Novel RSV Vaccines Under Development

Barney S. Graham, M.D., Ph.D.
Achievements and Future Challenges in the Surveillance of Respiratory Viruses
San Jose, Costa Rica
January 30, 2013
**RSV Genome Organization and Protein Functions**

**Nonstructural**
- NS1 (139)
  - inhibit Type I IFN induction
  - inhibit Type I IFN signaling
  - activate PI3K and NF-κB
  - inhibit apoptosis
- NS2 (124)

**Regulatory**
- M2-2 (90)
  - viral transcription ↓
  - RNA replication ↑
- M2-1 (194)
  - transcription processivity factor
- L (2165)
  - polymerase
- P (241)
  - phosphoprotein
- N (391)
  - RNA-binding

**Envelope Spikes**
- G (298)
  - attachment
  - neutralization and protective antigen
  - antibody decoy (secreted G)
  - fractalkine mimic
  - TLR antagonist
- F (574)
  - fusion and entry
  - neutralization and protective antigen
  - TLR4 agonist
- SH (64)
  - putative viroporin
  - inhibits apoptosis

**Inner Envelope Face**
- M (256)
  - assembly

**RNA Replication**
- M2-1 (194)
  - transcription processivity factor
- M2-2 (90)
  - viral transcription ↓
  - RNA replication ↑
Disease Severity is Greatest in Children <2.5 Months of Age

Boyce TG et al J Pediatr. 2000; 137:865

Biological challenges for vaccination

- Relatively weak induction of cellular responses
- Reduced capacity for somatic mutation of antibody
- Presence of maternal antibody
- Frequent reinfection
- Legacy of vaccine-enhanced disease
Biological Factors Associated with Difficult Vaccine Targets

• Infection is not easily controlled by natural immunity
  – High frequency of severe disease (filoviruses)
  – Persistent infection (HSV, HIV, HCV)
  – Reinfection is common (RSV, HIV)

• Alteration or evasion of host immune response
  – Interference with innate and adaptive immunity
  – Integration, sequestration, and immune sanctuaries

• Significant genetic variation or multiple serotypes
• Site of initial infection is major target organ for disease
• Animal models do no recapitulate pathogenesis of human disease
• Critical role for T cell-mediated immunity (HIV, HCV)
• Delay between infection and induction of cellular immunity (HCV)
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- Infection is not easily controlled by natural immunity
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Factors that Diminish Incentives for Industrial Vaccine Development

- Concern about safety
  - RSV

- Concern about achieving efficacy
  - HIV, RSV

- Sporadic or biodefense threats without a dependable commercial market
  - Ebola/Marburg
  - New emerging viral diseases
Factors that Diminish Incentives for Industrial Vaccine Development

• Concern about **safety**
  – RSV

• Concern about achieving **efficacy**
  – HIV, RSV

• Sporadic or biodefense threats without a dependable commercial market
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# Overview of RSV Vaccine Clinical Development

<table>
<thead>
<tr>
<th>No Efficacy – Serious Adverse Effects</th>
<th>No Efficacy – Inappropriate Immune Response</th>
<th>Low/No Efficacy – No Immediate Safety Concerns</th>
<th>Efficacy unknown – Currently in Clinical Testing</th>
<th>Efficacious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formalin-inactivated alum-precipitated whole virus</td>
<td>Subunit vaccine G protein – streptococcal conjugate</td>
<td>Subunit vaccine F glycoprotein in alum in adults</td>
<td>Live attenuated RSV nasally in children</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variables live attenuated RSV nasally in children</td>
<td>rA2cp248/404/1030/ΔSH ΔM2-2 Post-fusion F Rosettes</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Live virus vaccine delivered IM in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPIV-RSV live chimeric virus nasally</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FI-RSV Vaccine-Enhanced Disease

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>n</th>
<th>Infected (%)</th>
<th>Hospitalized (%)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI- RSV</td>
<td>31</td>
<td>20 (65)</td>
<td>16 (80)</td>
<td>2</td>
</tr>
<tr>
<td>FI-PIV-1</td>
<td>40</td>
<td>21 (53)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

Kim et al. Am J Epidemiol 1969;89:422
Correlates of FL-RSV Vaccine-Enhanced Illness

Properties to Avoid

• Antibodies with poor NT activity → Immune complex deposition
• CD4+ Th2-biased response → Allergic inflammation
### Options for Vaccine Evaluation

