Weill Cornell Medicine

Engineered Vectors and Virus-like Particles for Circular mRNA Expression

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Background & Unmet Need

- mRNA is a promising therapeutic modality, but is limited by the relatively short half-life of mRNA in the cytoplasm
- Another major challenge of mRNA therapeutics is achieving delivery to specific cell types, as mRNAs are taken up primarily by the liver when administered systemically
- Circular mRNAs are a promising alternative to linear mRNAs due to their lower rate of degradation and increased duration of expression
- One emerging approach for delivering mRNAs to specific cell types is virus-like particles (VLPs), which comprise the structural proteins needed to assemble a viral capsid without viral genomic material
- **Unmet Need:** Improved methods for delivery of mRNA therapeutics with stable in vivo expression

Technology Overview

- **The Technology:** Optimized vectors and virus-like particles for high efficiency expression of circular mRNAs in mammalian cells
- The inventors have expanded their RNA expression system, Tornado, to generate mRNAs by using an internal ribosomal entry site (IRES)
- This system can be used as a VLP transfer plasmid to generate VLPs packaging a circular mRNA
- In their proof-of-concept construct, the VLP transfer plasmid encodes a fluorescent reporter system for circular mRNA-specific translation
- **PoC Data:** Experimental VLPs increased levels of protein expression, producing >5-fold luminescence than controls 24 hours after transduction
- Spike-pseudotyped VLPs demonstrated selective delivery into ACE-2-expressing cells, showing that experimental VLPs can achieve cell-type specificity

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Patents:
Provisional Filed

Publications:
Unti & Jaffrey. *Cell Chem Biol*. 2024.

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Technology Applications

- Enhanced delivery of mRNA for production of therapeutic proteins or antibodies
- Enhanced delivery of mRNA encoding viral or cancer antigens for vaccination
- Enhanced delivery of gene editing proteins like Cas or cell therapy constructs like chimeric antigen receptors (CARs)

Technology Advantages

- Vectors and VLPs with circular RNA maintain more stable expression than those with linear RNA
- Extended expression of viral or cancer antigens, CARs, or gene editing proteins could enhance immune response, target cell killing, or gene editing efficiency (respectively)
- Circular mRNAs packaged into VLPs can be directed to specific cell-types

Supporting Data / Figures

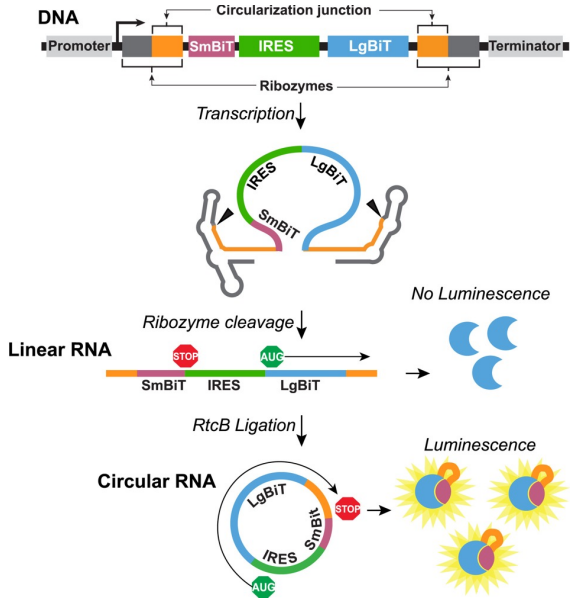

Figure 1: Overview of reporter construct for circular mRNA-specific expression using Tornado expression system.

