RSV F Nanoparticle Vaccine: Biological Rationale, Summary of the Clinical Data and Path Forward

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SVP, Research and Development
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Topics

• Target Populations for an RSV Vaccine
• The relative ineffectiveness of naturally induced immunity
• The Fusion protein in viral pathogenesis and as a “universal” vaccine
• The safety and efficacy of palivizumab and motavizumab provide important insights for RSV vaccine development
• Cotton rats as an in-vivo model for vaccine efficacy predicted palivizumab and motavizumab efficacy
• Summary of clinical trial data: the vaccine induces palivizumab-like antibodies (PCA), natural infection does not
• Clinical trial status and plans forward
  • Maternal immunization
  • Elderly and high risk adults
Target Populations for an RSV Vaccine

**Young Infants Via Maternal Immunization**

Provide protection for infants younger than six months and most at risk of serious RSV disease, prevent hospitalization, medical care and ongoing wheezing.

**Pediatric**

Decrease respiratory disease burden in children, prevent medical care and ongoing wheezing.

**Elderly**

Mitigate RSV disease burden that results from waning immunity and immunosenescence, prevent hospitalization and death.
Respiratory Syncytial Virus (RSV) in Infants

- Most common cause of infant LRTI Globally
  - Mortality exceeded only by Pneumo, HiB, and highest in LDCs\(^1\)

- Most frequent cause of infant hospitalization
  - 132,000–172,000 US hospitalizations annually \(^2\)

- Severe disease appears to lead to ongoing wheezing
  - Associated with recurrent wheezing for years \(^3\)

- Prophylaxis with palivizumab and motavizumab shown to reduce disease and medical care in in 5 randomized clinical trials

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2. MMWR , 2013, 263:141
RSV: A Predictable Epidemic

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0090515
Maternal Antibody Transfer

Active transport of mother’s antibodies into baby’s blood
- Mother’s antibodies from past infections and vaccines
- At full term baby has >100% of mother’s antibody levels.

Antibodies from natural RSV infection of mothers over decades are actively transported to infants blood

Physiologic mechanism for protecting the infants, assuming the antibodies are effective

Peak at term, relative concentration
Newborns 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**

**Age of Hospitalization**

Suara et al., CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 1996, p. 477–479
RSV Disease-Immune Responses to Infection are Inadequate

• RSV infections induce a robust immune response

• Infants who receive maternal antibodies are vulnerable
  – Maternal antibodies have developed from several decades of exposure
  – Maternal antibodies are neutralizing, high titer
  – Very high antibody titers are protective (Respigam, seroepidemiology)

• Immune responses are directed to both the F and G proteins
  – G drives strain changes
  – F is more conserved across strains and are ubiquitous
  – At the point where infants have the highest levels of F antibodies, they are vulnerable to severe disease

• Recurrent infections are the norm

• Common theme is viral infections: immune responses to infection are partially or not protective

• Site II on the F protein is clinically validated in randomized clinical trials (safety and efficacy)
The Changing Virus: Search for a “Universal” Vaccine

RSV Surface Glycoproteins
- Attachment Protein (G)
- Fusion Protein (F)

Frequency of Amino Acid Changes
In Glycoproteins G and F

Strain changes due to the G protein variability

The Fusion (F) protein changes less

Site II on the Fusion protein does not change in nature, is the target of Palivizumab

In Glycoproteins G and F:

- G F

- Frequency of Amino Acid Changes in G and F

- Substitutions per site

- Amino Acid residues

- Frequency of amino acid changes:
  - G: 6%
  - F: 8-10%
  - Site II (F): 6-9%
  - Attachment Protein (G): 6-9%
  - Fusion Protein (F): 5-6%

- Site II on the Fusion protein does not change in nature, is the target of Palivizumab
Efficacy in Term Infants: Effects of Site II Binding by Monoclonal Antibodies (Motavizumab)

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>Population</th>
<th>Placebo</th>
<th>Motavizumab</th>
<th>Fisher’s Exact Test p-value(^a)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>39/472 (8.3%)</td>
<td>13/938 (1.4%)</td>
<td>&lt; 0.001</td>
<td>0.168</td>
<td>(0.086, 0.308)</td>
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</table>

\(^a\) Prespecified interim analysis alpha spending level was 0.032

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION
RSV F Nanoparticle Vaccine: A Near Full Length, Stabilized F Protein

