

# **Development of Sendai Virus Vaccines to Prevent Pediatric Respiratory Infections**

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## ***Paramyxoviridae* family**

### ***Sub-family Paramyxovirinae***

#### **Genus *Respirovirus***

**Human parainfluenza virus, type 1 (hPIV-1)  
type 3 (hPIV-3)**

**Sendai virus (murine PIV-1)**

Genus *Rubulavirus*

Genus *Morbillivirus*

### ***Sub-family Pneumovirinae***

#### **Genus *Pneumovirus***

**Human respiratory syncytial virus (RSV)**

Genus *Metapneumovirus*

**Part I: Sendai virus as a vaccine for human PIV-1**

**Part II: Recombinant Sendai virus as a vaccine for RSV**

**Part III: Recombinant Sendai virus as a vaccine for human PIV-3**

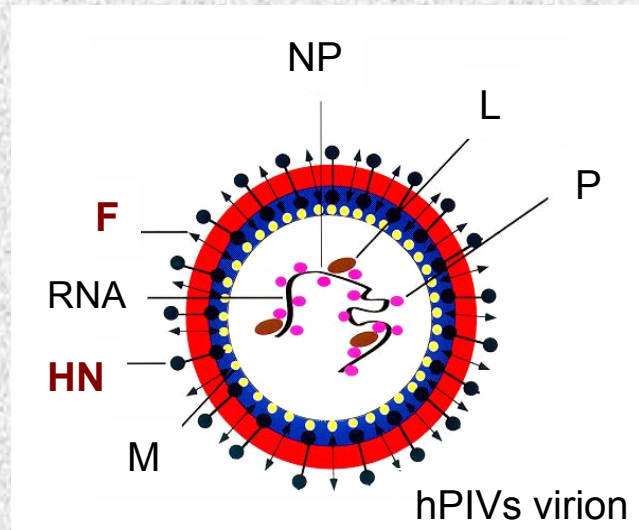
**Part I: Sendai virus as a vaccine for human PIV-1**

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**Part III: Recombinant Sendai virus as a vaccine for hPIV-3**

# hPIV-1 Epidemiology

- Age: 6 mo - 3 yrs
- Incidence: ~ 600,000 cases / year in US
- Severity: ~ 5% children are hospitalized (~30,000 / yr)



## Sequence identity shared between Sendai and hPIV-1

Gene	Amino Acid Sequence Identity between hPIV-1 and SV	Reference
<b>HN</b>	72%	Gorman WL, et al. <i>Virology</i> <u>170</u> :211-221, 1990
<b>F</b>	68%	Merson et al. <i>Virology</i> <u>167</u> :97-105, 1988.
<b>M</b>	87%	Power U, et al. <i>Virology</i> <u>191</u> :947-952, 1992.
<b>NP</b>	83%	Lyn D, et al. <i>J Gen Virol</i> <u>72</u> :983-987, 1991.
<b>P</b>	53%	Power U, et al. <i>Virology</i> <u>189</u> :340-343, 1992.
<b>L</b>	83%	Merson et al. <i>Virology</i> <u>167</u> :97-105, 1988.

Sequence homology correlates with shared antigenicity

Smith FS, Portner A, Leggiadro R, Turner V, Hurwitz. *Virology* 205:453-461, 1994.

Sangster M, Smith FS, Coleclough C, Hurwitz JL. *Virology* 212:13-19, 1995.

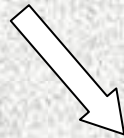
# Can Sendai virus work as a natural vaccine for human PIV-1?

Protection study in non-human primates  
(African green monkeys):

