RSV F Recombinant Nanoparticle Vaccine: Program Update, Maternal Immunization

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Agenda

- Target populations for an RSV vaccine
- Natural immunity due to RSV infection is relatively ineffectual, (Site II antibodies are effective )
- Novavax’ RSV F Recombinant Nanoparticle Vaccine
- Key preclinical & clinical data
- Maternal Immunization and implementation challenges
- Conclusions
Target Populations for an RSV Vaccine

- Young Infants Via Maternal Immunization
- Pediatric
- Elderly
The Very Young Receive the Mother’s RSV Antibodies Transplacentally but the Decades of Mother’s RSV Exposure Does not Evoke an Immune Response That is Highly Protective

Antibody Transfer

<table>
<thead>
<tr>
<th>RSV type</th>
<th>Serum source</th>
<th>GMT (log2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gambia</td>
<td>Houston</td>
<td></td>
</tr>
<tr>
<td>A Mothers</td>
<td>8.8 ± 1.3 (75)</td>
<td>8.8 ± 1.5 (106)</td>
<td>NS</td>
</tr>
<tr>
<td>Newborns</td>
<td>8.3 ± 1.4 (90)</td>
<td>8.8 ± 1.5 (106)</td>
<td>0.02</td>
</tr>
<tr>
<td>B Mothers</td>
<td>8.7 ± 1.4 (75)</td>
<td>7.9 ± 1.3 (106)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Newborns</td>
<td>8.7 ± 1.3 (83)</td>
<td>8.0 ± 1.6 (108)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Determined by the microneutralization test. Values are means ± standard deviations. Values in parentheses are n values.
* Differences between GMTs of mothers and newborns from The Gambia and those of mothers and newborns from Houston were determined with the two-tailed Student t test. NS, no significance.

Age of Hospitalization

Peak Hospitalization Rates when Maternal Antibodies are Near Peak

Average Number of RSV Hospitalizations By Age

Source: CDC, National Hospital Discharge Survey, 2005-2009

Suara et al., CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 1996, p. 477–479
6.4.2.1 Incidence of RSV Hospitalization

The incidence of RSV hospitalization in the MI-CP117 ITT population is presented in Table 6.4.2.1-1. The efficacy of motavizumab was confirmed, with motavizumab demonstrating a statistically significant 83% relative reduction in the incidence of RSV hospitalization (RR: 0.168, 95% CI: [0.086, 0.308]; p < 0.001) as compared to placebo.

<table>
<thead>
<tr>
<th>Table 6.4.2.1-1</th>
<th>MI-CP117: Incidence of RSV Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Placebo</td>
</tr>
<tr>
<td>ITT population</td>
<td>n/N (%)</td>
</tr>
<tr>
<td></td>
<td>39/472 (8.3%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Prespecified interim analysis alpha spending level was 0.032

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION
Natural Infection Induces Little Site II Antibody: Placebo and Day 0 Samples

Concordance slope w/o placebo = 1.08 (0.95–1.22)
RSV F Antigen: An Inviting Target

Budding RSV Virus

Attachment (G) Protein
Fusion (F) Protein

G Protein: highly variable

F Protein: highly conserved between serotypes

Frequency of Amino Acid Changes

Site II on the Fusion protein is the target of Palivizumab, is highly conserved from year to year and across isolates

RSV F Antigen: An Inviting Target

RSV F Antigen:

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Summary: Natural Infection vs. Promoting Site II Antibodies

• Natural infection induces only partially protective antibodies
• Exposure to wild-type RSV induces little Site II conformational binding antibody, i.e. is immunologically cryptic
• Site II is highly conserved, suggests involved in critical functions during pathogenesis
• Site II mAbs are known to block fusion
• Site II mAbs are highly effective at preventing clinically significant RSV disease
• Site II high affinity, or conformationally dependent, antibodies should also be protective
Novavax Vaccine Construct: 
Near Full Length, Recombinant F Protein

