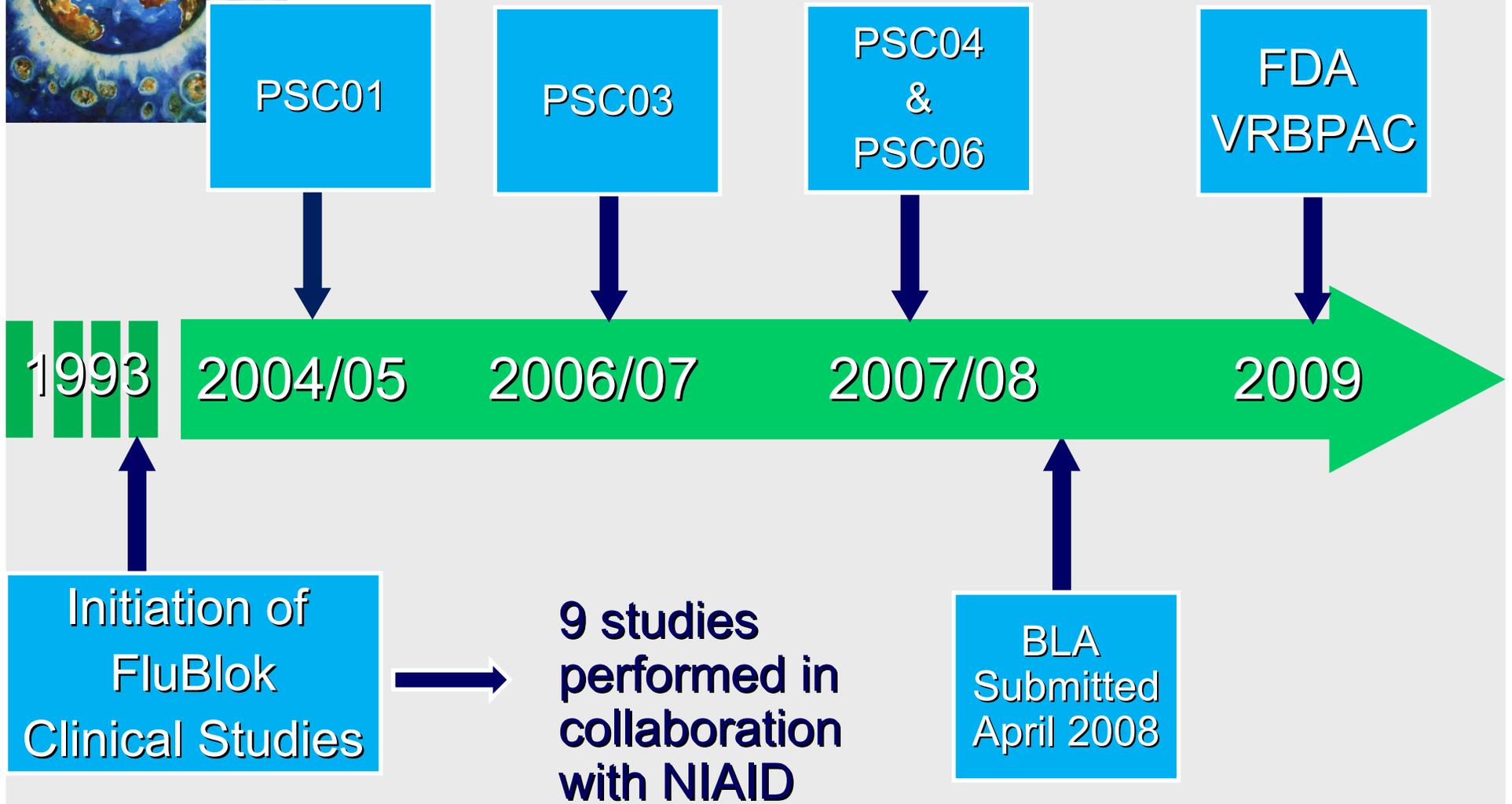


Safety & Immunogenicity of FluBlok Potential Benefits (*3x45 μ g rHA*)

- 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 large amounts of embryonated chicken eggs
- Manufacturing of FluBlok does not require biocontainment facilities
- Manufacture of rHA does not include formalin inactivation or organic extraction procedures