- Purified RSV F forms nanoparticles comprising multiple F protein trimers in hydrophobic interactions
- Deletions stabilize the F protein
- Preserve antigenic Site II, other ‘neutralizing’ sites

Smith, et al. 2012. PLOS. 7(11), e50852
F Protein Nanoparticle Vaccine Displays Site II: Palivizumab Binding

- Palivizumab binds avidly to the F protein nanoparticle vaccine

Antigenic site II: Amino acids 254-278
NSELLSLINDMPITNDQKKLMSNNV

**Cotton Rat as a Model of Protection Against RSV: IG**

**Comparison of Antibody Concentrations and Protective Activity of Respiratory Syncytial Virus Immune Globulin and Conventional Immune Globulin**

George R. Siber, Donna Leombruno, Jeanne Leszczynski, James McIver, Dinah Bodkin,* René Genin,* Claudette M. Thompson, Edward E. Walsh, Pedro A. Piedra, Val G. Hemmings, and Gregory A. Prince

Competitive inhibition of A549 syncytium formation and A549 cytopathic effect on day 3 is shown in Figure 2. Points represent the mean results of triplicate wells from a single experiment. Each symbol represents an individual rat. The peak challenge RSV concentration recovered from lung homogenates (A) or nose tissue homogenates (B) 4 days after challenge was 10,000 plaque forming units (PU) per ml. The lung and nasal RSV challenge concentrations were 10,000 and 1000, respectively. The plateau for each group was determined by adjusting the RSV infection dose on day 1 to achieve a low, medium, or high concentration of RSV at the peak challenge. The antibody concentrations at the time of peak challenge for the RSVIG-preimmunized rats were 1:1000 for lung and 1:500 for nasal. The antibody concentrations at the time of peak challenge for the RSVIG-preimmunized rats were 1:1000 for lung and 1:500 for nasal.

**RSV challenge/passive immunization with RSVIG**
- 99% lung reduction at PRNT 390
- 99% nasal titer reduction at PRNT 3500

Preclinical Basis for Respigam

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*Figure 2. Relationship between serum RSV titer by complement-enhanced plaque-reduction neutralization at time of challenge and RSV concentrations recovered from lung homogenates (A) or nose tissue homogenates (B) 4 days after challenge.*
Preclinical Basis for clinical evaluation of palivizumab

Protective level 25-30 µg/ml

Johnson, s. et al. JID, 176:1215-1223
Palivizumab Competing Antibody (PCA)

### Geometric Mean (µg/ml)

<table>
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<th>Group</th>
<th>Geometric Mean</th>
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<tr>
<td>FI-RSV 1/25 Lot 100</td>
<td>&lt;10</td>
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<tr>
<td>RSV-Infection 10E5 pfu</td>
<td>24</td>
</tr>
<tr>
<td>RSV F-Alum 30 µg</td>
<td>884</td>
</tr>
<tr>
<td>RSV F 30 µg</td>
<td>100</td>
</tr>
<tr>
<td>Placebo</td>
<td>&lt;10</td>
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<tr>
<td>Pali- Passive 15mg/kg</td>
<td>84</td>
</tr>
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</table>

### Competitive Inhibition 50% GMT (log2)

- Day 49 Pre-challenge
  - LLOQ: 84 µg/ml
  - 884 µg/ml
RSV A Neutralizing and Fusion Inhibiting Antibody

<table>
<thead>
<tr>
<th></th>
<th>FI-RSV</th>
<th>RSV-Infection</th>
<th>RSV F-Alum</th>
<th>RSV F</th>
<th>Placebo</th>
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<td>Neut-GMT</td>
<td>&lt;10</td>
<td>73</td>
<td>452</td>
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<td>&lt;10</td>
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<td>FI-GMT</td>
<td>&lt;10</td>
<td>95</td>
<td>697</td>
<td>51</td>
<td>&lt;10</td>
<td>320</td>
</tr>
</tbody>
</table>
An insect cell derived respiratory syncytial virus (RSV) F nanoparticle vaccine induces antigenic site II antibodies and protects against RSV challenge in cotton rats by active and passive immunization

Rama Raghunandan*, Hanxin Lu, Bin Zhou, Mimi Guebre Xabier, Michael J. Massare, David C. Flyer, Louis F. Fries, Gale E. Smith, Gregory M. Glenn

Novavax Inc., 20 Firstfield Road, Gaithersburg MD 20878, United States
RSV F Nanoparticle Vaccine Induces Antibodies Competitive with other Neutralizing mAb Sites on the F Protein

Cotton rat sera pooled from day 49 samples were used to compete site I, (1243) II, (1107, 1153) IV,V,VI (1112,1269) mAb in a competitive ELISA. Log$_2$ titers from 50% inhibition.

