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Update on the Phase I Clinical Trial of a Stabilized RSV Pre-fusion F Glycoprotein Vaccine, DS-Cav1

**10th Annual Global Virus Network Meeting
Veyrier-Du-Lac, France
Respiratory Virus Session
November 29, 2018**

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Disclosures

Nothing to disclose.

Vaccine Research Center



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2018 VRC Principal Investigators and Program Directors

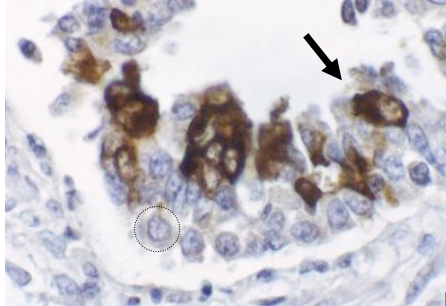


Outline

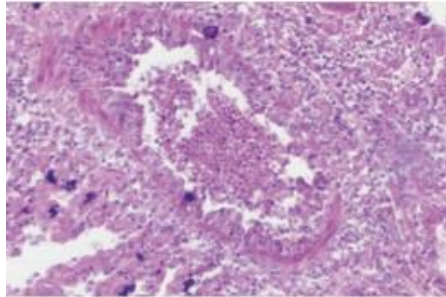
- RSV Fusion glycoprotein (F) and RSV biology
- Development of a stabilized pre-F RSV vaccine antigen (DS-Cav1)
- Interim results of VRC 317 clinical – DS-Cav1 in healthy adults

Respiratory Syncytial Virus

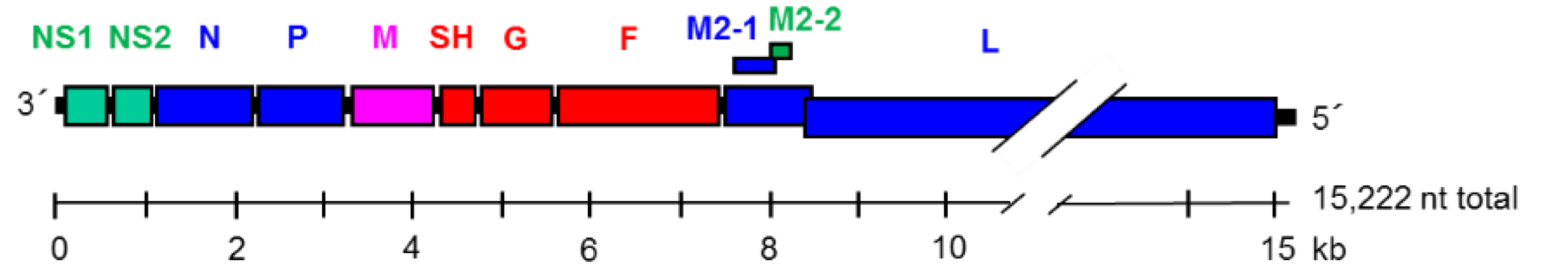
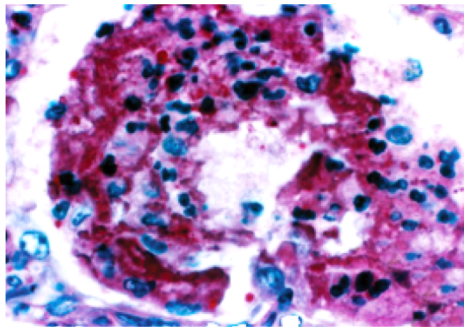
Polarized ciliated epithelium



Obstructed airway



Mucus



Nonstructural

- NS1** } - inhibit Type I IFN
- NS2** }
- M2-2** - Regulates transcription/replication

Nucleocapsid-associated

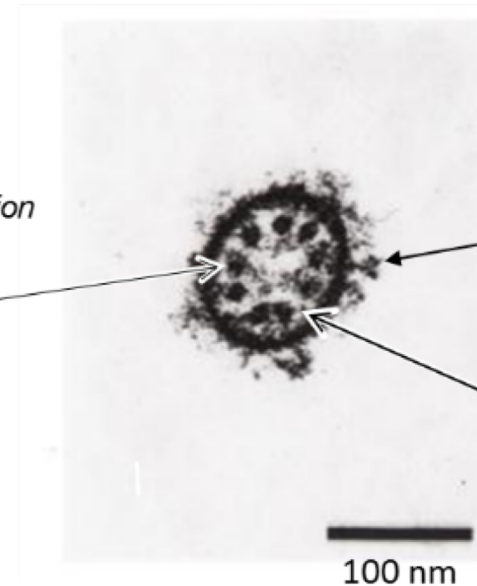
- N** - RNA-binding
- P** - phosphoprotein
- L** - polymerase
- M2-1** - transcription regulation

Surface exposed proteins

- SH** - ion channel
- G** - attachment
- F** - fusion and entry

Inner envelope face

- M** - assembly



Adapted from Peter Collins

Challenges for RSV Vaccine Development

- Severe disease occurs at the extremes of age (more difficult to vaccinate those age groups)
- Despite minimal variation in antigenicity, the virus suppresses and evades the human immune response
- History of vaccine enhanced disease

