NVAC and the Future of Vaccinology

Stanley A. Plotkin
“The impact of vaccination on the health of the world’s peoples is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth.”

Influenza
Ways to Improve Efficacy of Influenza Vaccines

• Add second lineage of type B (done)
• High hemagglutinin dose (done)
• Adjuvants such as MF-59 or AS01 or flagellin
• Add neuraminidase
• Add conserved epitopes NP, M2e, stalk HA
• Prime-boost (DNA, RNA, vector)
• Conserved stem antigen
**Conservative thinking.** Unlike the head, the stem of the influenza viral spike tolerates little change and is the target of several bNAbs.
Stalk-based Approaches

or prime-boost, peptides, VLPs
Short Effector Memory:

Pertussis
The Pertussis Problem

- Pertussis is serious in newborns, milder but common later in life.
- Replacement of WcP by AcP has eliminated serious reactions, but disease is resurgent in many countries because immunity wanes after AcP.
## Incidence of Pertussis in Wisconsin after TdaP

<table>
<thead>
<tr>
<th>Years after TdaP</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>35%</td>
</tr>
<tr>
<td>≥</td>
<td>12%</td>
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Koepke et al, JID 2014
Possible Improvements of Acellular Pertussis Vaccines

• Use newer circulating strains containing P3 + Ptx promoter
• Add stronger adjuvant to stimulate Th1/Th17 and Tfh cellular responses
• Use genetically or H$_2$O$_2$ detoxified PT
• Add other virulence factors: e.g. adenylate cyclase, tracheal cytotoxin, LPS
• DNA prime, AcP boost
• Live, attenuated *B. pertussis*
Obtaining the Right Functional Response: HIV
Why was Thai Trial Successful?

• Induced antibody-dependent cellular cytotoxic antibody against V1-V2 loop of IgG3 Isotype

but

• Efficacy was high early after vaccination and in low-risk groups, but faded with time.
Importance of Non-Neutralizing Antibodies

• Influenza – Infection induces ADCC antibodies, TIV does not. ADCC antibodies are strain cross-reactive.

• Other examples of important nNAb: Sindbis, Dengue, Rotavirus, LCMV

Jegaskanda et al, J Virol 2013
Excler et al, ClinVacc Immunol 2014
What is the Way Forward for an HIV Vaccine?

- Induction of broadly neutralizing antibodies through envelope trimer structures
- Building on prime-boost ADCC induction with better vector/adjuvants
- Induction of effector CD8+ cells to kill first infected cells using CMV vectors
Population – Specific Challenges:

Rotavirus
Effect of Rotavirus Vaccination in the U.S.
Rotavirus Vaccine Efficacy Against Severe Disease in Tropical Countries

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Country</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV1</td>
<td>Brazil</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Malawi</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>77%</td>
</tr>
<tr>
<td>RV5</td>
<td>Nicaragua</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Kenya</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>65%</td>
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<tr>
<td></td>
<td>Viet Nam</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>Bangladesh</td>
<td>46%</td>
</tr>
</tbody>
</table>
Hurdles to Immunization for a Live Oral Rotavirus Vaccine

Factors that lower viral titer

- Breast milk
- Stomach acid
- Maternal antibodies
- OPV

Factors that impair immune response

- Malnutrition - Zn, Vit A
- Interfering microbes - viruses and bacteria
- Other infections - HIV, malaria, TBC
Importance of the Microbiome to Oral Vaccination

• Infections change morphology of the intestinal mucosa

• Antibiotics decreased rotavirus infection in mice but increased antibody responses
  (Uchiyama et al, J. Inf. Dis. 2014)

• Or call prior infections modify immune responses?
Uncertain Correlates of Protection: Dengue
# Efficacy of Chimeric Dengue Vaccine in Thailand - Phase 2 + 3

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>Phase 2 Efficacy (C.I.)</th>
<th>Phase 3 Efficacy (C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>35% (6.7-54)</td>
<td>57% (44-64)</td>
</tr>
<tr>
<td>1</td>
<td>61% (17-82)</td>
<td>50% (25-67)</td>
</tr>
<tr>
<td>2</td>
<td>3.5% (-60-41)</td>
<td>35% (-9-61)</td>
</tr>
<tr>
<td>3</td>
<td>82% (39-96)</td>
<td>78% (53-91)</td>
</tr>
<tr>
<td>4</td>
<td>90% (11-100)</td>
<td>75% (55-87)</td>
</tr>
</tbody>
</table>

Possible Explanations for Low Efficacy of Chimeric Dengue Vaccine

- Higher challenge dose of type 2, or strain variation therefore more antibodies needed
- Dengue Type 2 infects monocytes rapidly and antibody thus not effective
- T cell response also needed
- Type 2 replicates poorly and antibodies were heterotypic, not homotypic
- Envelope protein in chimera has different conformation than in virus (de Alwis et al, J Virol)
- Structure of virus produced at 37°C different from virus injected by the mosquito