Clinical Development Timeline





FluBlok Clinical Development Program

BLA Studies
Supporting Licensure
n=3384 (3233)

PSC01
2004-2005

Efficacy and Safety
Study in
Healthy Adults
≥18 to 49 yrs
Placebo Controlled
and Two Dose
Levels of FluBlok

PSC03
2006-2007

Non-Inferiority
Immunogenicity
and Safety
Healthy Adults
≥65 yrs
Active
Controlled
Study
(Fluzone®)

PSC04
2007-2008

Field Efficacy
and Safety
Study in
Healthy Adults
≥18 to 49 yrs
Placebo
Controlled

PSC06
2007-2008

Non-Inferiority
Immunogenicity
and Safety in
Healthy Adults
50 to 64 yrs
Active Controlled
Study (Fluzone®)

n = number of subjects vaccinated with FluBlok

() = number of subjects receiving commercial formulation of FluBlok



Safety & Immunogenicity of FluBlok

Effectiveness: Non Inferiority Comparison FluBlok versus Fluzone

| | | H1 | H3 | B |
|-------|----|-------|-------|-------|
| GMT | 06 | FB>Fz | FB>Fz | |
| | 03 | FB>Fz | FB>Fz | |
| | | | | |
| % SCR | 06 | | FB>Fz | |
| | 03 | FB>Fz | FB>Fz | Fz>FB |

NI

Not NI

FB>Fz :FB signif. higher $p < 0.05$

Fz>FB :Fz signif. higher $p < 0.05$



Safety & Immunogenicity of FluBlok

| | Study 01 | Study 04 | Study 06 | | Study 03 | |
|------------------|------------------------|--------------------------|--------------------------|----------------|------------------------|-------------------|
| | 18-49 yrs | 18-49 yrs | 50-64 yrs | | ≥ 65 yrs | |
| | FluBlok | FluBlok | FluBlok | Fluzone | FluBlok | Fluzone |
| A/H1N1 | A/New Caledonia | A/Solomon Islands | A/Solomon Islands | | A/New Caledonia | |
| % Seroprotected | Green | Green | Green | Green | Green | Green |
| % Seroconversion | Green | Green | Green | Green | Green | Red |
| A/H3N2 | A/Wyoming | A/Wisconsin | A/Wisconsin | | A/Wisconsin | |
| % Seroprotected | Green | Green | Green | Green | Green | Green |
| % Seroconversion | Green | Green | Green | Red | Green | Green |
| B | B/Jiangsu | B/Malaysia | B/Malaysia | | B/Ohio | B/Malaysia |
| % Seroprotected | Red | Green | Green | Green | Green | Green |
| % Seroconversion | Green | Green | Red | Red | Red | Green |



FluBlok: PSC04 Summary of Efficacy

| | FluBlok (N=2344) | | Placebo (N=2304) | | FluBlok Protective Efficacy, % | 95% Confidence Interval |
|---|---------------------|------------|---------------------|------------|---|-------------------------------|
| | Cases, n | Rate, % | Cases, n | Rate, % | | |
| Positive culture due to a strain represented in the vaccine | | | | | | |
| Matched strains -CDC-ILI positive | 1 | 0.04 | 4 | 0.2 | 75.4 | (-148.0, 99.5) |
| Matched strains | 2 | 0.1 | 6 | 0.3 | 67.2 | (-83.2, 96.8) |
| Positive culture due to any strain, regardless of match to the vaccine | | | | | | |
| All strains CDC-ILI positive | 44 | 1.9 | 78 | 3.4 | 44.6 | (18.8, 62.6) |
| Type A CDC-ILI positive | 26 | 1.1 | 56 | 2.4 | 54.4 | (26.1, 72.5) |
| Type B CDC-ILI positive | 18 | 0.8 | 23 | 1.0 | 23.1 | (-49.0, 60.9) |

**FluBlok is efficacious despite suboptimal match
(95% drift)**



FluBlok:

