Development of Sendai Virus Vaccines to Prevent Pediatric Respiratory Infections

Xiaoyan Zhan

Department of Infectious Disease,
St. Jude Children’s Research Hospital
Memphis, TN, USA
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 Morbilliviruses

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

Part II: Recombinant Sendai virus as a vaccine for RSV

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amino Acid Sequence Identity between hPIV-1 and SV</th>
<th>Reference</th>
</tr>
</thead>
</table>

Sequence homology correlates with shared antigenicity

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, 7.6x10^7 EID$_{50}$, intranasal*

↓

Boost, day 126

**Group 2:**
Saline intranasal

↓

Allantoic fluid

**Challenge, day 154**
*human PIV-1, 10^6 PFU/monkey, intranasal*
Sendai virus induces a strong, durable virus-specific antibody response.
Sendai virus inoculations protect African green monkeys from subsequent infection with hPIV-1

<table>
<thead>
<tr>
<th>Animal</th>
<th>Virus isolation on day following challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>SV immune</td>
<td></td>
</tr>
<tr>
<td>M627</td>
<td>-</td>
</tr>
<tr>
<td>M628</td>
<td>-</td>
</tr>
<tr>
<td>N836</td>
<td>-</td>
</tr>
<tr>
<td>N837</td>
<td>-</td>
</tr>
<tr>
<td>N842</td>
<td>-</td>
</tr>
<tr>
<td>N845</td>
<td>-</td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>K089</td>
<td>-</td>
</tr>
<tr>
<td>M396</td>
<td>-</td>
</tr>
<tr>
<td>P778</td>
<td>-</td>
</tr>
<tr>
<td>P783</td>
<td>-</td>
</tr>
<tr>
<td>P790</td>
<td>-</td>
</tr>
<tr>
<td>P800</td>
<td>-</td>
</tr>
</tbody>
</table>
Safety and immunogenicity of intranasal murine parainfluenza virus type 1 (Sendai virus) in healthy human adults

Subjects: 9 healthy adults (average age 29 years)

SV (Enders), i.n., 5 \times 10^5 \text{ EID}_{50} \hfill 5 \times 10^6 \text{ EID}_{50} \hfill 5 \times 10^7 \text{ EID}_{50}

Results: Intranasal Sendai virus was uniformly well-tolerated
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

T7        NP     P/C     M           F           HN             L                          ribo

GCGGCCGC

AAC

ATG… RSV G …TAG

TTATAAGAAAAACTTAGGTGAAAGTGAGCGGCCGC

Not I

Not I

SV transcription termination (for G or F expression)

SV transcription initiation (for HN expression)
Strategy of Vaccine Evaluation: Animal immunization and challenge schedule

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

2. Immunization  
   - rSV-RSV-A2, **F**
   - rSV-RSV-A2, **G**
   - rSV-RSV-A2, **F+G**
   - rSV (wt)
   - (5 animals/group)

3. Challenge  RSV-A2 (1.5 x 10^6 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 form 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

<table>
<thead>
<tr>
<th>Imm. RSV-F</th>
<th>control (SV)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>F peptide pool</td>
<td>2 5 no</td>
<td>2 5 no</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imm. RSV-G</th>
<th>control (SV)</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>G peptide pool</td>
<td>10 11 no</td>
<td>10 11 no</td>
</tr>
</tbody>
</table>
Immunization with Sendai virus recombinants expressing RSV F, G or F+G elicited protection from RSV challenge.
Part II: Recombinant Sendai virus as a vaccine for RSV

Conclusion (II)

1. Sendai virus is a valuable platform for an RSV vaccine.


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

- Sendai virus
- hPIV-1
- Sendai Virus/RSV
- RSV
- Sendai Virus/hPIV-3
- hPIV-3
Acknowledgments

Karen Slobod  Pam Freiden  Allen Portner  Charlie Russell Lab
Julia Hurwitz  Bart Jones  Toru Takimoto  David Carey (ARC)
Chris Coleclough  Kris Branum  Sateesh  John DeVincenzo Lab
Robert Sealy  Jerry Shenop  Krishnamurthy  (LeBonheur Children’s
Scott Brown  Nanna Howlett  Irina Alymova  Hospital, Memphis)
Sherri Surman  Ruth A. Scroggs

This work was supported in part by NIH grant P01 AI54955, NIH P30-CA21765, and the American Lebanese Syrian Associated Charities (ALSAC).