Development of Sendai virus-based vaccines to prevent pediatric respiratory virus infections

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Abstract

Respiratory syncytial virus (RSV) and the human parainfluenza viruses (hPIV) are the leading causes of hospitalizations for viral respiratory tract diseases in infants and young children. Despite approximately 50 years of research, there is currently no vaccine available for any of these pathogens. Sendai virus (SeV) is a mouse respiratory virus that merits consideration as a Jennerian vaccine for hPIV-1 due to its similarity with hPIV-1 in terms of sequence, structure and antigenicity. The SeV backbone can also be manipulated using reverse genetics to create SeV-based RSV and hPIV-3 vaccines. We have prepared two recombinant SeV vaccines, expressing the fusion protein of RSV and the hemagglutinin-neuraminidase protein of hPIV-3, respectively. We found that a single intranasal vaccination with the combined recombinant SeVs (‘mixed-rSeV’) protected cotton rats from challenges with hPIV-1, hPIV-3 and RSV. This discovery, combined with our preliminary clinical demonstration that intranasal administration of unmodified SeV is safe in adults and children, makes a compelling case for advanced development of the SeV-based vaccine product.

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1. SeV-based vaccines target respiratory syncytial virus and the human parainfluenza viruses

Human respiratory syncytial virus (RSV) is the most important cause of hospitalizations for viral respiratory tract diseases in infants and young children. The next most important agents of pediatric viral respiratory diseases
are the human parainfluenza viruses (hPIVs), particularly hPIV-1 and hPIV-3 [1;2]. Unfortunately, a vaccine that is both safe and protective against RSV or any of the hPIVs has not yet been identified in the clinical arena. This situation represents a serious gap in preventive medicine and highlights an urgent need to forward new vaccine concepts.

The Paramyxovirus Vaccine Program at St. Jude Children’s Research Hospital is directed toward the study of Sendai virus (SeV), the murine counterpart of hPIV-1. This research was encouraged by our initial discovery of the extensive sequence and structural homology between murine SeV and hPIV-1. We found that amino acid sequence similarity between SeV and hPIV-1 averaged 75% across six viral genes [3], and that human B-cell and T-cell responses toward hPIV-1 cross-reacted with SeV [4;5]. Moreover, immune responses in mice toward SeV were cross-reactive with hPIV-1, and the intranasal inoculation of infant mice with hPIV-1 conferred protection against intranasal SeV challenge [6].

Our collaborative studies with investigators at the Tulane Primate Center showed that when SeV was administered to African green monkeys (AGM) by the intranasal route, the vaccine was well-tolerated. SeV induced a serum antibody response against both SeV and hPIV-1 within days, and the response was long sustained. Test animals showed hemagglutination inhibition (HAI) responses (all test monkeys developed HAI titers between 1:320-1:1280) and neutralizing activities (5/6 test monkeys exhibited ≥85% hPIV-1 neutralization at a 1:50 serum dilution). In addition, hPIV-1-specific IgA antibody was evident in the nasal cavity of vaccinees. All SeV-primed animals (n=6) were fully protected from a subsequent hPIV-1 challenge while all control animals (n=6) were infected. The results of these studies indicated that unmodified SeV was a safe and effective vaccine in a primate model [7] and highlighted its potential as a candidate human vaccine for hPIV-1.

Our work with SeV in non-human primates was repeated and confirmed by Skiadopoulos et al. [8]. Specifically, this research group demonstrated that SeV inoculation of monkeys was associated with no clinical symptoms and was protective against hPIV-1. They found that SeV was also safe in chimpanzees. The virus was measurable in the lower respiratory tract (LRT) of these animals, but the titer was less than that of bPIV-3 [9], a vaccine that was reported by the same group to be safe in human infants. Results thus highlighted the attractive safety and efficacy profiles of SeV.