Summary of Safety Data

- **Commercial formulation evaluated in a total of 3,233 adults in 4 randomized, controlled trials**
 - **2497 adults age 18-49 yrs**
 - **300 adults age 50-64 yrs**
 - **436 adults age ≥ 65 yrs**
- **Excellent tolerability and safety profile, with AE rates generally similar to the active comparator, Fluzone in two studies**
- **Only one treatment-related SAE (vasovagal syncope) and one possibly-related SAE (pericardial/pleural effusion) reported**



PanBlok: Pandemic Flu Vaccine based on rHA

1997 Hong Kong “bird flu”

- 8 weeks from development to product
- FDA authorized immediate use
- 200 healthcare workers & researchers vaccinated

Safety During Production

- No need to grow or handle a live virus

Authenticity of Antigens

- Antigen is exact match to natural H5N1 (or any other) virus
- No induced structural changes as occurs with reverse genetics

Manufacturing

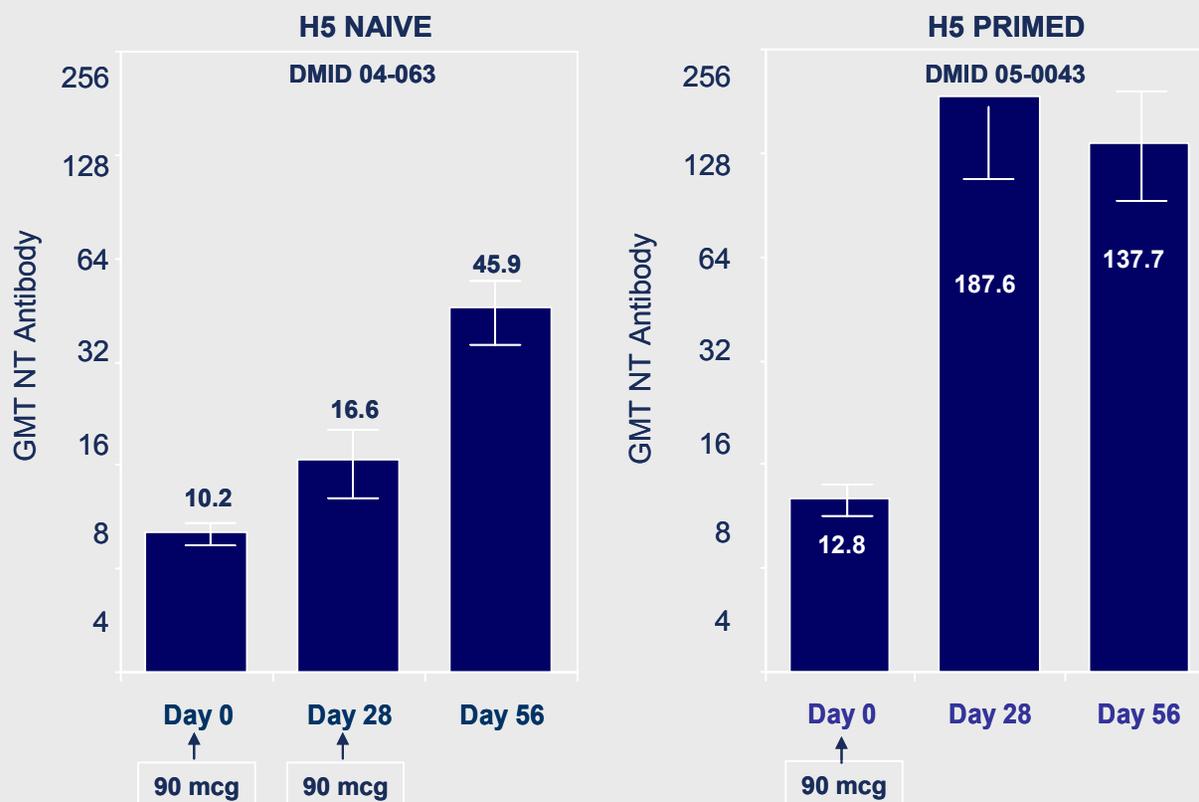
- Any monoclonal antibody facility
- More than adequate existing capacity