FI-RSV Vaccine-Enhanced Disease 50 Year Anniversary

Immunizations 1965-1966; Infections Winter of 1966-1967

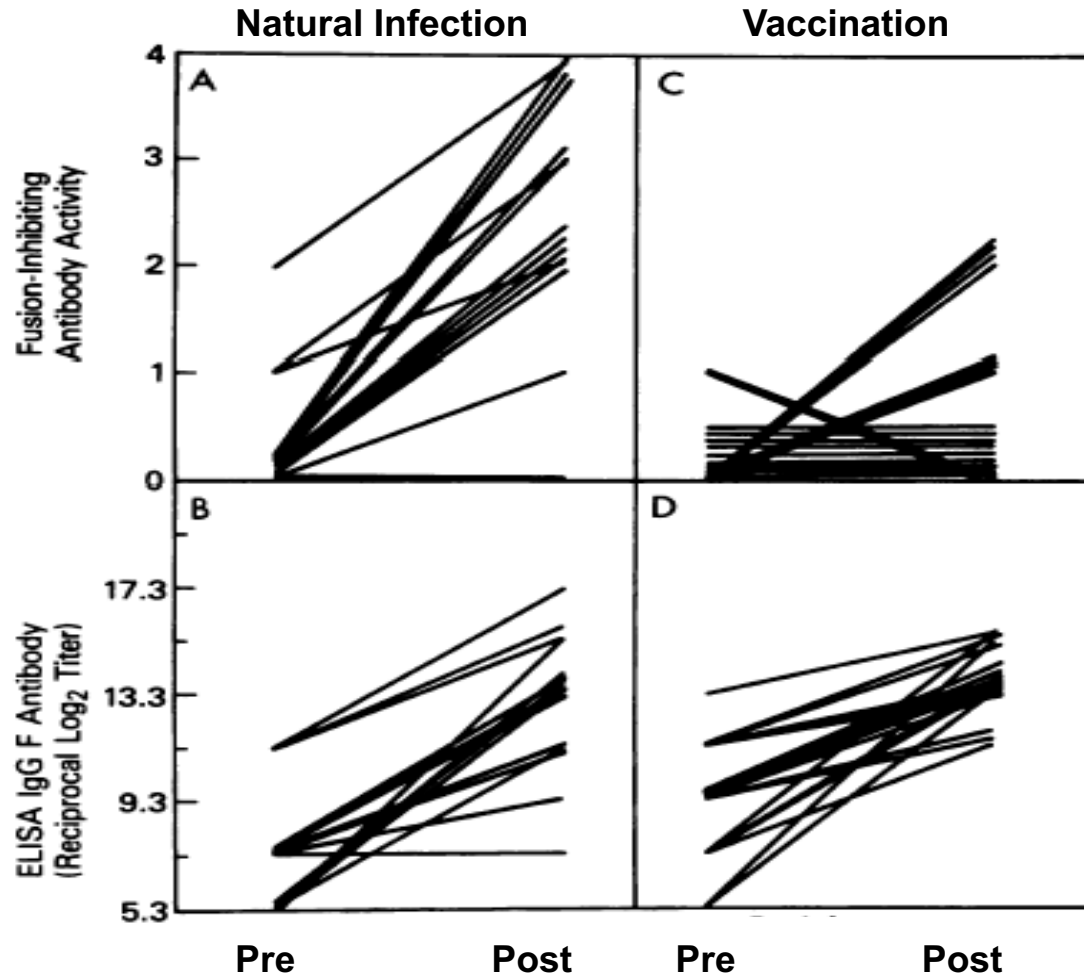
Vaccine	n*	Infected (%)	Hospitalized (%)**	Deaths***
FI- RSV	31	20 (65)	16 (80)	2
FI-PIV-1	40	21 (53)	1 (5)	0

* 1 injection (n=2); 2 injections (n=8); 3 injections (n=21)

** In unpublished 1962/3 trial - 21/54 infected; 10/21 hospitalized

*** 14 and 16 mo. of age; 3 injections starting at 2 and 5 mo. of age.
Both had bacterial pneumonia complicating RSV

FI-RSV Immunization Resulted in a Discordance Between Functional and Binding Antibody



**Fusion
Inhibition**

Dissociation between serum neutralizing and glycoprotein antibody responses of infants and children who received inactivated respiratory syncytial virus vaccine.

Murphy, Walsh et al JCM 1986; 24:197.

ELISA

Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity.

Murphy, Walsh et al JCM 1988; 26:1595

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P = PEDIATRIC M = MATERNAL E = ELDERLY

	PRECLINICAL				PHASE 1	PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/CHIMERIC	Codagenix, LID/NIAID/NIH RSV	LID/NIAID/NIH RSV			Intravacc ^P Delta-G RSV	Sanofi, LID/NIAID/NIH RSV ΔNS2/Δ1313/11314L ^P	Sanofi, LID/NIAID/NIH RSV 6120/ΔNS2/1030s ^P	
	LID/NIAID/NIH PIV1-3/RSV	Meissa Vaccines RSV			Pontificia Universidad Catolica de Chile BCG/RSV ^P	Sanofi, LID/NIAID/NIH RSV D46/NS2/N/ΔM2-2-HindIII ^P	SIPL, St. Jude Hospital SeV/RSV ^P	
WHOLE-INACTIVATED	Blue Willow Biologics RSV							
PARTICLE-BASED	AgilVax VLP	Fraunhofer VLP	TechnoVax VLP	VBI Vaccines VLP	Novavax ^P RSV F Nanoparticle	Novavax ^E RSV F Nanoparticle	Novavax ^M RSV F Nanoparticle	
	Artificial Cell Technologies Peptide microparticle	Georgia State University VLP	University of Massachusetts VLP	Virometix VLP				
SUBUNIT	Instituto de Salud Carlos III RSV F Protein	University of Georgia RSV G Protein			Beijing Advaccine Biotechnology RSV G Protein ^{P E}	Immunovaccine, VIB DPX-RSV-SH Protein ^E	NIH/NIAID/VRC RSV F Protein ^{E M}	
	Sciogen RSV G Protein	University of Saskatchewan RSV F Protein			GlaxoSmithKline ^{E M} RSV F Protein	Janssen Pharmaceutical ^E RSV F Protein		
NUCLEIC ACID	CureVac RNA	Inovio Pharmaceuticals DNA						
RECOMBINANT VECTORS	BravoVax Adenovirus				Vaxart ^E Adenovirus	Bavarian Nordic ^E MVA	Janssen Pharmaceutical ^{P E} Adenovirus	
						GlaxoSmithKline ^P Adenovirus		
IMMUNO-PROPHYLAXIS/COMBINATION	Arsanis Anti-F mAb	Biomedical Research Models DNA prime, Particle boost	Pontificia Universidad Catolica de Chile Anti-N mAb	UCAB, mAbXience Anti-F mAb		MedImmune, Sanofi ^P Anti-F mAb		MedImmune ^P Synaxis

