Development of Vaccines for Prevention of Respiratory Syncytial Virus (RSV) Disease in RSV-naïve Infants

Vaccines and Related Biological Products Advisory Committee Meeting

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Presentation Goals

- Provide an overview of RSV disease and prevention
- Review different RSV vaccine approaches and summarize immunologic mechanisms proposed to underlie vaccine-associated enhanced respiratory disease (ERD)
- Review recent workshops that addressed RSV vaccine development
- Discuss types of supportive preclinical and human data and the potential design of initial studies in RSV-naïve infants

RSV Disease and Prevention

- RSV infection greatly impacts health of infants and young children
- Treatment is largely supportive
- Passive immunization can confer protection against RSV disease
  - Respiratory Syncytial Virus Immune Globulin, Human [RSV-IVIG] (RespiGam)
  - Humanized Anti-RSV-F Monoclonal Antibody [Palivizumab] (Synagis)
    - Licensed "for the prevention of serious lower respiratory tract disease caused by RSV in children at high-risk of RSV disease"

RSV Vaccine Development

- Many products under development for active immunization
- Three main target populations
  - Adults ≥ 60-65 years of age
  - Pregnant women
  - **Infants**

Observations of Enhanced Respiratory Disease (ERD) in Infants

- Occurred in studies evaluating a formalin inactivated RSV (FI-RSV) vaccine in infants
- Increase in the proportion with severe RSV disease and in severity of illness in infants previously immunized with FI-RSV compared with controls
- Redirected vaccine development efforts towards first understanding mechanistic etiology of vaccine-associated ERD

Potential Mechanisms Underlying Vaccine-associated ERD

- Th2-dominant $CD4^+$ T-helper cell cytokine responses
- Absence of $CD8^+$ cytotoxic T lymphocyte (CTL) response
- Immune complex deposition in the lungs
- Low-affinity antibody response with minimal neutralizing activity

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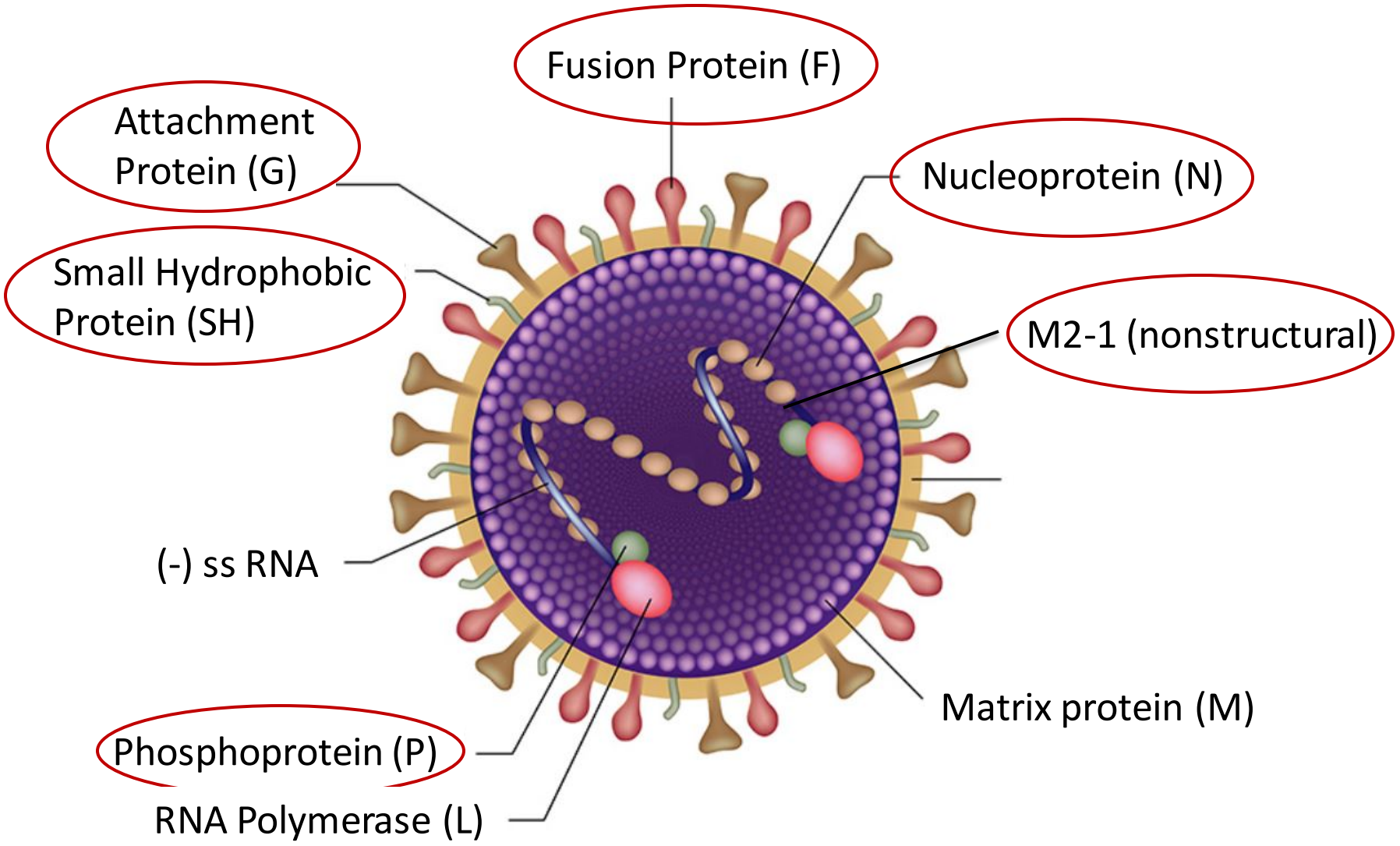
Potential RSV Antigen Targets for Vaccine Development