*mAb provided by Judy Beeler*
Target Populations for an RSV Vaccine

Young Infants via Maternal Immunization

Provide protection for infants younger than six months and most at risk of serious RSV disease, prevent hospitalization, medical care, wheezing

Pediatric

Decrease respiratory disease burden in children, prevent medical care, wheezing

Elderly

Mitigate RSV disease burden that results from waning immunity and immunosenescence, prevent hospitalization and death
Summary of Clinical Studies to Date

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

- **Study E101:** Safety and Immunogenicity and dose finding in Elderly Adults
  - Safety, dose selection

- **Study E201:** Safety, epidemiology and efficacy in Elderly Adults
  - Define attack rate, Vaccine efficacy
  - Enrolled

- **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
  - Enrolled
Study 201: Anti-F IgG in Women of Childbearing Age

- 2 dose, alum adjuvanted vaccines induced the highest titer
- ~15 fold higher than naturally induced F antibodies
Vaccine Immunity: Amplifying the Near Absence of Palivizumab Competing Antibodies

- Evaluated one 120 ug or two 60 ug dose regimen, with descending doses of AlPO4
- PCA levels ~400μg/ml in single dose 120ug F antigen/0.4 mg aluminum phosphate
- Day 0 PCA “Near absence” suggests that the site is immunologically cryptic, may be an important factor in reinfection
Protection via transplacental transport of mother’s antibodies into baby’s blood is effective:

- WHO global campaign to eliminate neonatal tetanus: 92% reduction
- CDC recommends Tdap vaccine in 3rd trimester of every pregnancy\(^1\)
- Seasonal flu vaccine recommended at any time during pregnancy
- RSV vaccine induced antibodies will be transferred; how will this determine the dosing regimen in women

Source: \(^1\)CDC: www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.html
PCA Responses in Women of Childbearing Age: Coverage of Infants Born at Different Gestational Ages

**PCA** Kinetic Curve for Single Dose (120µg RSV-F + 0.4 mg Al) Aligned Over CDC Birth Frequencies by Gestational Week Data

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

*PCA* = Palivizumab-Competing Antibodies
Modeling Effect of PCA via Maternal Immunization: Potential for Clinical Benefit for infants up to 5-6 months?

![Graph showing the decrease in Palivizumab-like antibodies over time with indications of "Protection". The graph includes lines for GMT, UCI 95%, LCI 95%, and a Baseline.]
Shifts in RSV/A MN Titer at Day 28

- 1- and 2-dose groups are pooled (identical at Day 28)
- 60 and 90µg groups are pooled to show overall impact of alum adjuvant at Day 28
- Peak GMT log$_2$ 10.0-10.5
Women with Lowest Baseline MN Titers Show the Greatest Increase in MN Titers
On (Ka) and Off (Kd) Measurements: Representative RSV F Binding Curves

Palivizumab
KD = 0.95E-10

Vaccinee day 30; ID 1112
KD = 2.29E-12
## Anti-F IgG Avidity Measurements: RSV Nanoparticle Vaccinees (60µg + AdjuPhos)

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>KD</th>
<th>Anti F EU*</th>
<th>Titer</th>
<th>Palivizumab-like IgG Titer</th>
<th>KD</th>
<th>Anti F EU*</th>
<th>Palivizumab-like IgG Titer</th>
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<tr>
<td>1104</td>
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<td>4,249</td>
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<td>Palivizumab</td>
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</table>

*Vaccine induced antibody binding affinity similar to Motavizumab*
Target Populations for an RSV Vaccine

- **Young Infants via Maternal Immunization**
  - Provide protection for infants younger than six months and most at risk of serious RSV disease, prevent hospitalization, medical care, wheezing.

- **Pediatric**
  - Decrease respiratory disease burden in children, prevent medical care, wheezing.