<table>
<thead>
<tr>
<th>Platforms</th>
<th>Antigens</th>
<th>Delivery</th>
<th>Target Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live-attenuated</td>
<td>F</td>
<td>Respiratory tract</td>
<td>Neonate (&lt;2 mo)</td>
</tr>
<tr>
<td>• RSV</td>
<td>G</td>
<td>Parenteral</td>
<td>Infants and children (&gt;6 mo)</td>
</tr>
<tr>
<td>• chimeric paramyxovirus vectors</td>
<td>SH</td>
<td>Other mucosal site</td>
<td>Siblings and parents of neonates</td>
</tr>
<tr>
<td>Gene-based vectors</td>
<td></td>
<td>Internal</td>
<td></td>
</tr>
<tr>
<td>• Nucleic acid – DNA or RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Replication defective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Replication competent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subunit or particle-based</td>
<td>Multiple</td>
<td></td>
<td>Young adult women</td>
</tr>
<tr>
<td>• Purified protein</td>
<td></td>
<td></td>
<td>• Pregnant women</td>
</tr>
<tr>
<td>• Virus-like particle</td>
<td></td>
<td></td>
<td>• Women of child-bearing age</td>
</tr>
<tr>
<td>• Virosome</td>
<td></td>
<td></td>
<td>Elderly (&gt;65 yr)</td>
</tr>
<tr>
<td>• Nanoparticle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peptides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-inactivated RSV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Considerations for Immunizing RSV-Naïve Infants

• Opportunity to prevent or delay first RSV infection
  – Reduced primary morbidity
  – Reduced childhood wheezing
• Opportunity to establish future immune response patterns (antibody specificity and T cell phenotype)
  – Improved immunity against reinfection
• Target age is critical
  – Peak age of hospitalization ~2.5 mo
  – ~50% of hospitalization occur >6 mo
  – If incidence is ~60% in first year, ~70% are RSV-naïve at 6 mo
## Selecting Target Age for Initiating Vaccination

<table>
<thead>
<tr>
<th></th>
<th>&lt;4 mo</th>
<th>&gt;6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic mutation</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Dendritic cell and APC maturation</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Clearance of maternally-derived antibody</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>No longer breast-feeding</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiosyncratic apnea and other rare adverse events</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Small airway size</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Relative Th2 bias</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Product</td>
<td>Sponsor</td>
<td>Type of Vaccine</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sanofi RSV vaccine</td>
<td>Sanofi</td>
<td>Subunit</td>
</tr>
<tr>
<td>BBG2na</td>
<td>Queen’s Univ Belfast</td>
<td>Subunit</td>
</tr>
<tr>
<td>MEDI-559</td>
<td>MedImmune</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td>MEDI-534</td>
<td>MedImmune</td>
<td>Live chimeric</td>
</tr>
<tr>
<td>MEDI ΔM2-2 &amp; others</td>
<td>NIAID +/- MedImmune</td>
<td>Live-attenuated</td>
</tr>
<tr>
<td>Novavax RSV</td>
<td>Novavax</td>
<td>Nanoparticle</td>
</tr>
<tr>
<td>Sendai-RSV chimera</td>
<td>St. Jude’s</td>
<td>Live chimeric</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td>Merck/Nobilon</td>
<td>Single-cycle</td>
</tr>
<tr>
<td>NanoBio RSV</td>
<td>Nanobio/Merck</td>
<td>Inactivated</td>
</tr>
<tr>
<td>MVA-BN RSV</td>
<td>Bavarian Nordic</td>
<td>Vector</td>
</tr>
<tr>
<td>GenVec RSV</td>
<td>GenVec</td>
<td>Vector</td>
</tr>
<tr>
<td>Universal RSV</td>
<td>Crucell/J&amp;J</td>
<td>Vector</td>
</tr>
<tr>
<td>RSV vac_Oka</td>
<td>Okairos</td>
<td>Vector</td>
</tr>
<tr>
<td>VEE-F</td>
<td>Alphavax</td>
<td>Vector</td>
</tr>
<tr>
<td>RNA replicon</td>
<td>Novartis</td>
<td>Vector-RNA</td>
</tr>
<tr>
<td>Mymetics RSV</td>
<td>Mymetics</td>
<td>VLP-Virosome</td>
</tr>
<tr>
<td>TechnoVax</td>
<td>Technovax</td>
<td>VLP</td>
</tr>
<tr>
<td>SynGem</td>
<td>Mucosis</td>
<td>VLP-lactococcus</td>
</tr>
<tr>
<td>RSV VLP Vac</td>
<td>LigoCyte</td>
<td>VLP</td>
</tr>
<tr>
<td>F protein</td>
<td>Novartis</td>
<td>Subunit</td>
</tr>
<tr>
<td>RSV vaccine</td>
<td>GSK</td>
<td>Subunit</td>
</tr>
<tr>
<td>AMV601 / RespiVac</td>
<td>Am’Vac</td>
<td>Subunit</td>
</tr>
<tr>
<td>PEV4</td>
<td>Pevion</td>
<td>Subunit</td>
</tr>
<tr>
<td>Epitope-scaffold</td>
<td>U. Wash/ TSRI)</td>
<td>Epitope-scaffold</td>
</tr>
<tr>
<td>SHE</td>
<td>Ghent/Immunovaccine</td>
<td>Subunit</td>
</tr>
<tr>
<td>T4-214</td>
<td>TI Pharma</td>
<td>Subunit</td>
</tr>
<tr>
<td>TWi RSV vaccine</td>
<td>TWi Biotech</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Sources: Company Website, Fierce Vaccines, RSV 2012 Symposium, Clinicaltrials.gov
## Comparing Product Concepts Based on Immunological Concepts