UPDATED: October 16, 2018

Indicates Change

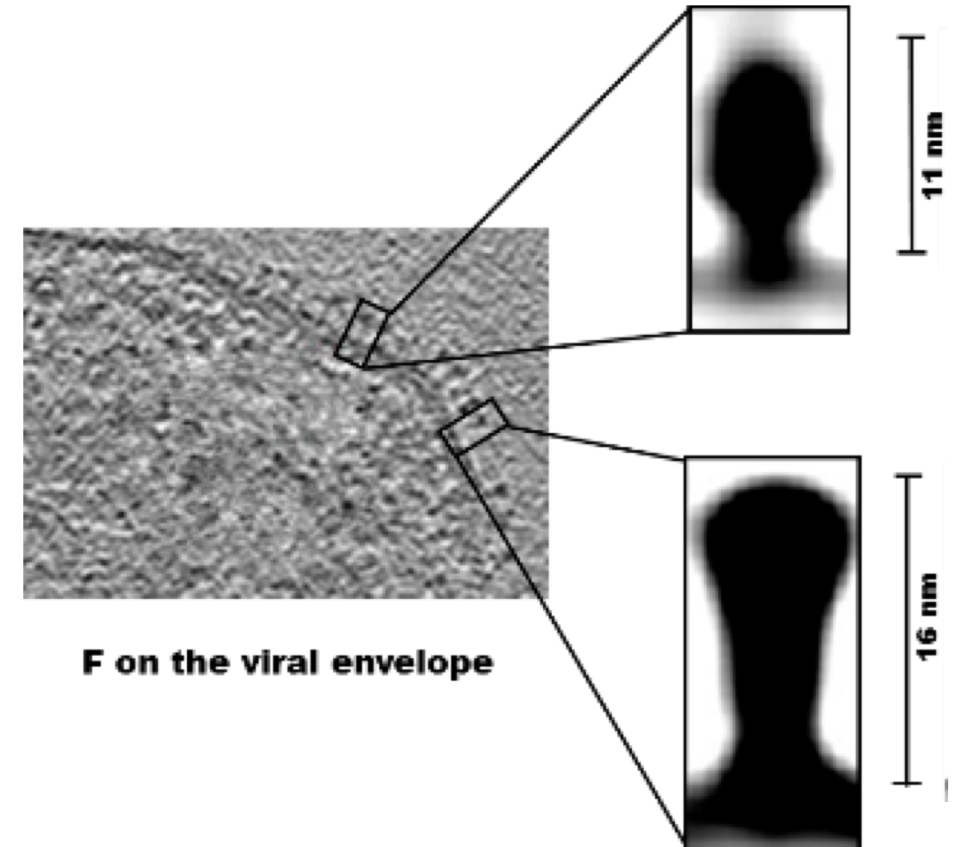
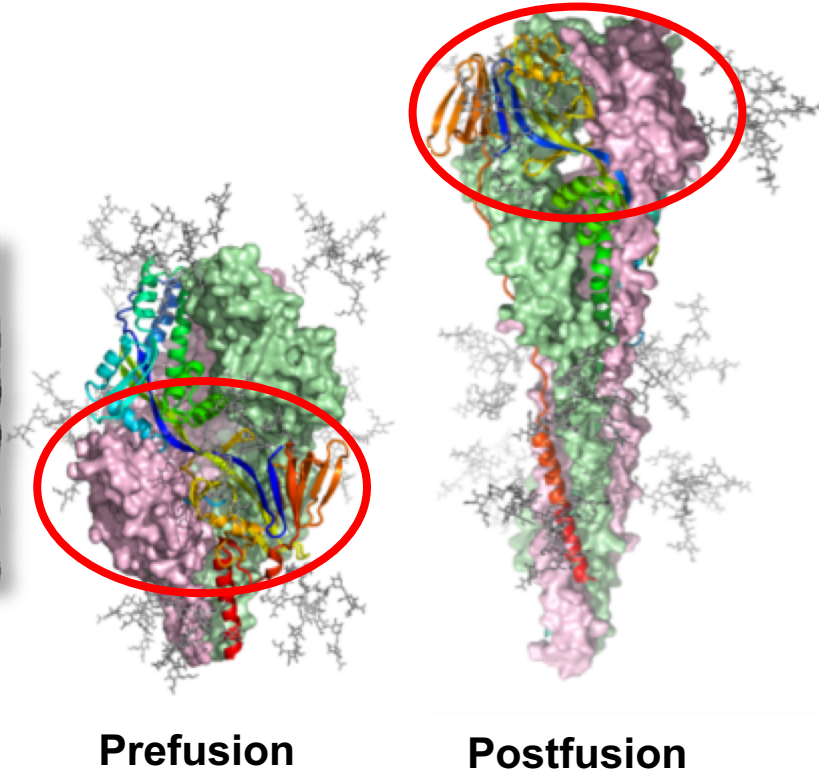
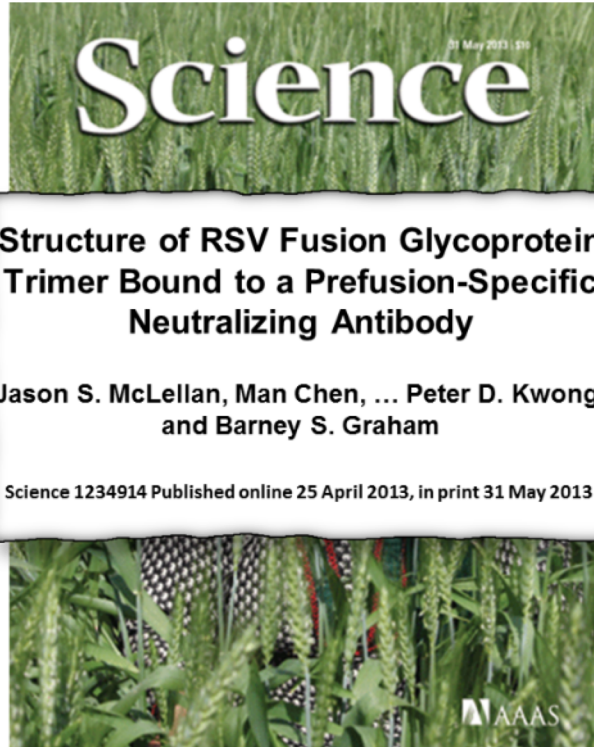
<http://vaccineresources.org/details.php?i=1562>