RSV Antigens Associated with Protection in Mice

Protein	Location	B-Cell Epitopes		CD8+ CTL Epitopes
		IgG	Neutralizing	
F Fusion	Envelope	Yes	Yes	Yes
G Attachment	Envelope	Yes	Yes	No
N	Nucleocapsid	Yes	No	Yes
M2-1	Non structural	No	No	Yes

Connors M et al., J Virol 1991

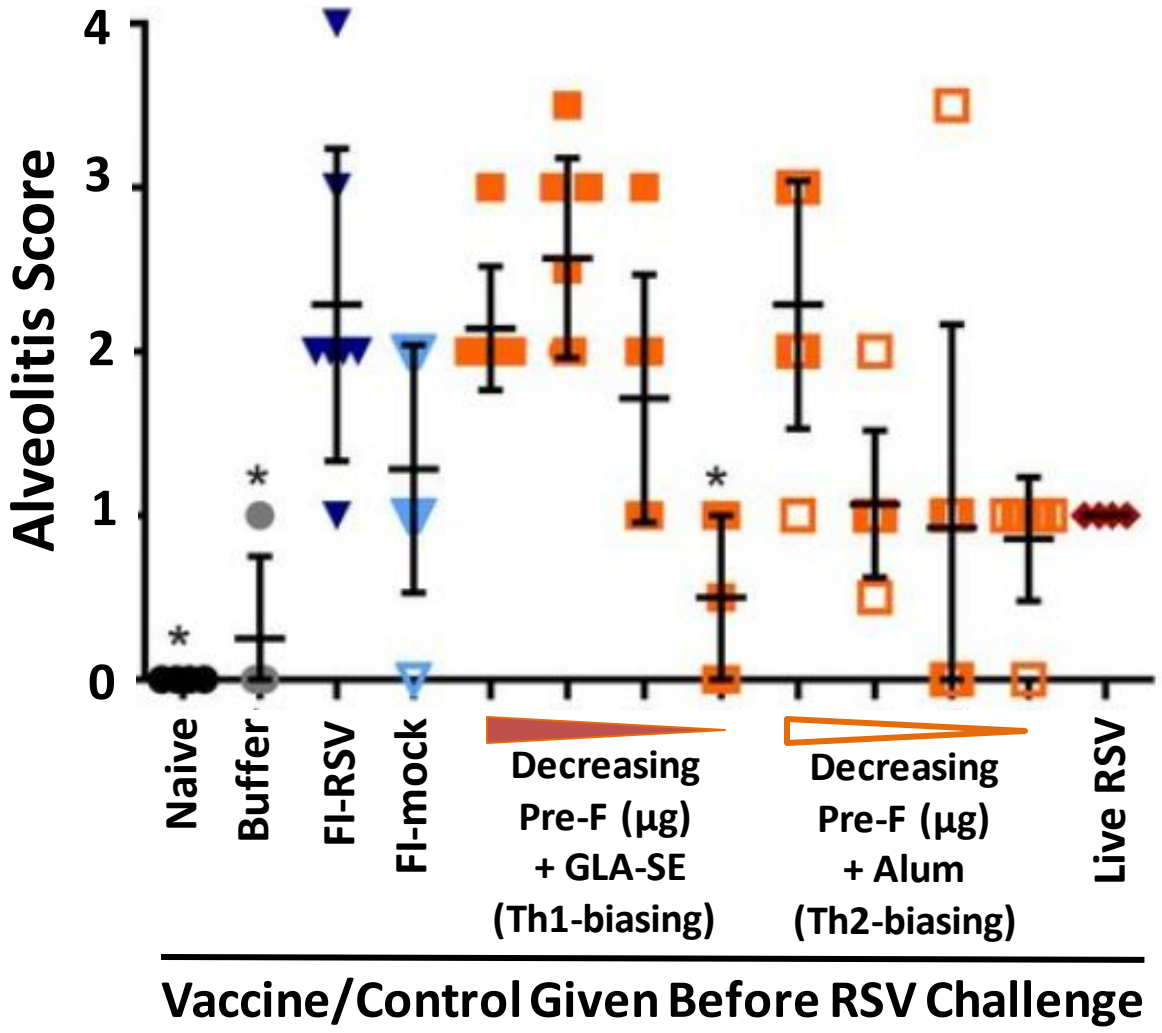
Vaccine Characteristics and Potential Risk of ERD