- **Elderly**
  - Mitigate RSV disease burden that results from waning immunity and immunosenescence, prevent hospitalization and death.
• **M203 in Pregnant Women, 3rd Trimester, FSI Q4 2014**
  – Randomized, observer-blinded, placebo-controlled
  – Intramuscular with vaccine in third trimester women
  – Safety of mothers and their infants through an RSV season, U.S. IND
  – Prospective F/U for RSV disease over a season
  – Maternal antibody transfer to infants
  – Antibody half-life in infants up to 6 months
  – All subjects followed for 1 year

• **M301 Efficacy in Pregnant Women, 3rd Trimester (2015)**
  – Efficacy: Prevention of medically attended RSV+ illness
  – Global RSV trial in Northern and Southern Hemisphere

• RSV MI program supported by PATH
RSV Vaccine for the Elderly

• 14,000 seniors and high risk adults die of RSV infection or complications per year in the U.S.*
• As many as 180,000 seniors are hospitalized for serious respiratory symptoms each year*
• Significant opportunity for an annual seasonal RSV vaccine

Four-year prospective surveillance for RSV in seniors (Falsey et al., NEJM 2005):
  o RSV infection developed annually in 3 to 7% of the healthy senior group
  o 89% of RSV infections were symptomatic

* U.S Centers for Disease Control
RSV Vaccine for Seniors: Phase 1 Immunogenicity Results

- 220 Elderly adults, >60 yrs, single dose RSV F Nanoparticle Vaccine administered w/Flu vaccine.
- Vaccine was well-tolerated and palivizumab-competing antibody (PCA) response was robust and durable.
- Selected unadjuvated nanoparticle F protein vaccine to move forward.
• E201 in Elderly, FSI Q4 2014
  – Randomized, observer-blinded, placebo-controlled 1:1 in 1,600 subjects
  – Primary endpoint: incidence of RSV+ Medically Attended Illness
  – Exploratory, vaccine effect on a RSV+ Medically Attended Illness
  – Will determine the attack rate and vaccine efficacy to power Phase 3
  – Safety of the vaccine

• E301 Pivotal Efficacy in Elderly and High Risk Adults (2015)
  – Primary endpoint, size and location determined by E201
  – Prevention of RSV disease in the elderly and high risk individuals
Conclusions

• ‘Naturally’ induced immunity is relatively ineffective
• The Fusion protein is important in viral pathogenesis. The safety and efficacy of palivizumab and motavizumab provide important insights for RSV vaccine development
• Cotton rats as an in-vivo model for vaccine efficacy predicted palivizumab and motavizumab efficacy
• The vaccine induces palivizumab-like antibodies (PCA), natural infection does not
• Correlates of protection will be evaluated in the context of a RCT
• The Novavax RSV F vaccine is in late stage and appears to be a promising candidate for development
Acknowledgement – the Novavax Team

Our foundation for success is rooted in the expertise and dedication of the people who performed the necessary activities. We appreciate and recognize the dedicated employees who contributed to this project:

**Adjuvant Production (Sweden):**

**Analytical Development:** Ali Aboosaiedi, Casper Alabanza, Elena Bogatcheva, Liming Fan, Yali Lu, Bruce McNair, Alan Ng, Sonyun Rizzo, Yanhong Wei, Zhiwen Yang, Emnet Yitbarek

**Contracts:** John Herrmann, Jesse Oropesa

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Jean Williams

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**Executive Assistants:** Bianca Collins, Jeanne Dolan, Laura Gibbs, Mary Riggin, Pamala Snively-Smith

**Facilities:** Dustin Berghers, Merv Hamer, Michael Hammonds, Ken Sybert, Cindy Utley, Jeff Young

**Information Technology:** Lee James, Serge Kadel, Kevin McGough, Paresh Patel

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**Quality Control:** Khalid Ahmad, Nota Aigbogun, Sabrina Cusick, Khalia Davis, Kirsha Forte, Thomas Gantt, Brian Howie, Tony Kallarackal, Tina Keeney, Janiece Lartman, Emily Miller, Cheryl Mowen, Nohea Nichols, Oluwayemisi Ojifinni, Vidhi Pankh, Raza Zaidi

**Regulatory:** Susan Hensley, Tim Wan

**Validation:** Joan Abrams, Dana Johnston
Fig. 3. Evaluation of serial dilutions of Palivizumab for microneutralization activity. Individual sera from unvaccinated subjects with known RSV A MN titers categorized as low, medium, and high, were spiked with three different concentrations of palivizumab (40, 80, or 120 μg/ml) and re-assayed by RSV A MN to evaluate the contribution of adding palivizumab with sera and neutralizing antibodies derived from natural infection. The inset displays RSV A MN titers observed due to the presence of increasing concentrations (0.25–120 μg/ml) of palivizumab to saline. Expected values were calculated by adding the log2 MN measured by a given amount of palivizumab in saline, to the baseline of the given sera.