

# **Workshop On New Technologies**

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# Why Are New Technologies Needed?

- Improved manufacturing
  - Safety
  - Speed
  - Capacity
  - Costs
  - Simplicity
- Alternative vaccine design and delivery
  - Enabling protective immunity
  - Capacity / costs
  - Logistics

# New Developments In Vaccine Production

- Alternative production systems: Influenza as example\*
  
- Classical split vaccine
  - Egg produced (1-3 doses/egg)
  - Issues
    - Egg supply
    - Surge capacity (existing production facilities)
    - Production speed
    - Facility size and costs

\* Rick Bright, PATH, USA

# Production systems for influenza vaccine

## Alternative 1

### Live attenuated influenza virus

- Approved products for seasonal flu
  - MedImmune (US) and IEM (Russia)
- 50-100 fold increase in yields
- Potential broader cross protection within subtype

### ➤ Issues

- Correlates of immunity/efficacy?
- Reduced efficacy in non-naïve adults
- Use in children and high risk groups limited
- Limited use in pre-pandemic settings (risk of reassortment)

# Production systems for influenza vaccine

## Alternative 2

### Production in mammalian tissue culture

- Approved products (Baxter, Solvay, Novartis)
- Issues
  - Capital costs and production costs
- Solutions
  - Disposable production and processing systems\*\*
    - WAVE replaces stainless steel fermenters and piping
    - Disposable columns etc...
- Economic analysis
  - Disposable fermentation process cost effective at all scales
  - Disposable process less cost effective at large scale

\*\* Catarina Flyborg, GE Healthcare, Sweden

# WAVE BIOREACTOR™



System 2/10



System 20/50



System 200



System 500/1000



# Production systems for influenza vaccine

## Alternative 3

- Production of VLPs in insect cells
  - Several players are developing technologies for antigen production
  - Speed of generation (12 weeks)
  - Currently in phase II (VLP, Novavax)
  - Most advanced alternative technology
  - Perceived as the only technology which will have an impact in next 5-10 years
- Production of VLPs using lentiviruses
  - Triple vector transduction of mammalian cells
  - VLPs collected in supernatant
- Production of VLPs in filamentous fungi
  - Production of antigen in culture medium

# Production systems for influenza vaccine

## Alternative 3

- Issues with (Influenza) VLP technologies
  - Early stage development
  - Low immunogenicity (adjuvants)
  - Regulatory hurdles for novel technologies
  - Safety (vectors, host cell components)
  - Funding

# Production systems for influenza vaccine

## Alternative 4

### Plants

- Tobacco plant based transient expression systems used for HA production (or VLPs)\*
  - Rapid biomass expansion
  - High yields
  - Limited immunogenicity/safety data
  - Applied to flu and malaria (transmission-blocking)
- Plant production also used for GMP production of anti-HBs antibodies\*\*
  - Stable expression in Tg *Nicotiana*
  - Used for production of HBs vaccine
  - Approved process

\* Yidadi Yusibov, Fraunhofer, USA

\*\* Merardo Pujol, CGEB, Cuba

# Main Flu New Technologies Messages

- Multiple solutions available
- Cost of vaccine not necessarily dependent on Ag production costs
- Only some new antigen production technologies will achieve impact
- Decision to invest into new production technology must take multiple parameters into account

# Challenges To Introducing New Technologies

## Disruptive technologies\*\*

- Disruptive technologies are *not* incremental or even radical improvements in conventional technologies. They bring completely new approaches that allow new products to emerge.
- DNA vaccination and needle free injection are example of disruptive technologies
- Multiple challenges associated with development of disruptive technologies
  - History full of new technologies which fail to be taken up
  - Success more frequently associated with introduction in niche markets followed by main stream

\*\* David Kaslow, Merck, USA

# DNA Vaccines

- The promise: Same technology used for different antigens (cheap and simple)
- Progress remains slow
- Three approved veterinary vaccines (horses, dogs and fish)
- In humans DNA performance remains insufficient
- Formulation critical to improve immunogenicity
- Choice of disease target is critical to permit introduction and uptake of this disruptive technology

