RSV Vaccines in Clinical Trials

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Disclosures

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• Consultant on RSV Vaccine Development:
  – GenVec
  – GSK
  – Novartis
  – Novavax
RSV Vaccine Technology Landscape 2003

Live-Attenuated

Subunit
RSV Vaccine Technology Landscape 2013

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[http://sites.path.org/vaccinedevelopment/files/2012/12/RSV_vaccine_landscape_snapshot.pdf](http://sites.path.org/vaccinedevelopment/files/2012/12/RSV_vaccine_landscape_snapshot.pdf)

Updated: 10/11/12
Devising RSV Vaccines: What Do We Know? What are the Obstacles?

• **Immunity**
  – Natural infection provides durable protection against lower respiratory tract illness (LRI), but not against repeated infections or mild illness
  – Neutralizing antibody protects against LRI
  – Maternal antibody may suppress antibody response in early infancy

• **Epidemiology**
  – Heterogeneous at-risk population (infants, children <5, elderly)

• **Safety**
  – Enhanced disease must be avoided
Enhanced RSV Disease

- Formalin-inactivated RSV (FI-RSV) developed in the early 1960s
- Vaccine administered to RSV seropositive toddlers and RSV naive infants
- The vaccine did not harm the toddlers, but when the infants later encountered wild-type (live) RSV, they experienced severe (enhanced) disease. Two (ages 14 and 16 months) died.

Kapikian et al. Am J Epidemiol 1969;89:1699
Potentiation of RSV LRI following formalin inactivated vaccine

Adapted from Kim et al., Am J Epidemiol 89:422-434, 1969
Possible Mechanisms of Enhanced RSV Disease

- **Humoral:** induction of non-neutralizing antibodies\(^1\), impaired affinity maturation of antibodies\(^2\), deposition of immune complexes\(^3\)

- **Cellular:** Overstimulation of Th2 CD4+ T cells, poor induction of IFN\(_{\gamma}\)-producing Th1 cells, NK cells and CD8 T cells\(^4,5\)

Implications of Enhanced RSV Disease for Vaccine Development

• Animal models are imperfect. Preclinical studies cannot provide a complete assessment of the risk of enhanced disease from administration of non-replicating vaccines to RSV-naïve children.

• Replicating (live) RSV vaccines
  – Safest alternatives for active immunization of RSV-naïve populations
  – Live-attenuated RSV candidate vaccines have been administered to hundreds of RSV-naïve children and have never been associated with enhanced disease.¹

• Non-replicating (subunit) RSV vaccines
  – For passive immunization of infants and children via maternal immunization
  – For immunization of non-naïve populations (older children, pregnant women, elderly)

Active Immunization of Infants & Young Children: Live Attenuated Vaccines

- **Paramyxovirus vectors**
  - Chimeric B/HPIV3: MEDI 534
  - (Sendai-virus vectored RSV F)

- **Live-attenuated native RSV**
  - Empirically derived attenuating mutations
    - MEDI 559 and the codon-stabilized version, cps2
  - ‘Rational’ vaccine design
    - RSV MEDI ΔM2-2
    - (RSV ΔNS2Δ1313/1314L)
Vectored RSV Vaccine: MEDI-534 (rB/HPIV3/RSV F)

- Well-tolerated in infants and young children (n=49)
- Immune response to HPIV3 (100%) exceeded immune response to RSV (50%)¹
- Sequence analysis revealed changes in RSV F noncoding region and ORF yielding decreased RSV F expression²
- Relationship between RSV F instability and immune response being analyzed

2. Tang RS et al. RSV 2012 Abstract #38, Santa Fe, NM
rA2cp248/404/1030/ΔSH: RSV with Attenuating Point and Deletion Mutations

cold passage (cp), temperature sensitive (ts), and gene deletions ▲
Initial clinical experience with rA2cp248/404/1030/ΔSH

- Well tolerated in RSV-naïve infants and children; highly restricted in replication

- Neut Ab responses in children >6 months

- Neut Ab responses limited in infants, but replication of 2\textsuperscript{nd} vaccine dose restricted (marker of immune response)

- Genetic instability in 30\% of isolates:
  - 4 of 5 attenuating elements detected in all recovered virus
  - No increased illness in vaccinees

Current status of rA2cp248/404/1030/ΔSH

- **MEDI-559 (MedImmune)**
  - Phase I/II study in RSV-naïve infants and children <23 months completed (NCT00767416); analysis underway

- **cps2 (MedImmune/LID, NIAID)**
  - genetically stabilized version (positions 248 (831L[TTG]), 1030 (Y1321K)$^1$, and 1313)$^1$
  - clinical trials to begin Q2 2013

RSV MEDI ΔM2-2: novel rRSV deletion mutant (MedImmune/ LID, NIAID)

- M2-2 is an RNA regulatory factor
- Deletion of M2-2 results in:
  - decreased RNA replication
  - increased transcription and antigen expression\(^1\) (more Ag/ infectious virion)
- RSV MEDI ΔM2-2 is currently being evaluated in RSV-naïve infants and children (NCT 01459198)

Maternal RSV Immunization:
Subunit RSV Vaccines
RSV fusion (F) glycoprotein is the primary target for subunit vaccines

- Most neutralizing antibodies directed against RSV F
- Little antigenic variation in RSV F (unlike RSV G)
- Previously RSV F vaccine candidates (PFP-1,2,3; RSV F/G/M) did not induce high titers of neutralizing antibodies and/or were difficult to manufacture
Recent advances in understanding RSV F structure have guided vaccine development

- RSV F exists in a prefusion and postfusion state
- Prefusion F is not naturally stable
- Recent data from Novartis and NIAID, NIH indicate that postfusion RSV F contains certain neutralizing epitopes, including the palivizumab epitope
  \textsuperscript{1,2}
- Other studies indicate that most of the neutralizing antibody found in human sera (RSVIg) is directed toward prefusion RSV F

RSV F Nanoparticle Vaccine is Currently Being Evaluated in Clinical Trials

- Developed by Novavax
- Engineered RSV postfusion F expressed in baculovirus forms nanoparticles
- Preclinical studies in cotton rats showed protection against RSV challenge
- Phase I studies in healthy adults completed
- Phase II studies in women of childbearing age initiated

Glenn GM Vaccine 2013 31: 524-532

Novartis postfusion RSV F vaccine protective in preclinical trials

- Cotton rats immunized with postfusion RSV F trimer developed high titers of RSV neutralizing antibody and were protected against viral challenge
- Similar RSV F subunit vaccine is being developed for clinical trials

Summary: RSV F subunit vaccines

- New RSV postfusion F subunit vaccines are in clinical trials or about to be tested in clinical trials

- Clinical trials will determine:
  - Magnitude of antibody response
  - Duration of antibody response
  - Ability of RSV postfusion F subunit vaccines to induce neutralizing as well as non-neutralizing RSV F antibodies
Immunization Strategies for Pathogens of Infancy and Early Childhood

• **Tetanus:**
  – Maternal and infant immunization

• **Pertussis:**
  – Maternal and infant immunization

• **Influenza:**
  – Maternal and infant immunization

• **RSV:**
  – ???
RSV Vaccines: Global implementation questions

• Will the protection observed in wealthy countries also be observed in resource limited settings, where RSV exposure and disease may be influenced by
  – Crowding
  – Limited access to water
  – Indoor air pollution

• For maternal immunization, how will maternal illnesses affect transplacental transmission of antibody?
  – HIV
  – Placental malaria
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