History of Subunit RSV F Protein Vaccines for RSV

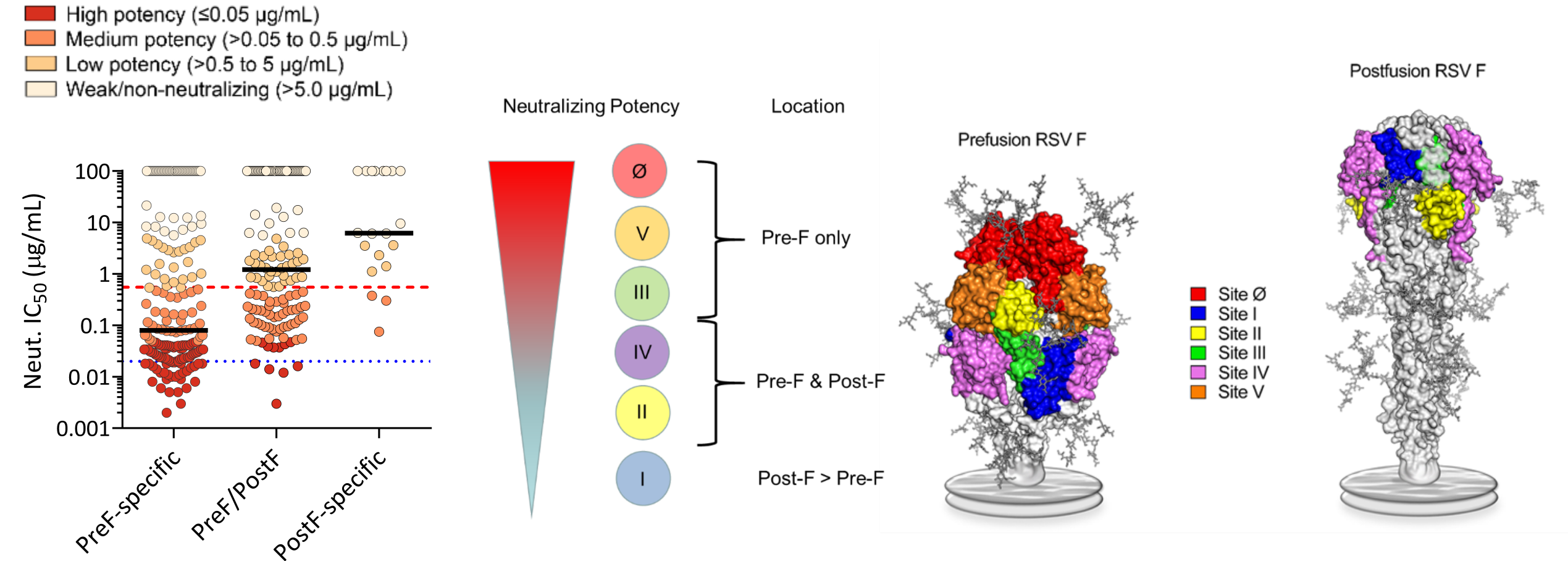
Company	Antigens	Production method	F structure	GMFR* NT	GMFR F ELISA	ELISA / NT
Lederle-Praxix → Wyeth	F-G	Purified from virus	? Postfusion	~5	~30	~6
Connaught → Sanofi	F-G-M	Purified from virus	? Postfusion	~2-4	~3-5	~1.5
Novavax	F	baculovirus	Postfusion	~2	~10	~4-5
GSK (PreF)	F	CHO	Not prefusion	3.2-4.9	~30	~6-10
Medimmune	F	CHO	Postfusion	~2	~14	~7

*GMFR = geometric mean fold rise

Structure of Prefusion RSV F Glycoprotein

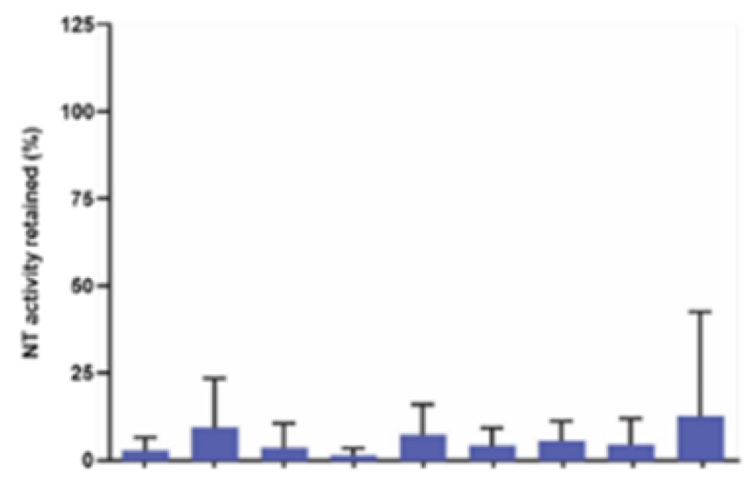
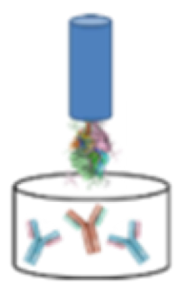


Neutralization-Sensitive Epitopes are Conformation Dependent

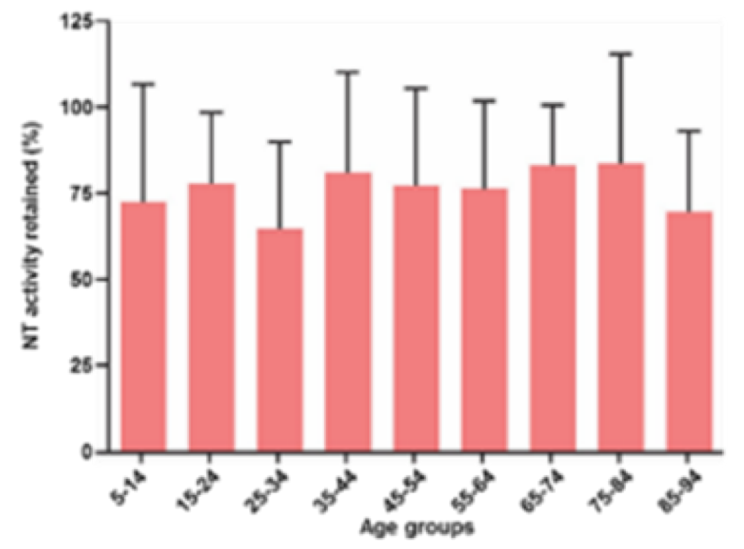
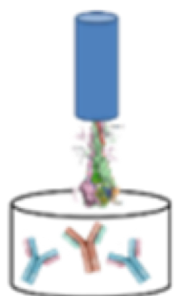


Gilman M, McLellan JS, Walker L, et al. Science Immunology 2016
 Graham BS. Current Opinion Virology 2017