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

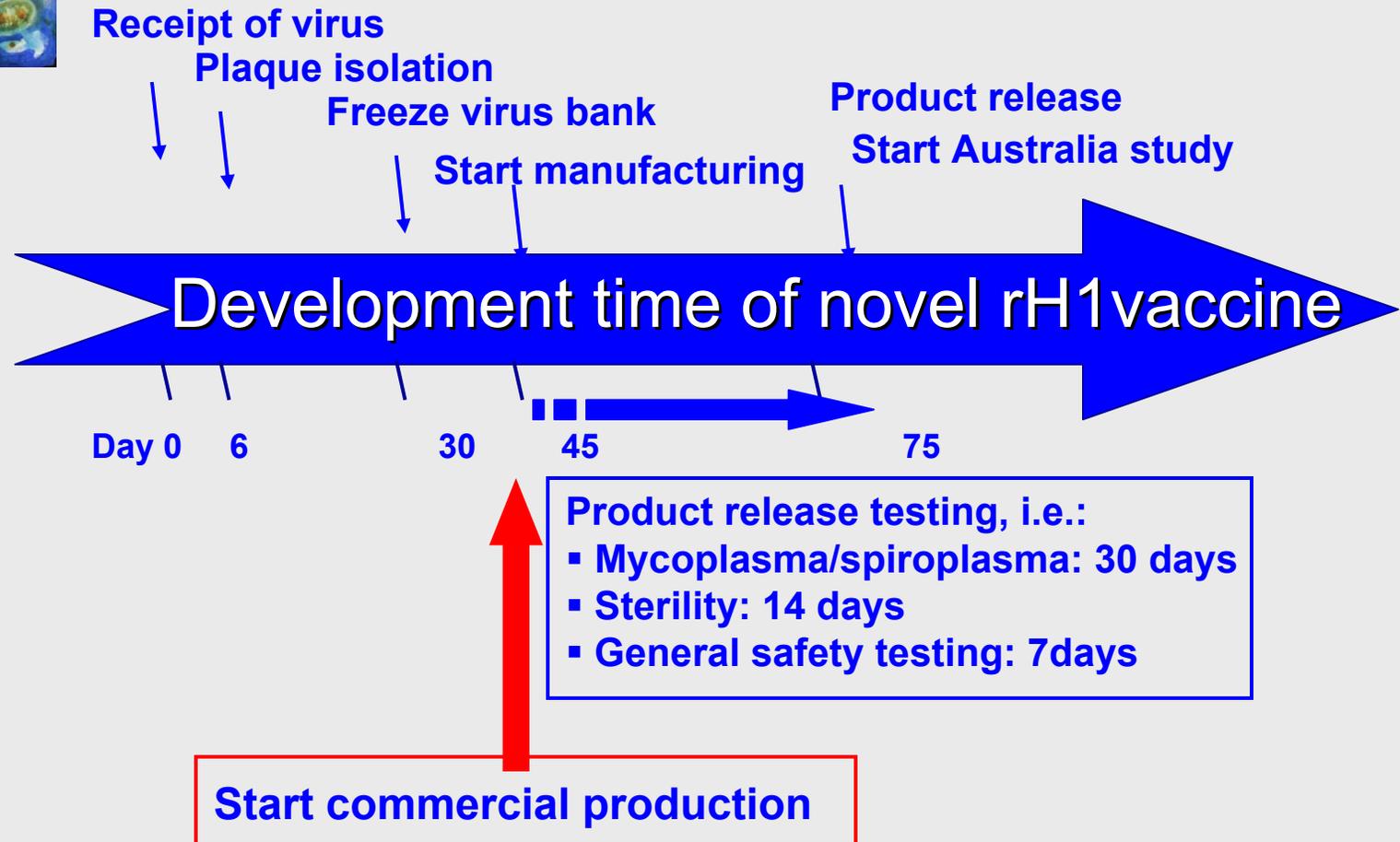
Serum Neutralizing (NT) Antibody Responses Following One or Two Doses of H5 Vaccine in Naïve Subjects or Following a Single Dose in H5 Vaccine-Primed Subjects

