

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