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Native F or G</th>
<th>MHC pathway</th>
<th>CD8 T cell induction</th>
<th>IL-4</th>
<th>Delivery route</th>
<th>Replication competence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-inactivated virus</td>
<td>-</td>
<td>II</td>
<td>-</td>
<td>++</td>
<td>IM</td>
<td>-</td>
</tr>
<tr>
<td>Protein subunits</td>
<td>++/-</td>
<td>II</td>
<td>-</td>
<td>+/-</td>
<td>IM</td>
<td>-</td>
</tr>
<tr>
<td>VLPs or virosomes</td>
<td>++</td>
<td>II +/- 1</td>
<td>+/-</td>
<td>-/+</td>
<td>IM</td>
<td>-</td>
</tr>
<tr>
<td>Vectors</td>
<td>++</td>
<td>1 &amp; II</td>
<td>++</td>
<td>-</td>
<td>IM or nasal</td>
<td>- or +</td>
</tr>
<tr>
<td>Naked DNA or RNA</td>
<td>++</td>
<td>1 &amp; II</td>
<td>+</td>
<td>-</td>
<td>IM</td>
<td>-</td>
</tr>
<tr>
<td>Recombinant, or chimeric viruses</td>
<td>++</td>
<td>1 &amp; II</td>
<td>+</td>
<td>-</td>
<td>nasal</td>
<td>+</td>
</tr>
<tr>
<td>WT or attenuated virus</td>
<td>++</td>
<td>1 &amp; II</td>
<td>+</td>
<td>-</td>
<td>nasal or IM</td>
<td>+</td>
</tr>
</tbody>
</table>
Passive Prophylaxis with Synagis

• Humanized mouse monoclonal antibody

• Monthly injections reduce hospitalizations by 50%

• Licensed for select high-risk infants

• Demonstrates neutralizing antibodies against the F glycoprotein are protective

Shane Storey, Nat Rev Drug Discovery (2010) 9, 15-16
Vaccine Antigen Selection: Rationale for Choosing F

Reasons for choosing F:
- Target of Synagis
- Higher sequence conservation than G
- Unlike G, F is absolutely required for virus entry
**Organization of RSV F Glycoprotein**

- Type I integral membrane protein essential for RSV entry and cell-to-cell fusion
- Primary target for neutralizing antibody.
- pH-independent class I viral fusion protein
- Multiple furin cleavage sites
- Two heptad repeat regions that form an anti-parallel six-helix bundle in post-fusion state.
- F1 has a cysteine-rich domain.

**Diagram Notes:**
- Unique to RSV
- Signal peptide
- Fusion peptide
- Heptad repeat
- Transmembrane domain
- Cysteine
- Disulfide bond
- N-linked glycosylation
- C-linked palmitylation
- Known or potential furin cleavage site
- Neutralizing antibody epitope
- Infection inhibiting peptide
New Technologies Have Made an RSV Vaccine Possible

Viral Vaccines

Major Conceptual and Technological Advances

Discovery of immunity

Cell culture

Molecular biology

Potential areas for new technical advances

Animal Models

B & T cell biology

Delivery devices

Genomics

Glycobiology

Informatics

Manufacturing

Nanobiology

Proteomics

Structural Biology

Vector biology

RSV ?
HPV
Rotavirus
Varicella
Japanese encephalitis
Hepatitis A
Hepatitis B
Rubella
Mumps
Adenovirus
Measles
Poliovirus
Influenza
Yellow fever
Rabies
Smallpox
Summary

• There is a robust pipeline of candidate RSV vaccines and antigen design is being facilitated by atomic structure

• We need RSV-devoted NGO involvement for advocacy, advancing candidates, and coordination of public-private partnerships

• Developing clinical trial infrastructure through North-South partnerships would facilitate clinical development

• The regulatory process will be facilitated if we avoid generic terms for new vaccine platforms and describe them by immunological and biophysical properties

• For RSV-naïve infants it may be best to achieve licensure first in children >6 mo of age
  – Expand safety database
  – Perform studies to evaluate herd (neonatal) immunity
  – Develop mathematical transmission models to refine timing and schedule for vaccination
  – Consider passive-active approaches
Viral Pathogenesis Laboratory

Sung-Han Kim, Syed Moin, Barney Graham, Kaitlyn Morabito, Azad Kumar, Kevin Graepel, Kayvon Modjarrad, Man Chen, Tracy Ruckwardt, Allison Malloy, Jason McLellan, Jie Liu, Erez Bar-Haim
Questions