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NEWS AND COMMENTARY

Sendai virus vectors

Pushing the envelope in the lung

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Sendai virus (SeV) is a single-stranded RNA virus (of the family Paramyxoviridae) that naturally infects the airways of rodents very efficiently, causing an acute respiratory illness. The principal aspects of the SeV life cycle and genome are typical of those of other paramyxoviruses, as illustrated in Figure 1.

Note that these enveloped negative-strand RNA viruses infect airway epithelial cells by interaction of their surface glycoproteins (HN and F) with cholesterol and sialic acid residues on the cell surface, and can immediately express mRNA by primary transcription in the host cell cytoplasm, replicate the viral genome, and then enter a secondary phase of gene expression, before generation of progeny virions by budding from the cell surface. SeV-based vectors were generated by deleting the *F* gene.

The ability of ΔF-SeV vectors to infect airway epithelial cells has led to its development as a recombinant gene transfer vector, potentially for use in diseases affecting the airways, such as cystic fibrosis. Previous studies have demonstrated the ability of SeV vectors carrying reporter genes or CFTR to mediate efficient, but transient, gene transfer in the airway epithelium of mice.[2,3,4] Another study has demonstrated that a second successive dose of an SeV vector was able to transduce the murine airways, at ~60% of the efficiency seen in naïve animals.[5]

Although these earlier studies represented a significant advance in broadening the armamentarium of recombinant vectors suitable for transducing the murine airway, it was unclear whether vectors based on this murine virus would be capable of transducing larger animals. The latter would be seen as a necessary step toward clinical use, both to fulfill regulatory requirements and as a test of the ability of the vector system to work across various species, including humans, *in vivo*. Furthermore, as this virus is by its nature transient, the potential limitations of successive repeated dosing bear further examination.

In a report in this issue of *Gene Therapy*, Griesenbach *et al.*[6] take these studies further, showing SeV-mediated transduction of the airways of a large animal model (the sheep) and studying the fundamental problem of repeated dosing in greater detail. The authors have developed methods suitable for delivery of SeV to the airways of the sheep. Using a Trudell Aeroprobe (Trudell Medical International; London, Ontario, Canada) they demonstrated very efficient localized gene transfer in that species. This finding is quite significant, as it is a necessary step toward clinical trials. As expected, however, expression of the SeV vectors in the sheep lung was limited to 14 days duration, further emphasizing the importance of repeated dosing.

The question of repeated dosing was also addressed in this report. Those studies indicated that when more than two doses of vector were administered; there was a progressive loss of gene transfer with subsequent

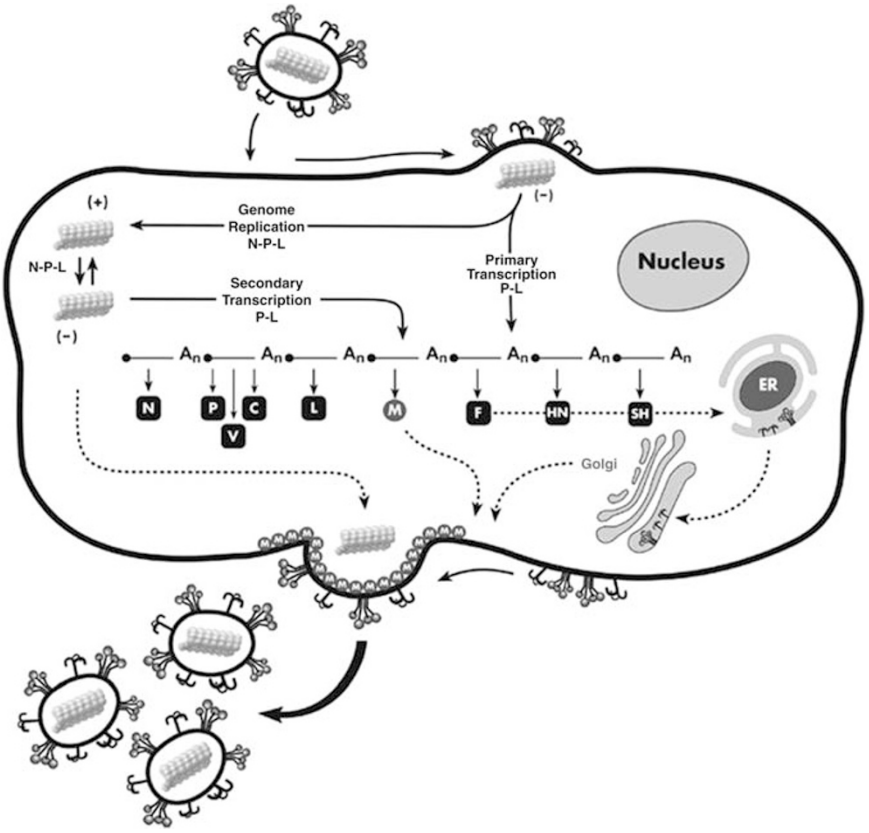

Figure 1 Life cycle of paramyxoviruses, including SeV (With permission from Knipe and Howley;[1] http://lww.com/).

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doses. This clearly indicates that some immunomodulation strategy would be needed if this vector class were to be used as a therapy for a disease like cystic fibrosis, in which long-term gene transfer is desired.

How then, does this new information serve to define the potential role of SeV-based vectors in pulmonary gene delivery? First, the studies reinforce the evidence that the use of this vector system could be very promising in experimental settings in which transient gene expression is desired, and expand that use to larger animals, such as the sheep. It is also conceivable that therapeutic indications in which transient gene expression is desired, such as the treatment of infectious diseases, could be effectively addressed with this system. The desire to apply this system to the treatment of genetic diseases, such as cystic fibrosis, seems farther off, as safe and effective immunomodulation might be particularly problematic in that patient population. That said, the field is definitely advanced by the enhanced understanding of the properties of this very efficient viral delivery system.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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