**Group 1:**  
**Sendai virus,**  
 $7.6 \times 10^7 \text{EID}_{50}$ , intranasal



Boost, day 126



**Challenge, day 154**  
**human PIV-1,**  
 $10^6$  PFU/monkey, intranasal

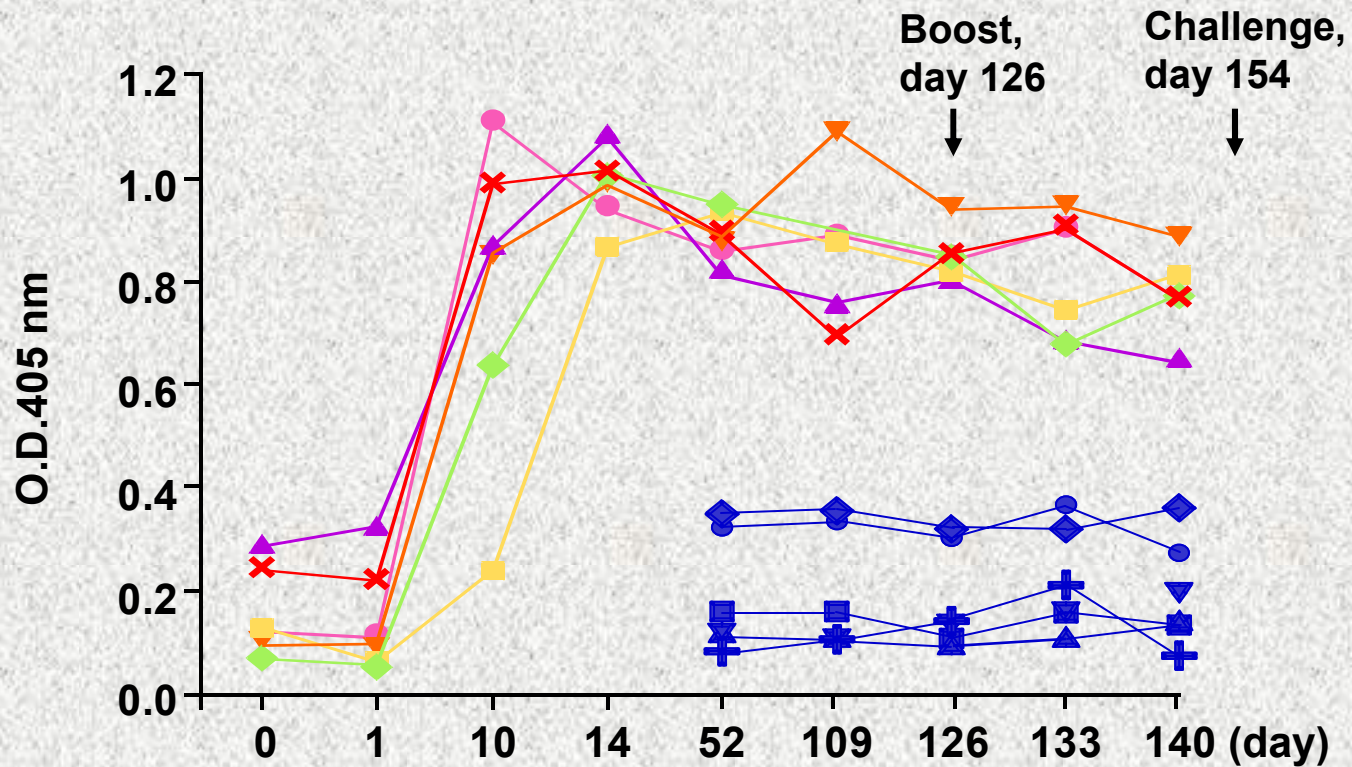
**Group 2:**  
Saline  
intranasal



Allantoic fluid



## Sendai virus induces a strong, durable virus-specific antibody response



## Sendai virus inoculations protect African green monkeys from subsequent infection with hPIV-1

Animal	Virus isolation on day following challenge							
	0	1	2	3	4	5	7	8
<b>SV immune</b>								
M627	-	-	-	-	-	-	-	-
M628	-	-	-	-	-	-	-	-
N836	-	-	-	-	-	-	-	-
N837	-	-	-	-	-	-	-	-
N842	-	-	-	-	-	-	-	-
N845	-	-	-	-	-	-	-	-
<b>Control</b>								
K089	-	-	+	+	+	+	+	-
M396	-	-	+	+	-	-	-	-
P778	-	-	+	+	+	+	-	-
P783	-	-	+	+	+	+	+	-
P790	-	-	+	+	+	+	+	-
P800	-	-	+	+	+	+	-	-

**Adults**



**Children**



**Younger children**  
hPIV-1 serum positive  
hPIV-1 serum negative



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Safety and immunogenicity of intranasal murine parainfluenza virus type 1 (Sendai virus) in healthy human adults