Post-fusion F does not remove NT activity from human serum

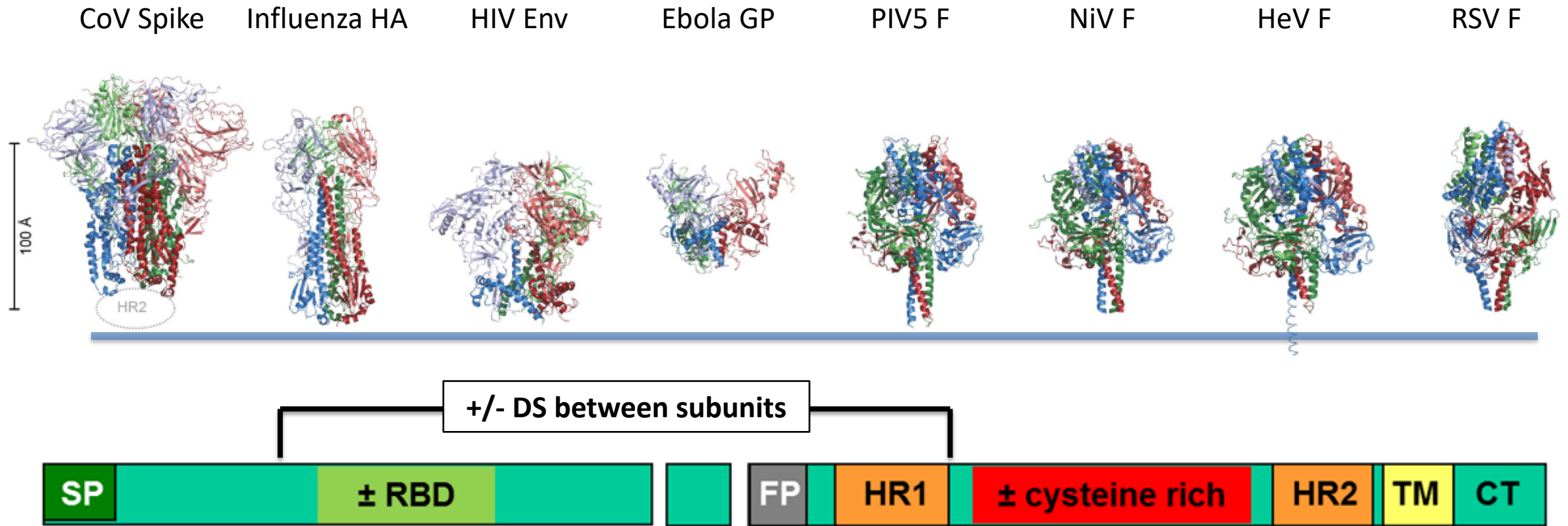


Pre-F
removes
most NT
activity

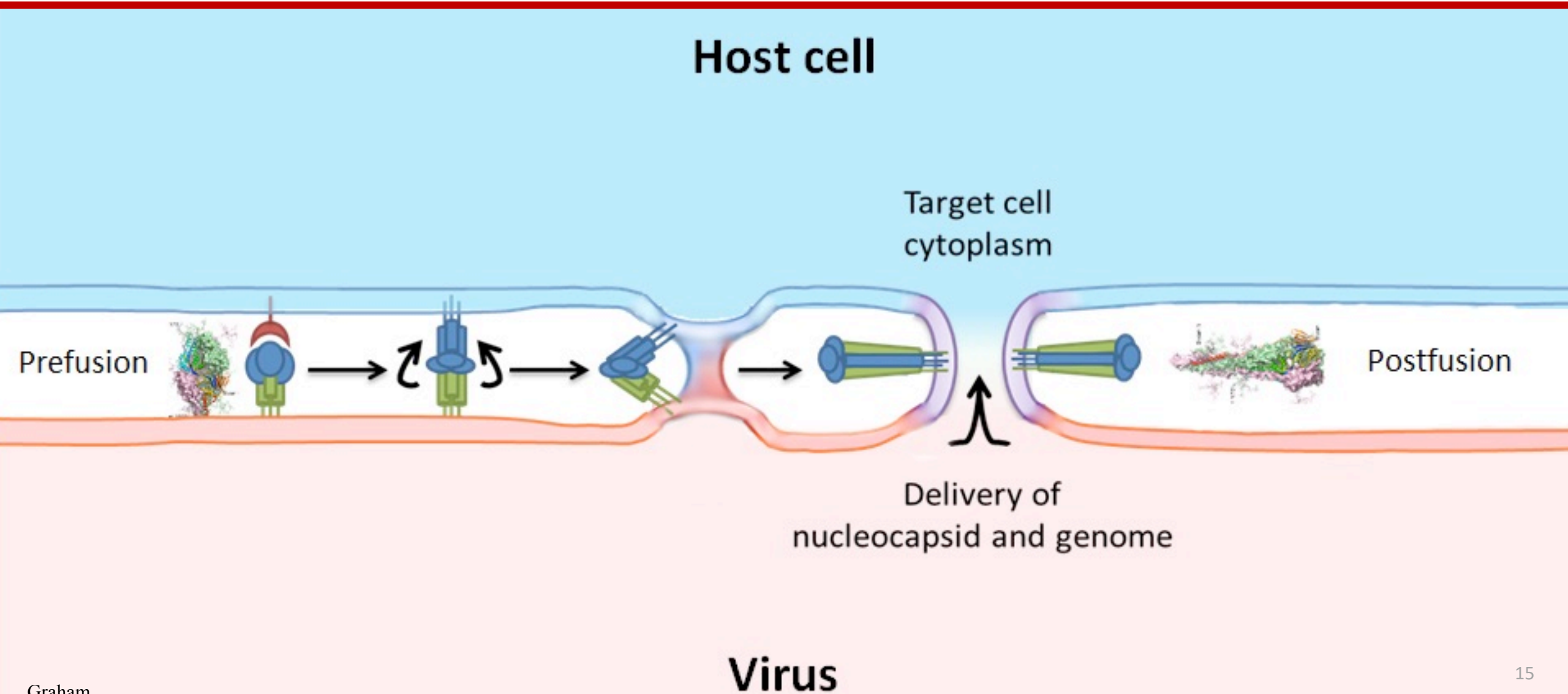


Post-F
removes a
small fraction
of NT activity

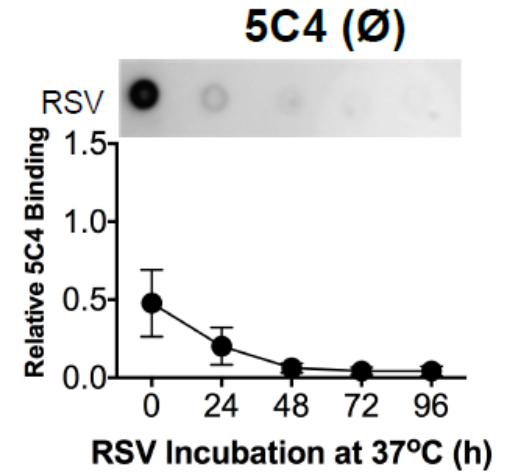