- 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



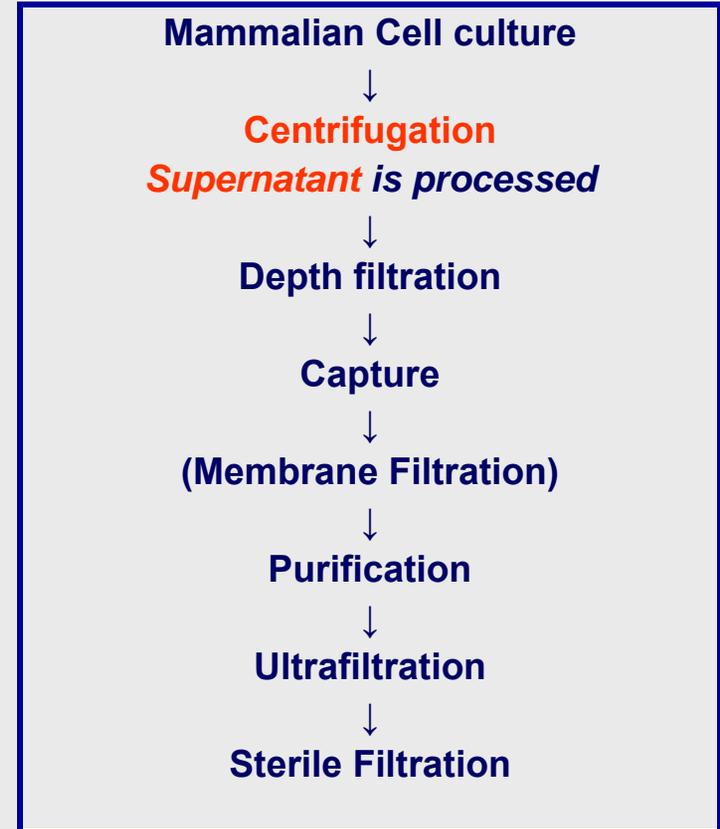
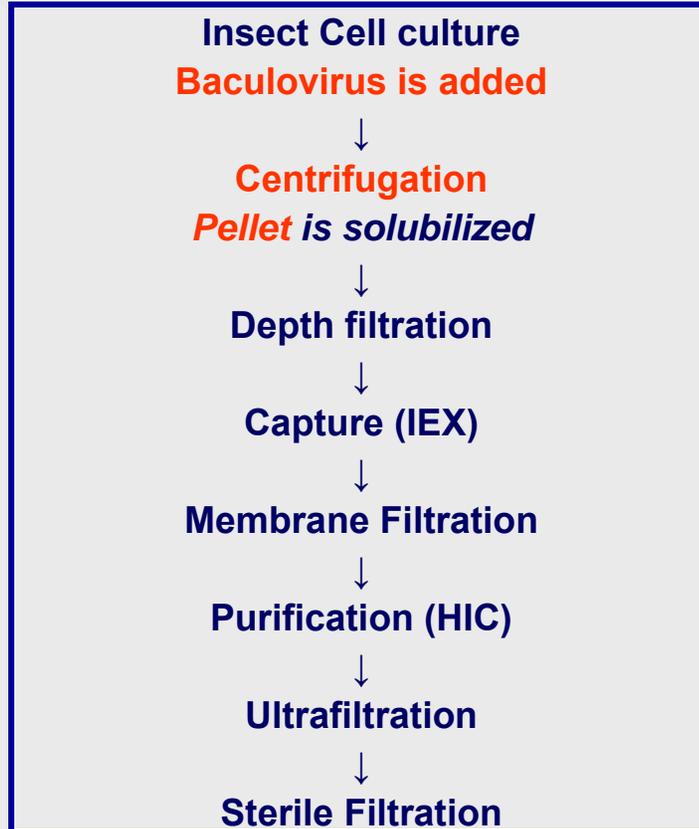


Implications for Pandemic Preparedness Development Timeline rH1 Vaccine





Pandemic Vaccine Production



- ❑ Worldwide capacity for cell culture is 2.5 M L
- ❑ 9M doses of 15µg/10,000L/5-days
- ❑ Billions of doses can be produced w.i. weeks

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



Final comments

- 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
 - FDA product approval
 - Scale-up manufacturing
 - Test vaccine in children
 - Alternative formulations (patch?)