Immune Response	Vaccine Approaches			
	Whole Virus, Inactivated	**Protein and Peptide Subunit**	**Gene-Based and Vectored**	**Live-Attenuated**
	FI-RSV	- F, pre or post fusion - G protein - G peptide	- MVA - Human or Chimpanzee Adenovirus - Naked DNA/RNA	RSV engineered with attenuating mutations
Neutralizing Antibody Response	Variable to low	Low to high	Low to high	Mucosal IgA and serum IgG
RSV-Specific CD8+ CTL	No	No	Yes	Yes
Th1/Th2	Th2	Th2 > Th1	Th1	Th1
ERD risk	Caused ERD in infants and toddlers	Some have shown ERD in animal models	Many have not shown ERD in animals	Tested in seronegative infants with no ERD observed so far

Higher **Lower**

Cotton Rats Primed with Purified F Developed Alveolitis after RSV Challenge

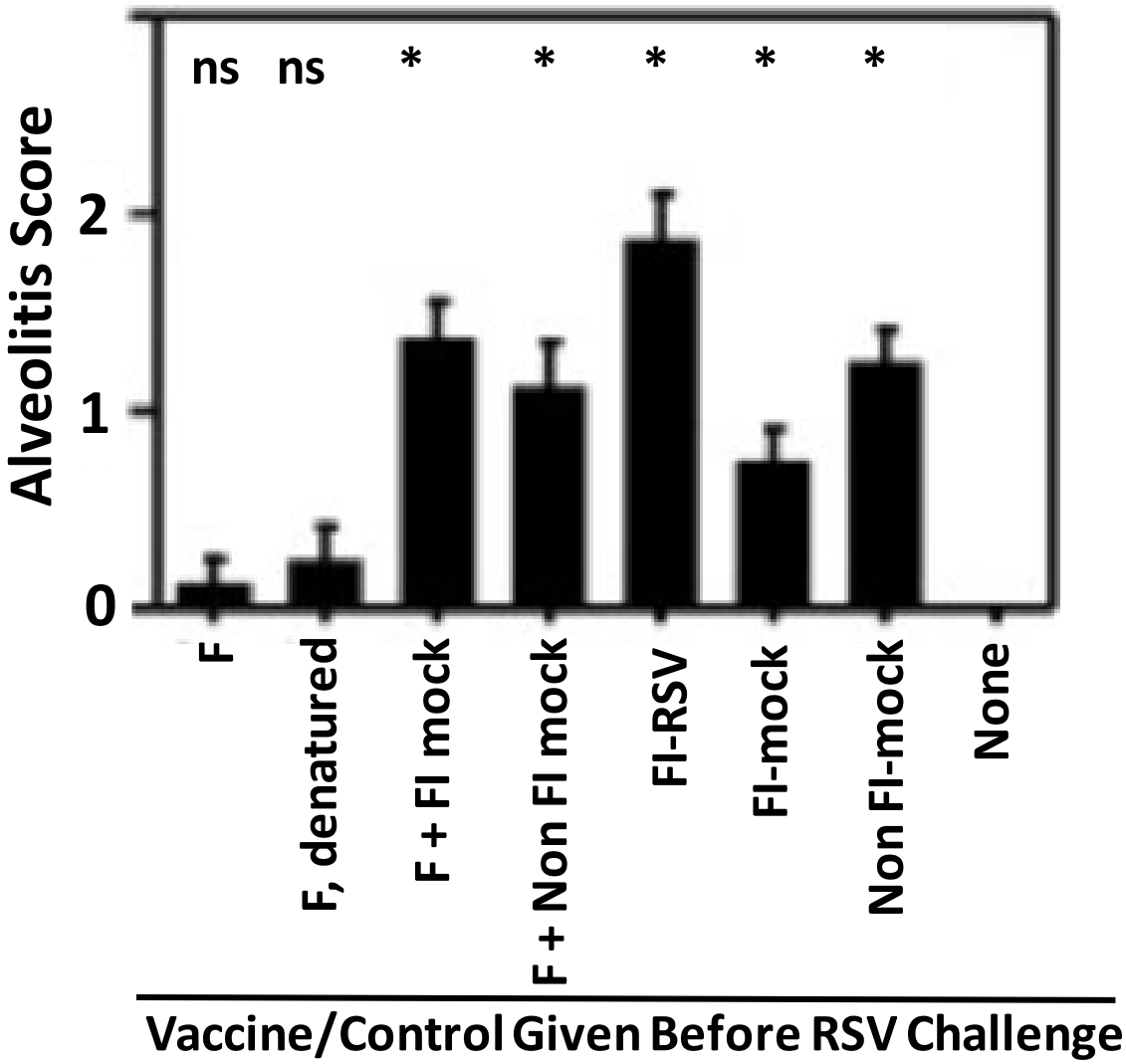
- ERD seen after immunization with purified PreF or PostF, irrespective of adjuvant



Mock = supernatant from uninfected HEp-2 cells

Adapted from Schneider-Ohrum et al., J Virol, 2017

Cellular Components can Induce Alveolitis in the Cotton Rat Model of ERD



F = RSV F protein

Mock = supernatant from uninfected HEp-2 cells

Adapted from Shaw et al., Vaccine 2012

WHO Conference March 2015

"WHO Preferred Product Characteristics for RSV Vaccines" is a draft document that provides the following perspectives:

- Safety data in adults and RSV-experienced children 12 months to 5 years of age should precede evaluation of RSV-naïve infants
- Studies in RSV-naïve infants should extend over two RSV seasons for efficacy, cross-protection, and durability of response
- Case definitions proposed as endpoints for field trials for severe and very severe RSV lower respiratory tract infection using:
  - RT-PCR testing
  - SpO2
  - Pulse oximetry
  - Clinical signs of chest in-drawing (severe) vs. inability to feed or unresponsive to touch (very severe).

FDA/NIH Conference June 2015

- Key concepts included:
  - No single animal model demonstrates all features of FI-RSV associated ERD in infants.
  - Th2-biased immune responses following challenge of immunized animals are consistently associated with the ERD syndrome.
  - A high-magnitude antibody response with poor neutralizing activity may be causally related to ERD.
  - RSV-specific CD8+ T cells mediate virus clearance, but in the context of high viral loads on a background of low neutralizing antibodies can also contribute to pathology.
  - Lung eosinophilia, while not causally related to ERD, is a marker of a Th2-type cytokine response and deserves careful consideration if present in vaccinated animals post challenge.