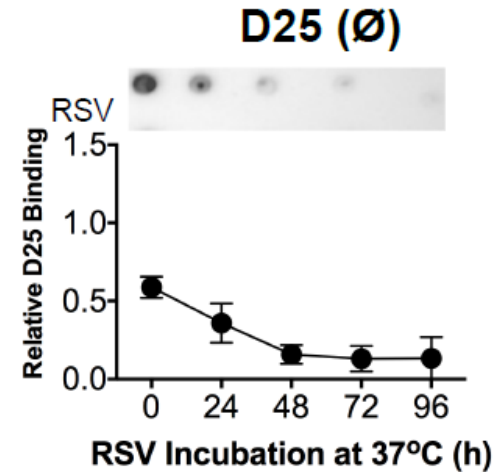
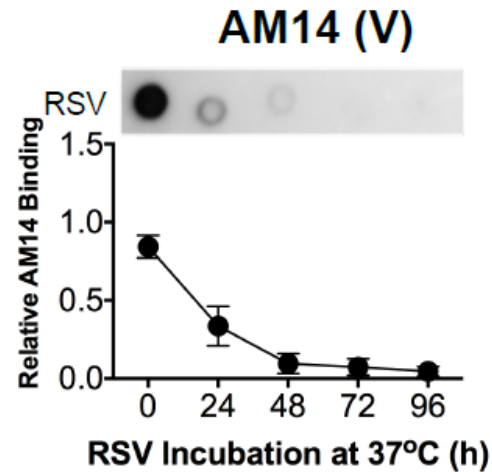
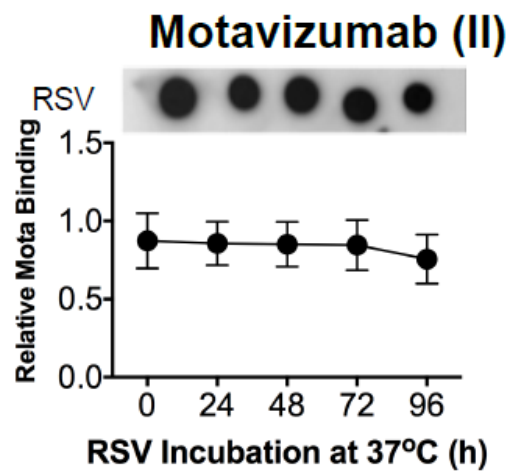
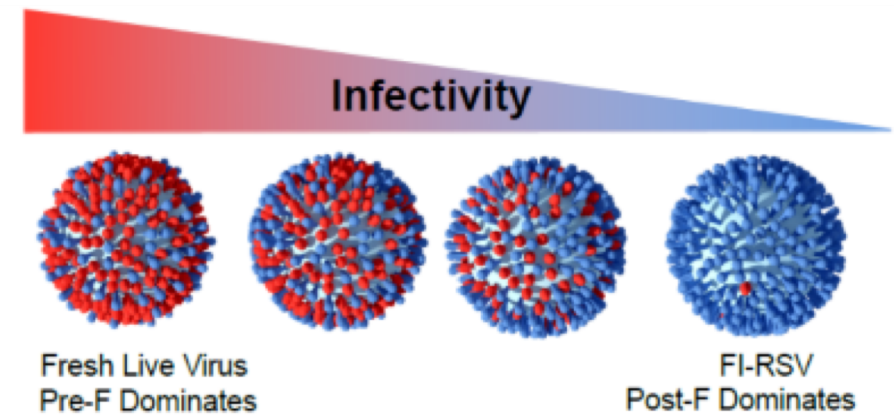
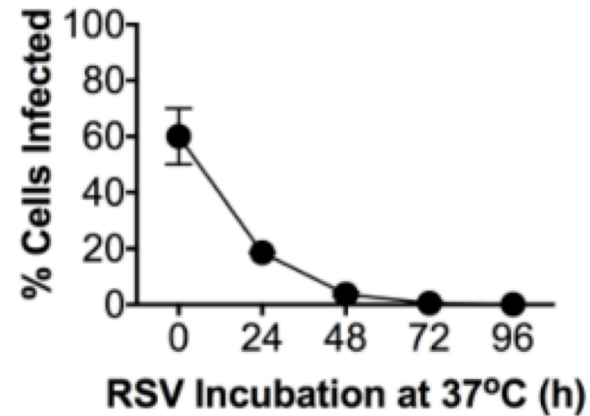
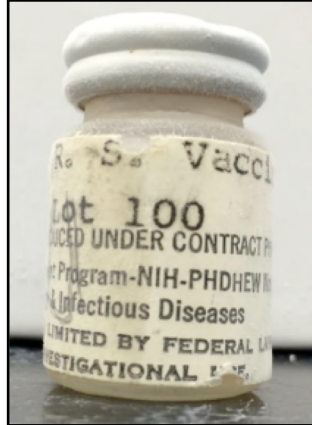
Class I Fusion Proteins



