RSV F Recombinant Nanoparticle Vaccine: 
*Summary of Clinical Data*

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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
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, immunogenicity, and dose finding in Elderly Adults (n=220)**
  – Safety, dose selection

• **Study E201: Safety, epidemiology and efficacy in Elderly Adults (n=1600)**
  – Define attack rate, Vaccine efficacy
  – Currently Enrolling

• **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
  – Currently Enrolling

• **Study P101: Safety and immunogenicity in pediatrics**
  – Seropositive children 2-5 years of age
  – Currently Enrolling
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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Placental Fc Receptors and the Transfer of Maternal IgG
The ratio of cord blood to maternal Ab titers at birth was 1.01

Higher baseline log₂ cord blood Ab titers (log₂ titers >11.1) were significantly associated with a decreased risk of a 4-fold rise in titer (hazard ratio [HR], 0.6)

Antibody half-life was calculated at 38 days (95% CI, 36–42 days)

“there is no clearly defined protective titer“
Naturally Derived Immunity is Robust and Present In Infants, Yet Infants Have the Highest Rates of Hospitalization

Can a vaccine add to the immunity and bridge the gap?

Suara et al., CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 1996, p. 477–479
Vaccine: Near Full Length, Recombinant F Protein

A

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109
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---NNRANN ----------------RR FL--6
---NN -------------------------- FL--7

B

137
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--- KKQKQQ - GVGSAIASGVAV -- Δ6
--- KKQKQQ - GSAIASGVAV -- Δ8
--- KKQKQQ - AIASGVAV -- Δ10 (#683)
--- KKQKQQ - ASGVAV -- Δ12
--- KKQKQQ - GVAI -- Δ14
--- KKQKQQ - AV -- Δ16
--- KKQKQQ -- Δ18

C

Smith, et al. 2012. PLOS. 7(11), e50852
Near Full Length RSV F with an Intact Transmembrane Domain Forms Nanoparticles When Expressed in Baculovirus/SF9

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

Palivizumab Binding Site
Antigenic site II: Amino acids 254-278
NSELLSLINDMPITNDQKKLMSNNV
RSV F Nanoparticles

- >10,000 RSV F nanoparticles sorted into self-similar groups of classes.
- Particles with protrusions arranged as **apposing** RSV F trimers seen in 2D.
F Protein Nanoparticle Vaccine Displays Site II: Palivizumab Binding

Palivizumab binds to the F protein nanoparticle vaccine

Antigenic site II: Amino acids 254-278
NSELLSLINDMPITNDQKKLMSNNV

- Palivizumab and motavizumab have been shown to prevent RSV-related disease in 5 randomized clinical trials
- Entirely unique data set for a novel vaccine
  - Mechanism of action
  - Biological immune correlate
  - Pharmacokinetics in humans
  - Predictive animal challenge model
Vaccine Immunity: Amplifying the Near Absence of Palivizumab Competing Antibodies (PCA)

- PCA levels at 400μg/ml, potential for placental concentration effect
- Palivizumab ‘protective’ at 30μg/ml in CR
- PCA “Near absence” suggests that the site is immunologically cryptic, important to reinfection
Anti-F IgG Responses are Robust, Durable After Immunization

Anti-F IgG Responses: Fold Rise through Day 112

- Placebo (N=53)
- Phase 1 Model (N=19)
- 1x (N=23)
- 2x (N=20)
- 1x+AL (N=26)
- 2x+AL (N=25)
- 1x (N=28)
- 2x (N=26)
- 1x+AL (N=30)
- 2x+AL (N=25)

Geo Mean ELISA Unit

- Day 0
- Day 7
- Day 28
- Day 56
- Day 84
- Day 112
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

**Concordance slope w/o placebo = 1.08 (0.95-1.22)**

**Concordance Slope = 1.04**

![Graph showing concordance between Anti-F IgG and PCA](image-url)
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

Shifts in RSV/A MN Titer at Day 28

- % of Treatment Group with RSV/A MN Log2 Titer > Value on Horizontal Axis
- RSV MN Log2 Titers

Graph shows the shifts in RSV/A MN titer at Day 28 with different groups: Day 0, Placebo; Day 0, adjuvanted; Day 0, unadjuvanted; Day 28, placebo; Day 28, unadjuvanted; Day 28, adjuvanted.
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

Numbers = N for the group analyzed.
Modeling Effect of Neutralizing Antibodies Transferred via Maternal Immunization: Potential for Clinical Benefit for infants

Day 28 RSV A Neutralizing Antibodies: M201

![Graph showing decay of titers over time](image)
PCA Responses in Women of Childbearing Age: Implications for Coverage of Infants Born at Different Gestational Ages

CDC Birth Frequencies by Gestational Week Data

* 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

- Peak Transplacental Antibody Transfer
- > 90% of 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 5-6 months?

![Graph showing the effect of maternal immunization on antibodies over time](image)

- **GMT**
- **UCI 95%**
- **LCI 95%**
- **Baseline**

“Protection”*
A anti-human IgG Fc CM5 sensor chip was prepared Palivzumab or human serum was injected and IgG was captured on the chip surface. RSV F vaccine protein (100 nM) was injected through for 300 s followed by buffer for 10 min. 1:1 fitting model was applied and Ka and Kd were calculated.

**Palivizumab**
- $K_a = 2.375 \times 10^5$ (/Ms), $K_d = 2.449 \times 10^{-5}$ (/s)
- $K_D = 1.05 \times 10^{-10}$ (M)

**Vaccinee day 30**
- $K_a = 1.755 \times 10^5$ (/Ms), $K_d = 4.022 \times 10^{-7}$ (/s)
- $K_D = 2.29 \times 10^{-12}$ (M)
# Anti-F IgG Binding Measurements in Vaccinees

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<th>Anti F EU*</th>
<th>Palivizumab-like IgG</th>
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* ELISA unit  
** Calculated palivizumab-like IgG concentration determined using competitive ELISA
Methods: Kinetics summary of RSV F protein binding to various mAbs. RSV F protein bind to either palivizumab and various mAbs with high affinity. CM5 chips were coated with RSVF protein by amine coupling method. Serial dilution of mAbs at 40nM, 20nM, 10nM, and buffer control were used to bind RSVF on the chip. After binding, dissociation was initiated with buffer. Association and dissociation rates were calculated based on 1:1 fitting model.

RSV F(K262M) includes the point mutation at amino acid residue 262 as compared to RSV F nanoparticle vaccine.
Rate of RSV Infections Decreased by 50% in RSV F Vaccinees

**Western Blot Analysis**

- Immunized at the beginning of RSV season, complete by day 56
- Assessed for new onset infections between day 56 and d112 by Serology (Western Blot)*
- Evidence of recent past infection balanced between placebo and vaccinees
- Rate of new infections in placebo, 20%
- Rate of new infections in vaccine, 10%
- Reduction of new infections of 50%

*Assay performed by Baylor College of Medicine
Conclusions

- A recombinant nanoparticle is intrinsically 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.
- The polyclonal sera KD rates are more in line with motavizumab.
  - Motavizumab > palivizumab for prevention of RSV disease.
- 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.
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