Karen S. Slobod<sup>a,d,\*</sup>, Jerry L. Shenep<sup>a,d</sup>, Jorge Luján-Zilbermann<sup>a</sup>, Kim Allison<sup>a</sup>, Brita Brown<sup>b</sup>, Ruth Ann Scroggs<sup>a,c</sup>, Allen Portner<sup>a,c,e</sup>, Chris Coleclough<sup>b,e</sup>, Julia L. Hurwitz<sup>b,e</sup>

**Subjects:** 9 healthy adults  
(average age 29 years)

**SV (Enders), i.n.,** 5  $10^5$  EID<sub>50</sub>  
5  $10^6$  EID<sub>50</sub>  
5  $10^7$  EID<sub>50</sub>

**Results:** Intranasal Sendai virus was uniformly well-tolerated

## **Part I: Sendai virus as a vaccine for human PIV-1**

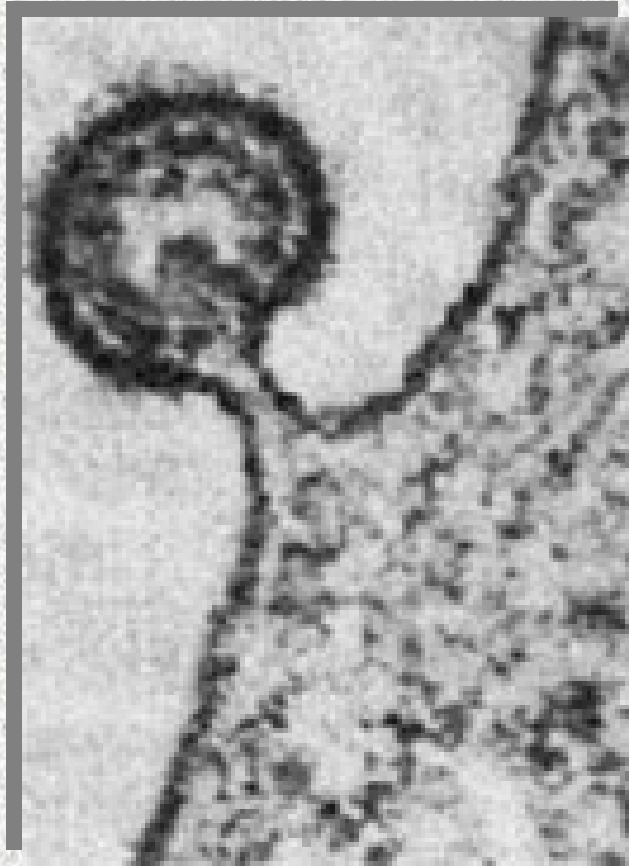
### **Conclusion (I)**

1. Sendai virus is an effective vaccine for hPIV-1 in a non-human primate model
2. Sendai virus is well-tolerated in human trials to date.
3. Clinical trials are progressing.