RSV F mediates viral entry

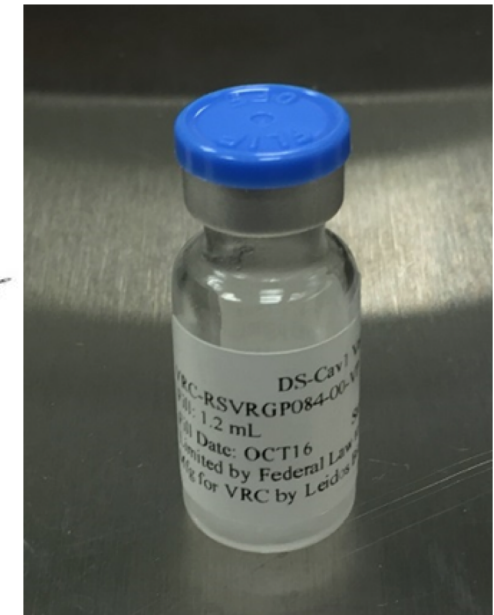
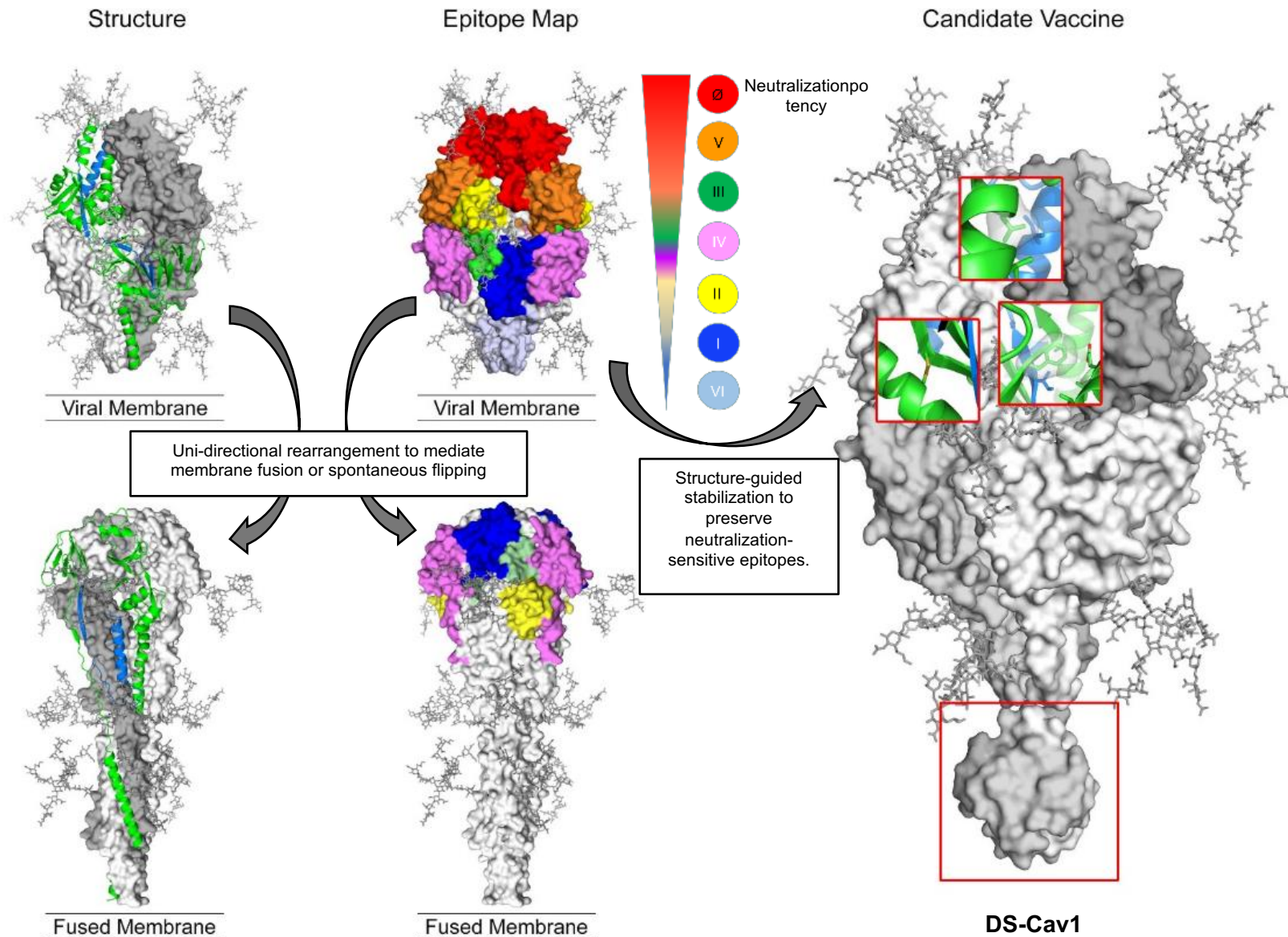


FI-RSV was a Post-F Antigen



Earlier vaccines suffered from a lack of understanding of protein structure

RSV F Structure, Antigenicity, and Stabilization



Candidate Vaccine in Phase I Clinical Trial

VRC 317 Study Schema

VRC 317 Study Schema				
Group	Subjects	Dose	Day 0	Week 12
1	15	50 mcg	DS-Cav1	DS-Cav1
2	15		DS-Cav1 + alum	DS-Cav1 + alum
3	15	150 mcg	DS-Cav1	DS-Cav1
4	15		DS-Cav1 + alum	DS-Cav1 + alum
5	15	500 mcg	DS-Cav1	DS-Cav1
6	15		DS-Cav1 + alum	DS-Cav1 + alum
Total	90*	All DS-Cav1 vaccinations are administered with needle and syringe into the deltoid muscle. *Up to 100 subjects may be enrolled if needed to evaluate safety or immunogenicity.		