Smith, et al. 2012. PLOS. 7(11), e50852
RSV F Nanoparticle Vaccine Technology

- Purified, recombinant near-full-length RSV F fusion glycoprotein trimers
- Trimers spontaneously assemble into 40-60 nm nanoparticle structures
- Present neutralizing sites such as Site II, palivizumab binding site, in a multimeric format

RSV F Recombinant Protein Nanoparticles

Near Full Length, Recombinant RSV F

RSV F trimer

McLellan JS

RSV F Nanoparticle
Summary of Clinical Studies

- **Study 101**: Safety and immunogenicity in healthy adults (n=120)
  - Stimulated robust immune responses
  - Induced production of palivizumab-competing antibodies

- **Study M201**: Safety and immunogenicity, WOCBA (n=330)
  - Confirmation of safety and immunogenicity in target population

- **Study M202**: Safety dose finding in women of childbearing age (n=720)
  - Selection of dose and schedule for pregnant women

- **Study M203**: Safety and immunogenicity in 3rd trimester women infants
  - Active immunization of mothers, safety, transplacental antibody transfer and half life
    - **Ongoing**

- **Planned Study M301**: Global Multi-Season Efficacy Trial
  - Immunization of Third Trimester Women
  - Prevention of Severe RSV disease in Infants
Clinical Immunological Assays

- RSV anti-F IgG
- Palivizumab-competitive ELISA
- Neutralizing antibodies
  - RSV-A
  - RSV-B

Anti-F IgG Responses are Robust, Durable After Immunization

M201, Women of Childbearing Age
Induction of Palivizumab Competing Antibodies
M202, Women of Childbearing Age

- PCA levels at 400μg/ml, potential for placental concentration effect
- Palivizumab efficacious with trough levels of 30μg/ml in controlled trials
- PCA “Near absence” suggests that the site is immunologically cryptic, important to reinfection

**European Summary Basis for Approval**

**Near-Absence of PCA**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>responders</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>Group B</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Group C</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>Group D</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Group E</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>Group F</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>Group G</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>Group A</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Two-dose, 60μg</td>
<td>110</td>
<td>77</td>
</tr>
<tr>
<td>One-dose, 120μg</td>
<td>130</td>
<td>80</td>
</tr>
</tbody>
</table>

*~400μg/ml*
Concordance Between Increased Anti-F and PCA After Vaccination

- The general population has little or no measurable palivizumab competing antibodies (PCA) from natural infection
- Post-vaccination Anti-F IgG and PCA track closely
Immunization with RSV F Nanoparticle Vaccine Induces Neutralizing Antibodies

- Groups are pooled to show overall impact of alum adjuvant at Day 28.
- Peak GMT $\log_2$ 10.0-10.5
- Rise in MN proportional to rise in pali-like antibodies
Subjects with the Lowest Baseline MN Titers Benefit the Most

RSV/A Microneutralization Titer Response After One Dose: Effect of Baseline Titer and Presence of Adjuvant

- Unadjuvanted
- Adjuvanted

numbers = N for the group analyzed
Maternal Transfer of Vaccine Related Antibodies: Highly Effective Strategy

- **Active transport of mother’s antibodies into baby’s circulation**
  - Mother’s antibodies from past infections or immunization are actively concentrated
  - Begins at 20th week of gestation.
  - At full term baby has >100% of mother’s antibody levels.

- **Concentration effect can be quite large**
  - Tetanus abs >160% of mothers level

- **Current immunization practice**
  - Neonatal tetanus, WHO campaign, all WCBA
  - Influenza-any gestational age
  - Pertussis in US/UK-3rd trimester

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Mother’s Blood  |  Baby’s Blood

**Placental Fc Receptors and the Transfer of Maternal IgG**
### Table 2

Transplacental transport ratios.

