Vector-Based Replicons for Enhanced Genetic Payload Delivery and Vaccine Formulations

Safe, efficacious, and commercially tractable platform to deliver genetic payloads.

Technology

The tenOever Lab has developed a novel approach to transform negative-sense RNA viruses into safe, efficacious, and commercially tractable platforms to express a biological cargo of interest in a desired tissue for 10-14 days. This novel platform leverages species-specific biology to overcome limitations of current vector-based therapies all while enabling inexpensive large-scale manufacturing in fertilized chicken eggs. The innovators modify components of attenuated influenza A virus (IAV) or Sendai virus (SeV) strains to render them replication incompetent in all but fertilized eggs where they can be manufactured. Indeed, in unpublished data, these vectors demonstrate wild-type levels of replication in fertilized chicken eggs but no replication in mammalian cell lines. Likewise, *in vivo* data in mice, hamsters, and ferrets demonstrate no spread of these vectors despite maintaining expression at the primary target site for 10-14 days, all in the absence of immune engagement. Optimal *in vivo* targets thus far have focused on the lungs or hypothalamus. Biological cargos that have been successfully delivered *in vivo* include reporters, prime and base editors, immunomodulating cytokines, and recombinant antibodies. In summary, these vectors offer a novel approach for effective gene delivery, which capitalizes on the existing and underused GMP-grade manufacturing methodology of egg-based vaccines to produce a fast-tracked solution to current gene therapies.

Background

Gene therapies hold immense promise for treating diseases for which no other medical interventions exist. To date, the FDA has approved 30 different gene therapies, such as Zolgensma for Spinal Muscular Atrophy, Kymriah for Pediatric B-cell acute lymphoblastic leukemia, and Luxturna for retinal dystrophy. However, effective and safe delivery of gene therapies remains a substantial challenge. Current gene therapy platforms, such as adenovirus, lentivirus, and adeno-associated virus, have achieved significant successes but still face limitations and have recently received unfavorable clinical outcomes, such as Sarepta's Elevidys, which gained approval in June 2023 but resulted in the death of 16-year-old patient in 2025. This innovative species-specific replicon-based approach offers an alternative to current gene therapy platforms with several advantages, including temporal expression, no risk of DNA integration, and a facile GMP manufacturing pipeline. Taken together, this novel delivery approach represents an exciting solution to pioneer the development of next-generation gene therapies.

Development Stage

Technology ID

TEN01-03

Category

Life Sciences/Platform Technology
Life Sciences/Drug Delivery Systems
Life Sciences/Therapeutics/Gene Therapy
Life Sciences/Materials/Vectors
Life Sciences/Genetic Engineering
Life Sciences/Vaccines

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The IAV and SeV platforms have been the subject of an ongoing DARPA effort that is now in its eleventh year. Presently the IAV-based platform is being evaluated by the FDA following submission of a pre-IND package.

Applications

- **Development of gene therapies:** The SeV-based platform could be used to correct the expression of pathogenic mutations in diseases such as Cystic Fibrosis (CFTR), Primary Ciliary Dyskinesia (DNAI1, DNAH5, CCDC39), Alpha-1 Antitrypsin Deficiency (SERPINA1), or Birt-Hogg-Dubé Syndrome (FLCN).
- **Universal influenza vaccine:** The IAV-based platform could be adapted to deliver HA epitopes of all circulating influenza A and B viruses for lifelong universal influenza protection.
- **Vaccination of companion animals or livestock:** The low cost of replicon manufacturing makes it a viable platform for non-human vaccination.

Advantages

- **Inexpensive large-scale clinical-grade manufacturing:** Our species-specific replicon approach leverages the well-established and currently under-utilized egg-based vaccine manufacturing infrastructure.
- **No host genome integration:** IAV nor SeV have a DNA phase in their replication cycle, eliminating the risk of integration into the host genome.
- **Bypasses seroprevalence:** The vast global reservoir of IAV strains and the lack of natural SeV infection in humans ensure seroprevalence can be avoided.
- **Established commercialization and safety profiles:** Similar vector-based platforms for both IAV and SeV have already received FDA approval.
- **Customizable cargo:** The IAV and SeV platforms could deliver antigens or transgenes up to 2kb and approximately 12kb, respectively.

Intellectual Property

NYU has a pending U.S. non-provisional patent application covering the composition of these vector-based platforms, including the miRNA silencing cassette and different biologic cargo, for the prevention and treatment of disease.