**Part I:** Sendai virus as a vaccine for human PIV-1

**Part II:** **Recombinant Sendai virus as a vaccine for RSV**

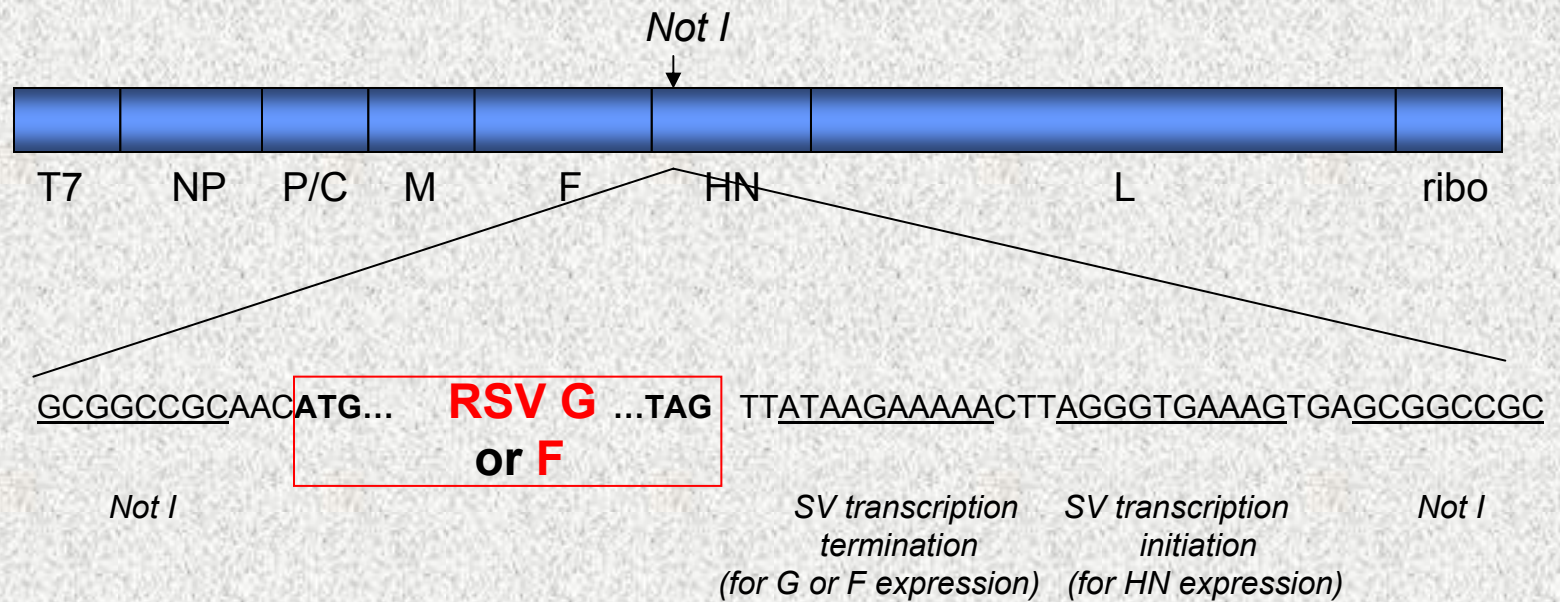
**Part III:** Recombinant Sendai virus as a vaccine for hPIV-3



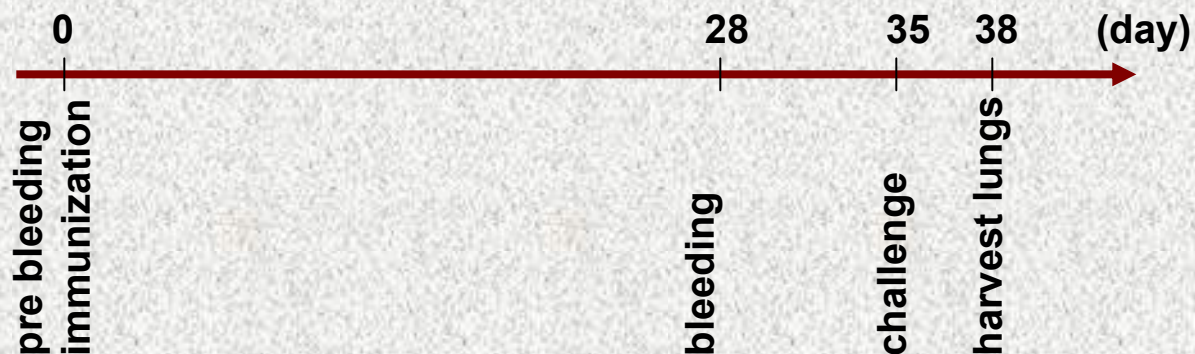
## Respiratory Syncytial Virus (RSV)

- ❑ Leading cause of viral lower respiratory tract illness in children and in high-risk adults
- ❑ > 120,000 infant hospitalizations annually in US.
- ❑ Worldwide, is estimated to cause approximately 900,000 deaths per year.
- ❑ No effective vaccine to date