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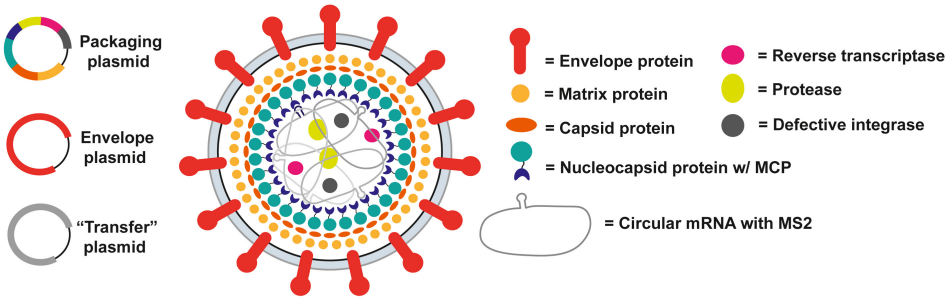

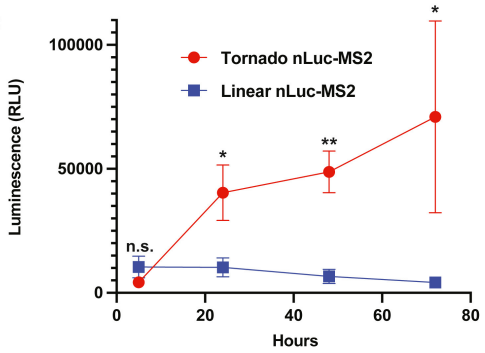

Figure 2: Top: Schematic of the circular mRNA VLP system **Bottom:** Luminescence from cells transduced with VLPs that were produced using either the Tornado translation system (Tornado nLuc-MS2) (red) or a linear mRNA expression system (Linear nLuc-MS2) (blue) at 5, 24, 48, and 72 h after transduction.

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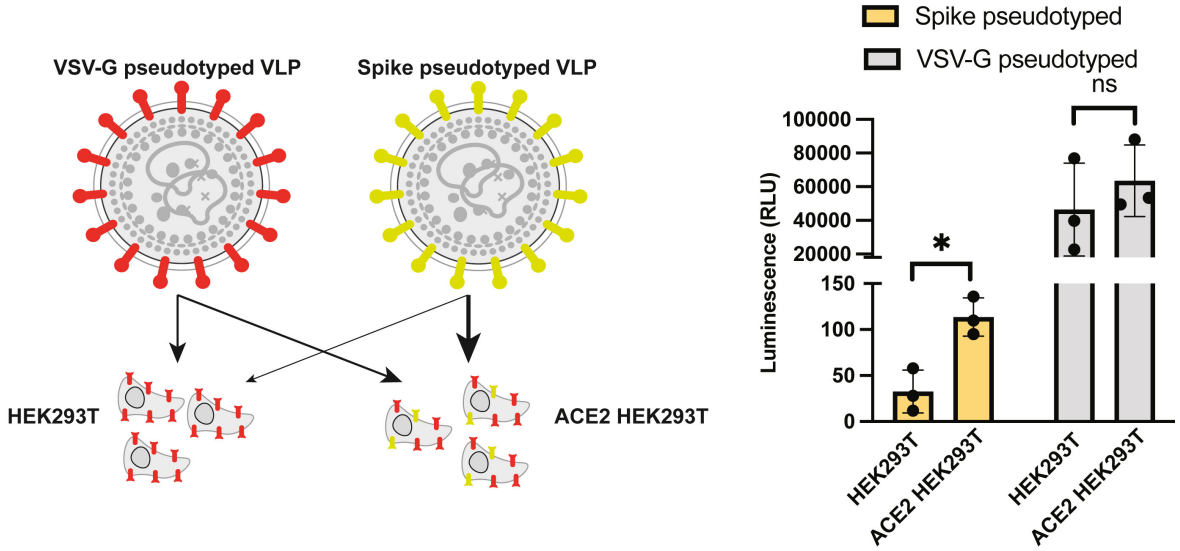

Figure 3: **Left:** Schematic of cell-type specific delivery of circular mRNA using spike pseudotyped VLPs **Right:** Luminescence from HEK293T cells and ACE2-expressing HEK293T cells transduced with VSV-G pseudotyped or spike pseudotyped VLPs containing circular nLuc mRNA ($*p < 0.05$). RLU = Relative luminescence units.

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