<table>
<thead>
<tr>
<th></th>
<th>Preterm &lt;32 weeks</th>
<th>Preterm &lt;37 weeks</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linder [32]</td>
<td>0.89</td>
<td>1.51</td>
<td>1.44</td>
</tr>
<tr>
<td>Wesumeruma [31]</td>
<td>0.62</td>
<td></td>
<td>2.03</td>
</tr>
<tr>
<td>Okoko [30]</td>
<td></td>
<td></td>
<td>1.01</td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linder [20]</td>
<td>0.4(^a)</td>
<td>0.92</td>
<td>1.14</td>
</tr>
<tr>
<td>Wesumeruma [31]</td>
<td>0.96</td>
<td></td>
<td>1.52</td>
</tr>
<tr>
<td>Okoko [30]</td>
<td>0.75</td>
<td></td>
<td>1.36</td>
</tr>
<tr>
<td><strong>Hib</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Berg [25]</td>
<td>0.26</td>
<td>0.58</td>
<td>0.74</td>
</tr>
<tr>
<td>Wesumeruma [31]</td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Okoko [29]</td>
<td>0.4</td>
<td></td>
<td>1.14</td>
</tr>
<tr>
<td><strong>Difteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Berg [25]</td>
<td>0.53</td>
<td>1.03</td>
<td>1.18</td>
</tr>
<tr>
<td>Wesumeruma [31]</td>
<td></td>
<td></td>
<td>2.39</td>
</tr>
<tr>
<td>Okoko [30]</td>
<td>0.72</td>
<td></td>
<td>1.43</td>
</tr>
<tr>
<td><strong>Tetanus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Berg [25]</td>
<td>0.86</td>
<td>1.13</td>
<td>1.89</td>
</tr>
<tr>
<td>Wesumeruma [31]</td>
<td></td>
<td></td>
<td>1.33</td>
</tr>
<tr>
<td>Okoko [30]</td>
<td>0.86</td>
<td></td>
<td>1.79</td>
</tr>
</tbody>
</table>

Transplacental transport ratios are defined as the ratio between infant to maternal serum samples.

\(^a\) GA <28 weeks.
Guinea Pig Model of Transplacental Transport: Antibody Transfer as Measured by anti F IgG, Neutralization and PCA

**Figure 2: Anti-RSV F IgG Titers**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RSV F</th>
<th>RSV F + AlPO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sow</td>
<td>10³</td>
<td>10⁴</td>
<td>222%</td>
</tr>
<tr>
<td>Pup</td>
<td>10³</td>
<td>10⁴</td>
<td>306%</td>
</tr>
</tbody>
</table>

**Figure 3: PCA Titers**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RSV F</th>
<th>RSV F + AlPO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sow</td>
<td>10³</td>
<td>10⁴</td>
<td>156%</td>
</tr>
<tr>
<td>Pup</td>
<td>10³</td>
<td>10⁴</td>
<td>209%</td>
</tr>
</tbody>
</table>

**Figure 4: RSV/A Neutralizing Titers**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RSV F</th>
<th>RSV F + AlPO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sow</td>
<td>10³</td>
<td>10⁴</td>
<td>166%</td>
</tr>
<tr>
<td>Pup</td>
<td>10³</td>
<td>10⁴</td>
<td>219%</td>
</tr>
</tbody>
</table>

Immune Responses in Sows (n=8-9) and Pups (n=14-17) on the day of delivery: Anti-RSV F IgG Titers (Figure 2) and Palivizumab competing antibody (PCA) (Figure 3) were determined by ELISA and reported as GMT with 95% CI. Neutralizing antibody titers against RSV-A2 (Figure 4) were determined by plaque assay and expressed as GMT with 95% CI. Number on histograms indicate the percent antibody transfer.
PCA Responses in Women of Childbearing Age: Implications for Coverage of Infants Born at Different Gestational Ages

CDC Birth Frequencies by Gestational Week Data

U.S. Births (in thousands)

- > 90% of Births

* PCA = Palivizumab-Competing Antibodies
PCA Responses in Women of Childbearing Age: Implications for Coverage of Infants Born at Different Gestational Ages

CDC Birth Frequencies by Gestational Week Data

U.S. Births (in thousands)