# Generated recombinant Sendai viruses Expressing RSV F or G glycoproteins



## Strategy of Vaccine Evaluation: Animal immunization and challenge schedule



1. Animal model Cotton rat (*Sigmodon hispidus*)
2. Immunization 

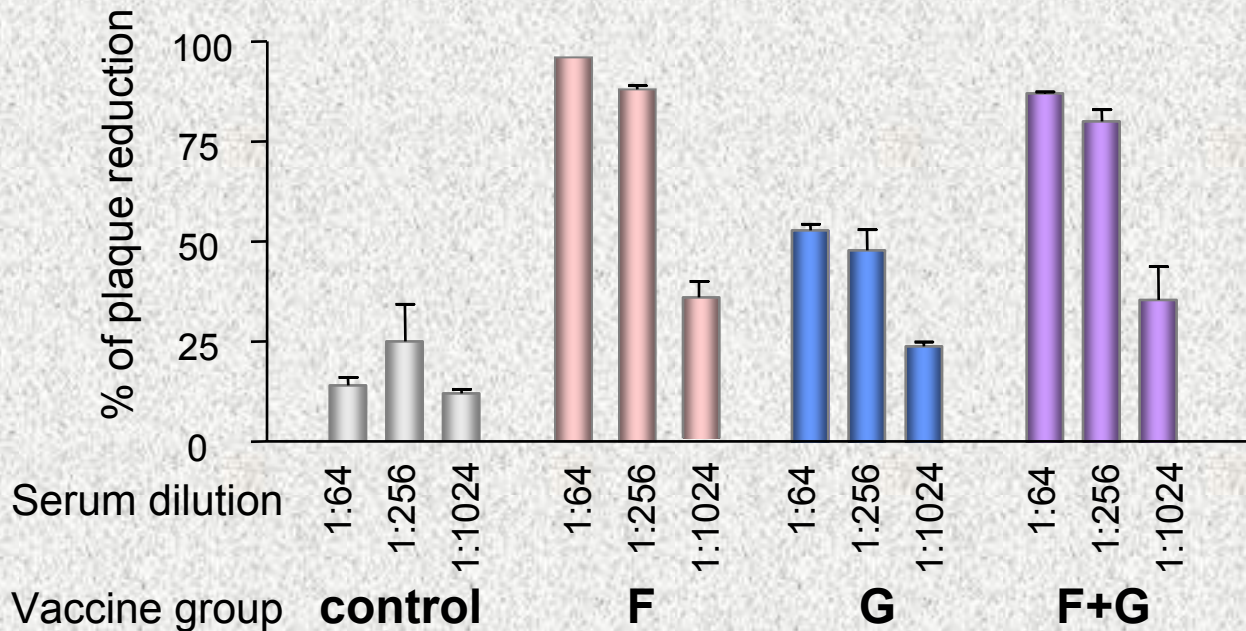
rSV-RSV-A2, <b>F</b>	} (2 x10 <sup>6</sup> PFU/rat)
rSV-RSV-A2, <b>G</b>	
rSV-RSV-A2, <b>F+G</b>	
SV(wt)	

(5 animals/group)
3. Challenge RSV-A2 (1.5 x10<sup>6</sup> PFU/rat)

## Experimental Assays

1. **Neutralization** – to detect the viral-specific neutralization capability
  - different dilutions of serum (1:64, 1:256, 1:1024)  
RSV
  - Incubated for 1 hour
  - infected host cells – plaque assay
2. **Elispots** – to detect the viral- specific T cell response
  - collected mediastinal lymph nodes (MLN), made single cell suspension
  - coated Elispot plates with anti-INF-r
  - mixed cells from MLN with RSV G or F peptide pools
  - after 48 hours culture, developed and read out the spots.
3. **Viral titration**– to detect the amount of virus in the lung
  - homogenized lung
  - made a serial dilution
  - infected host cells – plaque assay

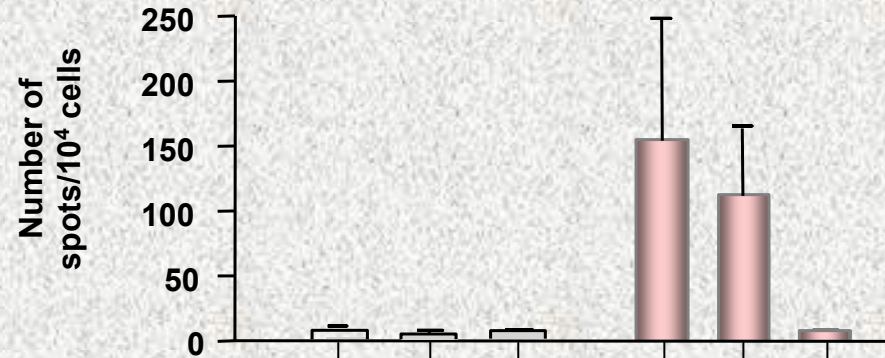
## Immunization with Sendai virus recombinants expressing RSV F, G or F+G elicited RSV-specific neutralizing antibody responses