(Rey et al, Nature 2013)
Antigens Needed for Protection Uncertain: Cytomegalovirus
Outcome of Exposure to Transplanted Kidney from a CMV-seropositive donor (D+) in Renal Transplant Recipients
Neutralizing antibody to gB

Vaccines, 0, 1, 6 mo

50% Protection

GMT for 118 seropositive controls
Sanofi-Pasteur gB/MF59 in Kidney or Liver Transplant Patients
Proportion of days that patients in the three subgroups at risk of CMV infection

HCMV Structure, HCMV Virions are Comprised of Three Major Layers

Antibodies Against the CMV gH/gL/UL128-131 Pentamer

• Comprise majority of neutralizing antibody in convalescent serum

• Early appearance in maternal infection correlates with protection against transmission to fetus
Ways Being Tried to Generate Responses to CMV Pentamer

- Replication – Defective Virus
- VLPs
- Soluble pentamer proteins
- Self-Amplifying RNA
- DNA - Plasmids
Value of Structural Biology:

RSV
Respiratory Syncytial Virus

• Number one respiratory infection of infants (0-2 yrs)
• Also, important in elderly
• Prior inactivated vaccine worsened disease because Fusion antigen was altered, leading to formation of immune complexes
• ? Need for “just right” antibody and CD8+ T cell responses
• Live viruses insufficiently attenuated
Fig. 4. Antigenic sites of hRSV F glycoprotein. The location of the different antigenic sites is shown in both the prefusion (a) and postfusion (b) conformation of hRSV F. Antigenic site III is delineated by a circle which includes residues identified by mutag...


**Structural, antigenic and immunogenic features of respiratory syncytial virus glycoproteins relevant for vaccine development.**

Melero JA¹, Mas V², McLellan JS³.
The Right T Cell Responses
T Cell Stimulating Vaccines

TB – Needed T cell response is polyfunctional and cytotoxic, such that it will kill infected macrophages

Malaria – Antibodies to circumsporozoite protein important, but T cell response needed to kill infected cells in the liver. May need other antigens
The Vaccine Industry
The BIG 5 Vaccine Manufacturers

- GlaxoSmithKline
- Merck
- Pfizer-Wyeth
- Pfizer
- Sanofi Pasteur

The BIG 4 Vaccine Manufacturers
## Smaller Market Share or Limited Range

<table>
<thead>
<tr>
<th>CSL</th>
<th>Astellas</th>
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<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Avant</td>
</tr>
<tr>
<td>MedImmune-AstraZeneca</td>
<td>Bioport</td>
</tr>
<tr>
<td>Serum Institute of India</td>
<td>Emergent</td>
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<td></td>
<td>ID Biomedical</td>
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<tr>
<td></td>
<td>Solvay</td>
</tr>
<tr>
<td></td>
<td>Statens Serum Inst.</td>
</tr>
<tr>
<td></td>
<td>Takeda</td>
</tr>
</tbody>
</table>
Producers Outside North America and Europe

- **Japanese Local Producers**: Biken, Takeda, Kitasato, Kaketsuken, Japan BCG
- **Indian Local Producers**: Panacea, Bharat, Shanta, Biological E., Indian Immunologicals, Zydus
- **Korean Local Producers**: Green Cross, LG
- **Latin American Local Producers**: Butantan, Fiocruz, Birmex, Bio-Manguinhos, Finlay Inst.
  - Biofarma [Indonesia]
  - Saovabha [Thailand]
  - Razi [Iran]
  - IVAC, Vabiotech [Viet Nam]
  - Microgen [Russia]
  - Sinovac + 46 different producers (China)
Projected Growth of the Vaccine Market by Adult And Pediatric Segments

$ Billions

Adult: 2010  23% , 2011 26% , 2012 27% , 2013  31% , 2014  34%
Pediatric: 2010  14% , 2011 16% , 2012 17% , 2013  20% , 2014  21%

Vaccine Fact Book, 2012
Pharma, page 53
Why is There an Increase in the Vaccine Market?