First Enrollment Feb 21,
2017

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Interim Analysis

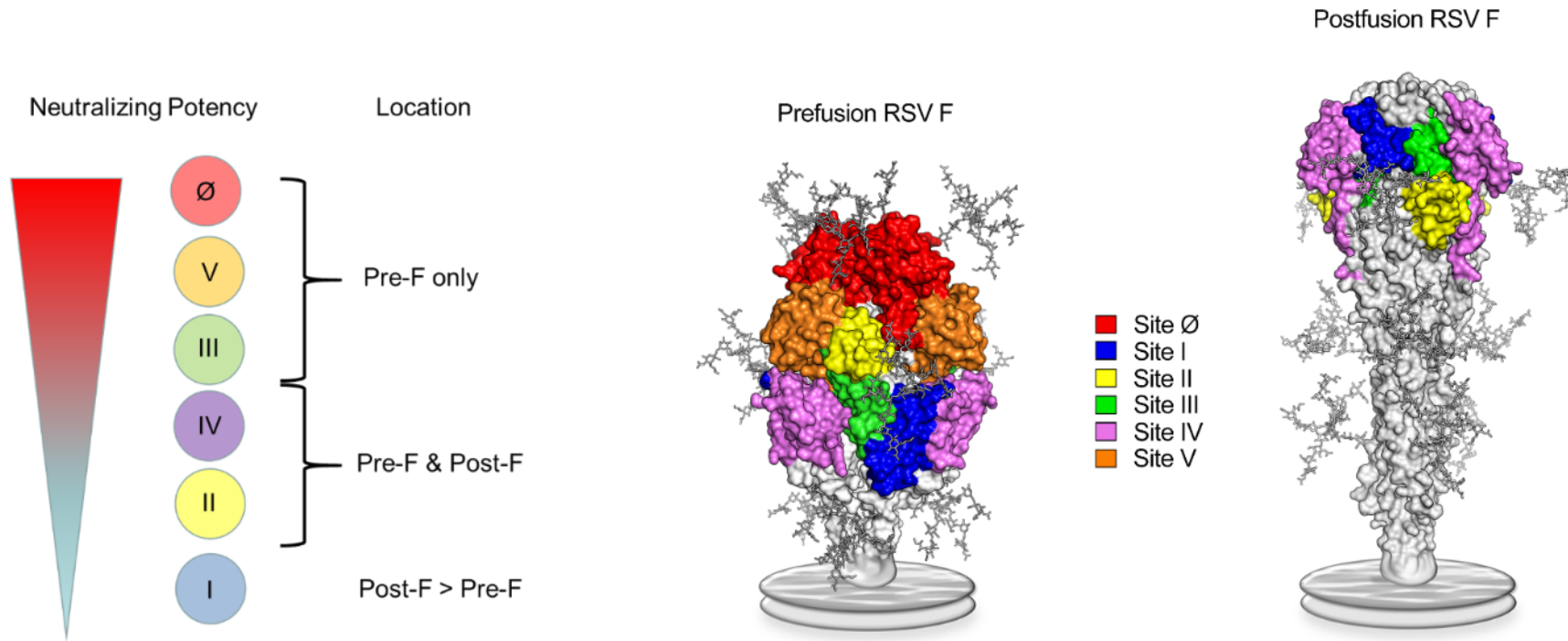
N=40
10 each from Groups 1-4
50 or 150 mcg +/- alum



First Enrollment Feb 21, 2017

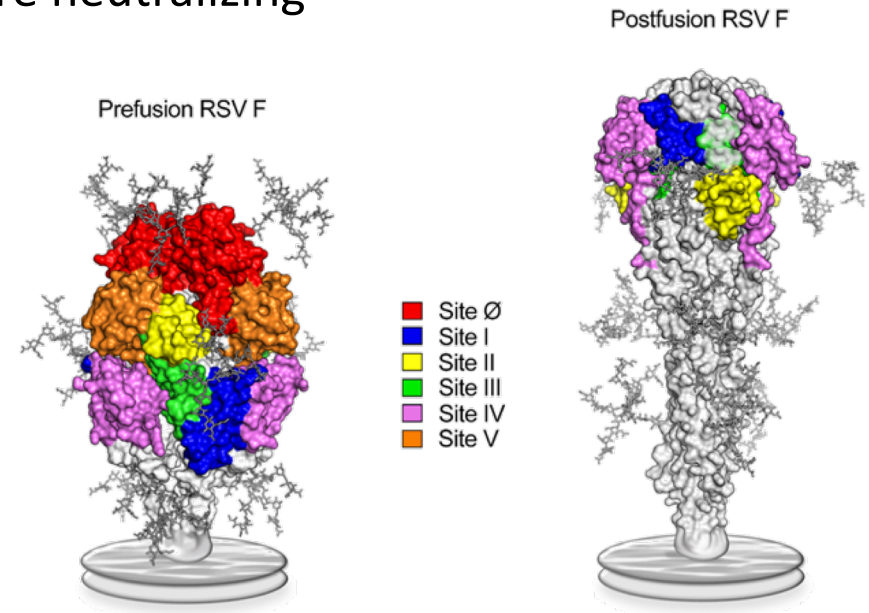
Structure-Guided Solution for RSV Vaccine Development is Based on Conformation-Dependent Immunogenicity

- Solving atomic structure of prefusion RSV F revealed a new target of vulnerability
- Stabilized Pre-F establishes a precedent and clinical proof-of-concept for structure-based vaccine design



Summary

- Stabilized RSV pre-F candidate trimeric subunit vaccine (DS-Cav1)
 - Induces >10-fold rise in NT activity (~3-4 extra months of protection in neonates than post-F)
 - Minimal effect of alum and small effect of dose on magnitude
 - ELISA/NT response ratio is <1 indicating induced antibodies are neutralizing
 - Antibody response is pre-F specific
 - IgG and IgA are boosted
 - Pre-existing serum IgA to pre-F anticipates NT response
- Ongoing work
 - Detailed T cell and B cell analysis including:
 - Longitudinal pre-F and post-F specific B cell phenotyping
 - Repertoire analysis of memory B cells induced by vaccination
 - Serological analysis including
 - Epitope-specific antibody binding
 - Mucosal antibody measurements



Viral Pathogenesis Laboratory in NIAID VRC



VRC, NIAID and Collaborators

NIAID Vaccine Research Center

John Mascola

Richard Koup

Jason Gall

Peter Kwong

Adrian McDermott

Jeffrey Boyington

Wing-Pui Kong

Abe Mittelman

Diane Scorpio & Animal Care Program

Richard Schwartz & Vaccine Production Program

Frank Arnold, KC Chang, Lisa Kuelto, Joe Horwitz

David Lindsay & Vaccine Clinical Material Program

Julie Ledgerwood & Clinical Trial Program

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Mario Roederer

Daniel Douek

Robert Seder

Nancy Sullivan

Judy Stein

Lingshu Wang

Wei Shi

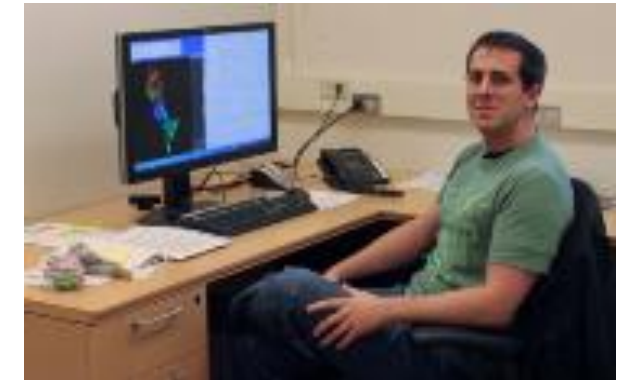
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