Based on results from pre-clinical studies, we initiated a first clinical trial to test the safety of intranasal SeV. This FDA- and IRB-approved clinical trial tested our unmanipulated SeV vaccine, which was produced at St. Jude Children’s Research Hospital in a free-standing Good Manufacturing Practices (GMP) Facility. The clinical protocol was designed such that three cohorts of three hPIV-1 seropositive, healthy young adults would receive intranasal SeV at a dose of 5 x 10^5, 5 x 10^6, or 5 x 10^7 EID_{50}, respectively [10]. The preliminary data from this clinical trial has thus far demonstrated safety of the SeV vaccine, a result that was expected based on historical experience. A review of the literature shows that despite abundant use of SeV in research laboratories and considerable contact between children and mice, there are no confirmed reports of human disease associated with natural SeV infection [11]. The safety of SeV is predicted in humans because of its natural host-range restriction, in part due to its unique sensitivity to the innate immune activities induced by human interferon [12].

Besides representing an important vaccine for hPIV-1, SeV also lends itself to manipulation by reverse genetics. Our ability to manipulate infectious SeV provided us with an arsenal of technology for the development of new vaccines [13-17]. SeV can accommodate and express a foreign gene(s) under the control of SeV gene-start and gene-stop signals. The vector can efficiently express a gene(s) up to 3.2 kb, although the replication as well as the final virus titer is proportionally reduced as the inserted gene length increases.

With reverse genetics technology, we created two new recombinant SeV (rSeV) that expressed RSV fusion protein (rSeV-RSV-F) or hPIV-3 hemagglutinin-neuraminidase (rSeV-PIV3-HN) protein genes, respectively (these gene products represent important targets of both B-cell and T-cell activities). For each of the new rSeVs, we showed that a single intranasal inoculation of the vaccine elicited potent protection from infection in a cotton rat model; cotton rats immunized with rSeV-RSV-F were protected against homologous and heterologous RSV challenges, with no indication of enhanced immunopathology [14]; cotton rats immunized with rSeV-PIV3-HN were protected against both homologous and heterologous hPIV-3 challenges [16]. Animals immunized with a mixture of the two recombinants (termed ‘mixed-rSeV’) were protected against hPIV-1, hPIV-3 and RSV [16].
2. Conclusion

The Paramyxovirus Vaccine Program at St. Jude Children’s Research Hospital has tested a mixed-rSeV product as an exciting new candidate vaccine for RSV, hPIV-1 and hPIV-3. The following information encourages further study of SeV-based vaccine products:

1) SeV has been shown to protect against hPIV-1 in two independent non-human primate studies, by two independent research groups, demonstrating its success as a Jennerian vaccine [7;8].

2) The two independent groups also demonstrated that there were no adverse events caused by SeV in AGM. Skiadopolous et. al. further showed that there were no adverse events when SeV was administered to chimpanzees [8]. In fact, the SeV grew to a lesser extent than bPIV3 in chimpanzee lungs, suggesting a superior safety profile [9].

3) Recombinant SeV products were found to elicit robust and durable protection in cotton rats against RSV and hPIVs [13-17].

4) Unlike the formalin-fixed RSV vaccine [18], the rSeV-RSV-F vaccine was shown to induce no enhanced immunopathology in the cotton rat model [13-15].

5) A mixed-rSeV vaccine (comprising rSeV-RSV-F and rSeV-PIV3-HN) conferred protection against hPVI-1, hPIV-3 and RSV in a cotton rat model [16].

6) SeV was shown to be uniquely sensitive to human IFN-alpha-induced innate responses of humans, explaining its natural host-range restriction [12].

7) Clinical trials with SeV in adults and children have thus far confirmed the safety profile defined in non-human primates [10].

8) SeV grows rapidly in both eggs and vaccine-approved Vero tissue culture cells, ensuring expeditious and cost-effective production of SeV-based vaccines.

These efficacy and safety data support translation of the rSeV vaccine products to clinical study. Should the mixed-rSeV vaccine prove safe and effective in humans, a great number of lives may be saved each year throughout the world.

3. Acknowledgements

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4. References


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