• New vaccines give higher profits

• Hib, Hepatitis B and Pneumococcal vaccines changed the paradigm of a “cheap” vaccine
Reasons Why Vaccine Manufacturers Launch a Development Program

1) Market

2) Market

3) Market

> 500 M $
How Market is Determined

1) Epidemiologic data
   e.g. Pneumococcal conjugate
2) Demand from consumers in developed countries
   e.g. Lyme Disease, Acellular Pertussis
3) Demand from authorities in developed countries
   e.g. Mening C
4) Expert opinion
   e.g. Mumps
5) Guesses, buttressed by precise but inaccurate data.
   e.g. Hepatitis B
Vaccine Development: a Long and Risky Journey
Technological, Resources and Regulatory Challenges

Product Development

<table>
<thead>
<tr>
<th>Research</th>
<th>Development (pre-clinical)</th>
<th>Clinical Development</th>
<th>Filing for License</th>
<th>Product Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 year</td>
<td>1-2 years</td>
<td>3-4 years</td>
</tr>
<tr>
<td>Probability of market entry (percent)</td>
<td>5</td>
<td>10</td>
<td>10-20</td>
<td>20-50</td>
</tr>
<tr>
<td>Costs (US$ m)</td>
<td>5 - 25</td>
<td>5 - 100</td>
<td>10 - 100</td>
<td>25 - 200</td>
</tr>
<tr>
<td>Time (years)</td>
<td>4 - 6</td>
<td>1 - 2</td>
<td>4 - 6</td>
<td>1</td>
</tr>
</tbody>
</table>
Meningococcal B Vaccine

• In 1990s, it appeared to be necessary to complement Mening A/C/W/Y
• In 1995, Novartis started project
• Conjugation of B capsule non-starter
• In 2000, Novartis discovered reverse vaccinology
• Mening B vaccine licensed in 2015
• Interest of ACIP had declined
• Breakthroughs come from academia and government, and now biotech

• Importance of “proof of concept”

• An approach is useless unless it can be scaled up (e.g. vectors)

• Mice lie, or at least exaggerate
Coalition for Epidemic Preparedness Innovations
“We consider an international vaccine-development fund to be urgently needed to provide the resources and the momentum to carry vaccines from their conception in academic and government laboratories and small biotechnology firms to development and licensure by industry.

This support would permit efficacy assessment to begin – and thereby avert a repetition of the Ebola crisis.”

Establishing a Global Vaccine-Development Fund.
Plotkin SA, Mahmoud AA, Farrar J.
Challenges

1. The pipeline is weak for most EIDs characterized by market failure

2. Unilateral, uncoordinated government efforts to fund R&D preparedness are inefficient and unsustainable in addressing global epidemic risks

3. Clinical & regulatory pathways are not easily adaptable to epidemic contexts

4. Incentives are lacking to motivate greater industry engagement
## Stages of Development

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Immunogenicity and safety in mice</td>
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<tr>
<td>Protection in relevant animal challenge model</td>
</tr>
<tr>
<td>GMP production, validation of methods – CEPI</td>
</tr>
<tr>
<td>Toxicity studies</td>
</tr>
<tr>
<td>Phase I</td>
</tr>
<tr>
<td>Phase IIa</td>
</tr>
<tr>
<td>Phase IIb – if possible</td>
</tr>
<tr>
<td>Stockpile</td>
</tr>
<tr>
<td>Conditional approval for emergencies – CEPI</td>
</tr>
<tr>
<td>Phase III</td>
</tr>
<tr>
<td>Licensure</td>
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</table>
CEPI process to date

CEPI startup phase: June 2016 – July 2017

- Adopted interim entity, CEO and secretariat
- Finalized strategic plan
- Finalized interim governance arrangements, including selection of BoD and SAC members
- Drafted CEPI preliminary business plan for first five years of operation (subject to revision)
- Chose targets: MERS, Lassa, Nipah
- Securing initial commitments and contributions for CEPI launch
- Davos, January 2017
- G7 Summit, May 2017
- G20 Summit, July 2017
What Should NVAC do for the Future of Vaccinology?

- Select and name important targets for vaccine development in the U.S.
- Promote development of new delivery systems such as intradermal, sublingual, electroporation
- Study personalized medicine: vaccinomics
- Urge USG support of CEPI for vaccine development against emerging diseases
### Product Development

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<tr>
<td>Probability of market entry (percent)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Cost (UW$m)</td>
<td>5-25</td>
<td>5-100</td>
</tr>
<tr>
<td>Time</td>
<td>4-6</td>
<td>1-2</td>
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### Clinical Development

<table>
<thead>
<tr>
<th></th>
<th>Phrase 1 1Year</th>
<th>Phrase 2 1-2 Years</th>
<th>Phrase 3 3-4 Years</th>
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</thead>
<tbody>
<tr>
<td>Probability of market entry (percent)</td>
<td>10-20</td>
<td>20-50</td>
<td>50-90</td>
</tr>
<tr>
<td>Cost (UW$m)</td>
<td>10-100</td>
<td>23-200</td>
<td>50-400</td>
</tr>
<tr>
<td>Time</td>
<td>4-6</td>
<td>4-6</td>
<td>4-6</td>
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### Filling For License vs. Product Submission

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<td>Probability of market entry (percent)</td>
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<tr>
<td>Cost (UW$m)</td>
<td>5-15</td>
<td>5-10</td>
</tr>
<tr>
<td>Time</td>
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<td>1</td>
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