- Peak Transplacental Antibody Transfer
- > 90% of Births

All Births

* PCA = Palivizumab-Competing Antibodies
PCA Responses in Women of Childbearing Age: Coverage of Infants Born at Different Gestational Ages

Palivizumab Competing Antibody Kinetic Curve for Single Dose Aligned Over CDC Birth Frequencies by Gestational Week Data

- Palivizumab Protective at = 25-30 µg/mL
- > 90% of Births
- Peak Transplacental Antibody Transfer

Third trimester Immunization

* PCA = Palivizumab-Competing Antibodies
Modeling Effect of PCA via Maternal Immunization: Potential for Clinical Benefit for Infants Up to 6 months?

"Protection"*
M203 in Pregnant Women, 3rd Trimester, FSI Q4 2014
• Randomized, placebo-controlled, n=50 (1:1)
• Safety of mothers and their infants through an RSV season
• Maternal antibody transfer to infants
• Antibody kinetics in infants up to 6 months

M301 Efficacy in M301 P3, 3rd Trimester (FSI Q4 2015)
• Efficacy: Prevention of severe RSV + LRTI in infants
• Multi-season global study in Northern and Southern Hemisphere
• Identification of a correlate of risk
• RSV Maternal Program Supported by PATH
Maternal Vaccination: Understanding the Challenges of Implementation

• Precedent exists (Tdap, influenza), yet implementation remains poor or modest in many countries

• Aim to understand determinants of uptake
  – Lack of safety and effectiveness data in pregnant women?
  – Widely held misconception that less medical intervention during a pregnancy is better for the fetus?
  – Practical barriers such as a lack of infrastructure for storing vaccines in antenatal clinics?

• Unique challenges for RSV?
  – Educating the Obstetrician
  – Disease/ Vaccination awareness campaigns
  – Epidemiology of RSV disease in pregnant women
Conclusions

• A near full-length recombinant nanoparticle is intrinsically a desirable antigen and presents neutralizing sites in a multimeric format to the immune system
• The RSV F nanoparticle may bridge the gap in maternally acquired infant immunity and provide protection
• The vaccine induces high levels of palivizumab competing antibodies and neutralizing antibodies at levels expected to confer protection
• Natural infection induces only very low levels of PCA, potentially explaining why natural immunity is not fully protective
• Further development of the vaccine is warranted
Gratitude for the Extended Team

Discovery
Gale Smith, Mike Massare, Ye Liu, David Flyer, Yingyung Wu, Hanxin Liu

Clinical/Regulatory/Project Management
Louis Fries, D. Nigel Thomas, Allison August, Eloi Kpamegan, Judy Wen, Dewal Jani, Somia Hickman, Matt Lawlor, Amy Fix, Kathleen Callahan, and Gregory Glenn.

Academic Collaborators and Investigators: Drs. JoAnne Langely, Pedro Piedra, Flor Munoz, Geeta Swamy, Richard Beigi, Mark Steinhoff, Kevin Ault, Keith Vrbicky

In Collaboration with PATH:
Our Thanks to : Deborah Higgins, Cheryl Keech, John Donnelly, Catherine Hennings, Margaret Wecker, Jorge Flores, Tamra Madenwald
Preterm Births by Gestational Age
(2012, Save the Children, March of Dimes, WHO)

Figure 1: Preterm births by gestational age and region for 2010

- Preterm births <28 weeks
- Preterm births 28 to <32 weeks
- Preterm 32 to <37 weeks

Preterm birth by the numbers:
- 15 million preterm births every year and rising
- 1.1 million babies die from preterm birth complications
- 5-18% is the range of preterm birth rates across 184 countries of the world
- >80% of preterm births occur between 32-37 weeks of gestation and most of these babies can survive with essential newborn care
- >75% of deaths of preterm births can be prevented without intensive care
- 7 countries have halved their numbers of deaths due to preterm birth in the last 10 years

Based on Millennium Development Goal regions.
Source: Illencwe et al National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications
Palivizumab-Competitive ELISA: Assay Methodology