# Viral Vectors

- Many viral vectors in development\*
  - Yellow fever virus vector for JE
    - Also dengue
  - Multiple poxvirus vectors
    - TB, malaria, HIV, influenza
  - New adenoviral vectors
    - HIV, malaria, TB
- Vectors traditionally used for T cell induction
  - But also useful for antibodies
- Prime-boost approaches with viral vectors enable induction of functional CD8 responses

\* Adrian Hill, Oxford, UK

# Viral Vectors

- Challenges
  - Safety and regulatory pathway
    - Many veterinary products licensed
    - Concern about STEP trial
  - Manufacturing scale-up
  - Efficacy of T cell inducing vaccines
    - HIV, TB, malaria
      - CD8 mediated protection in malaria phase IIa
  - Deployment of Prime-Boost Vaccines

# Virus-Like Particles

## VLPs\*\*

- Demonstrated clinical responses and immunogenicity (antibodies and T cells)
  - Therapeutic Hep B VLP Phase I-II (Bangladesh)
  - Therapeutic Hep C VLP Phase I (Canada)
  - Therapeutic HIV vaccine using HepB VLP platform (preclinical)
  - Dengue VLP (preclinical)
  - Cervix cancer vaccine VSSPs (Very Small Size Proteoliposomes)
  - Prostate cancer vaccines (GnRHm1-TT peptide / VSSP / Montanide ISA 51)

\*\* Gerardo Guillén, CGEB, Cuba

# Adjuvants

- “2009 is an excellent year for adjuvants” \*\*
  - Approval of adjuvanted pandemic vaccines (eg AS03 – FDA)
  - Cervarix (AS04) approval by FDA
  - Many adjuvants in mid to late development

## However:

- Disconnect between scientific evidence and public perception
- Adjuvants are needed for many new vaccines and communication to public must become an integral part of development pathway
- Audience suggested that communication on adjuvants should become topic of future vaccine conferences

\*\* Martin Friede, WHO, Switzerland

## Some New Adjuvants

| Class              | component     | phase 1   | phase II  | phase III | licensed           |
|--------------------|---------------|-----------|-----------|-----------|--------------------|
| TLR3               | Poly I:C      | cancer    |           |           |                    |
| TLR4               | MPL           | leish     | herpes    | malaria   | HPV, HBV           |
|                    | MPL           |           | pneumonia | cancer    | Allergy            |
|                    | RC530         | HIV       |           |           |                    |
|                    | GLA           | flu       |           |           |                    |
| TLR5               | flagellin     | influenza |           |           |                    |
| TLR7               | Imiquimod     |           | cancer    |           |                    |
| TLR8               | Resiquimod    |           | cancer    |           |                    |
| TLR9               | CpG, IC41     | influenza | Allergy   | HBV       |                    |
|                    |               | TB        | cancer    |           |                    |
| Saponins           | QS21          | pneumonia | cancer    | malaria   |                    |
|                    | QS21          | HIV       | Alzheimer |           |                    |
| O/W emulsion       | squalene      | HIV       | HBV, CMV  |           | Seasonal influenza |
|                    | tocopherol    |           |           |           | Pandemic influenza |
| W/O emulsion       | squalene      |           | malaria   |           |                    |
|                    | mineral oil   |           | cancer    |           |                    |
| Polysaccharides    | Inulin        | HBV, flu  |           |           |                    |
| Cationic liposomes | DDA           | TB        | influenza |           |                    |
| Virosomes          |               | malaria   |           |           | HAV, influenza     |
| poly-electrolytes  | Polyoxidonium |           |           |           | influenza          |

# Needle Free Delivery

- Development of needle free systems initiated by WHO and followed up by PATH
- Many studies under way to evaluate feasibility and usability
- ID delivery not as promising as initially perceived
- Exploring potential applications
- New needle free device supported by PATH\*

\* Darin Lee Zehrung, PATH, USA

# Conclusions

- Many new technologies are under development to enhance immunogenicity, production and delivery of vaccine candidates
- Challenges
  - scientific validity
  - manufacturing feasibility
  - regulatory approvability
  - public acceptability