## Immunization with Sendai virus recombinants expressing RSV F or G elicited RSV-specific T cell responses

Mediastinal Lymph  
Nodes (MLN)

Elispots



Imm. RSV-F	control (SV)			F		
F peptide pool	2	5	no	2	5	no



Imm. RSV-G	control (SV)			G		
G peptide pool	10	11	no	10	11	no



## **Part II: Recombinant Sendai virus as a vaccine for RSV**

### **Conclusion (II)**

1. Sendai virus is a valuable platform for an RSV vaccine.
2. G, F and G+F combination primed cotton rats generate RSV-specific antibody and T cell responses.
3. G, F and G+F combination vaccines protect cotton rats from RSV challenge.
4. G, F and G+F combination vaccines also are capable to protect cotton rats from heterologous RSV challenge.
5. Recombinant Sendai virus elicits long-lasting antibody responses, important for pediatric vaccines.

**Part I:** Sendai virus as a vaccine for human PIV-1

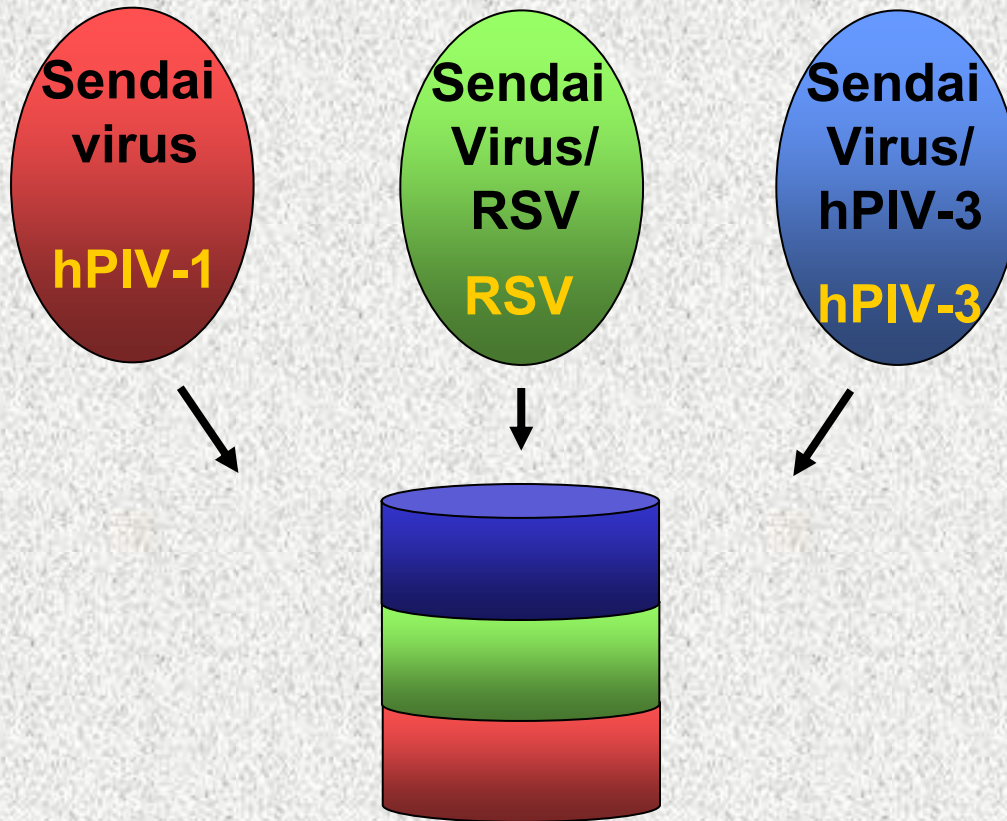
**Part II:** Recombinant Sendai virus as a vaccine for RSV

**Part III:** Recombinant Sendai virus as a vaccine for hPIV-3

Recombinant Sendai viruses expressing F and HN of hPIV3 elicit hPIV3-specific neutralizing antibody responses.

Recombinant Sendai viruses expressing F and HN of hPIV3 protect cotton rats from hPIV3 challenge.

## Recipe of pediatric respiratory virus vaccine



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