Roberts JN et al., Vaccine 2016

Use of Pre-clinical Models to Evaluate Candidate Vaccines

- Extrapolation from animal models that reproduce features of ERD might inform risk of ERD in humans
- Considerations when evaluating preclinical data
  - Animal model used
  - Vaccine dose (assessment may include dose de-escalation)
  - RSV challenge dose and timing relative to immunization
  - Establishing criteria for ERD

Clinical Studies in Adults

- Can assess reactogenicity of vaccine candidates, but not risk for ERD
- Human challenge studies in adults might help select promising vaccine candidates or identify correlates of protection
- Immune responses in adults represent boosting of pre-existing immunity and therefore may not predict a protective immune response in RSV-naïve infants

Clinical Studies in RSV-experienced Infants

- Can assess reactogenicity of vaccine
- Usefulness in assessing risk of ERD for RSV-naive subjects is uncertain
- Persistence of maternal antibody may inaccurately imply RSV experience, although less likely after 6 months of age

Considerations and Potential Approaches to Studies in RSV-naïve Infants

- Risk of ERD might be higher at younger ages
  - Studies in RSV-naïve infant subjects ≥ 6 months may help to predict risk of ERD in younger infants
    - ERD was observed in infants > 6 months of age, suggesting ERD can be detected in older children
    - RSV serology is confounded by maternal antibody in infants < 6 months of age

Chin J et al., Am J Epidemiol 1969; Kapakian AZ, et al., Am J Epidemiol 1969; Fulginiti VA; et al., Am J Epidemiol 1969; Kim HW, et al., Am J Epidemiol 1969

Considerations and Potential Approaches to Studies in RSV-naïve Infants

- Vaccine-associated ERD may not be clinically discernable from naturally-occurring severe RSV disease
  - Studies could evaluate the relative risk of severe RSV disease between vaccine recipients and controls
- Risk of ERD may increase as immunity wanes
  - May need to follow subjects past one RSV season (or until their first documented RSV infection)
  - Oldest FI-RSV-immunized infant developed severe RSV disease at 18 months

Summary

- Prevention of RSV disease in infants is an important public health need worldwide
- Observations of FI-RSV vaccine-associated ERD in RSV-naïve infants have presented a challenge to development of safe and effective vaccines for infants
- Proposed immunologic mechanisms contributing to ERD include a Th2-dominant CD4+ T-cell response, immune complex deposition in the lungs, development of low-affinity antibodies, and lack of RSV-specific CTLs

Summary

- Animal models can mimic some features of ERD observed with FI-RSV, and are being used to assess ERD risk from candidate vaccines
- Studies in adults and RSV-experienced (i.e., seropositive) children might provide support for the initial studies in RSV-naïve (seronegative) infants using an age de-escalation approach
- Types of supportive data and study design may be product-specific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Backup slides

Preclinical Data Supporting Studies in RSV-naïve Infants

Animal	Advantages	Disadvantages and Considerations
Murine	• Low-cost • Homogeneous • Well-characterized genetics	• Relatively resistant to RSV: high dose inoculation manifests mild disease
Cotton Rat	• Lung histopathology after challenge resembles histopathology seen in children given FI-RSV	• Vaccine dose must be optimized to allow sufficient viral replication in setting of low levels of vaccine-induced neutralizing antibodies

Preclinical Data Supporting Studies in RSV-naïve Infants

Animal	Advantages	Disadvantages and Considerations
Bovine Model	• Bovine RSV disease closely resembles human disease • FI-BRSV –associated ERD manifests in calves with close resemblance to human ERD • Bovine and human RS viruses share close homology: potential to assess immunogenicity/effectiveness	• Logistically challenging and expensive • Size of animals may compromise adequacy of histopathologic examination (skip lesions)
Nonhuman Primates	• Pulmonary eosinophilia and IL-13 and IL-5+ T cells identified post RSV challenge FI-RSV-vaccinated macaques	• Studies typically small and expensive • Relatively RSV-infection resistant • Intratracheal administration • Immunohistopathology of ERD not detected