



Weill Cornell Medicine

Tunable Gene Therapy Expression System Regulated by Acyclovir

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Tunable Gene Therapy Expression System Regulated by Acyclovir

Background & Unmet Need

- Existing gene therapy systems rely on constitutive protein expression
- However, not all genetic diseases require continuous replacement of the defective gene product
- Prolonged or excessive expression of therapeutic proteins can also lead to toxicity
- Tailored therapy is essential as patients differ in required gene product levels, balancing therapeutic efficacy and toxicity
- Gene expression can be regulated by controlling the inclusion or exclusion of exons, a process known as alternative splicing
- Challenges related to off-target effects, efficiency, immunogenicity, and safety have arisen in gene expression systems employing alternative splicing
- **Unmet Need:** Simplified and safer method for regulating gene expression

Technology Overview

- **The Technology:** A system that utilizes acyclovir to regulate gene expression via alternative splicing of a poison exon
- A novel splicing cassette which incorporates exon 7 of survival motor neuron 1 (SMN1) as a poison exon
- The poison exon contains an in-frame stop codon, and a TSL2 stem loop modified with an acyclovir binding aptamer that can control inclusion of the exon
- In the presence of acyclovir, the poison exon is removed from mature mRNA allowing functional protein expression
- Acyclovir is an FDA-approved antiviral that is known to be well tolerated during chronic dosage
- **PoC Data:** Insertion of the splicing cassette into a luciferase reporter gene led to significant repression of reporter expression, with dose-dependent induction up to 300-fold upon acyclovir addition

Inventors:

Samie Jaffrey
Qian Hou

Patents:

US Application Filed
EP Application Filed

Publications:

Hou et al. *Nat Methods*.
2025.

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Cornell Reference:

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Technology Applications

- Incorporated into current gene therapy systems for better-controlled gene expression in terms of both levels and timing
- Adaptable tool for cellular biology research, where controlling protein expression is essential

Technology Advantages

- Utilizes FDA-approved acyclovir for regulation, offering a safer and more specific approach
- Avoids the addition of exogenous amino acids, reducing the risk of protein misfolding and immune responses

Supporting Data / Figures

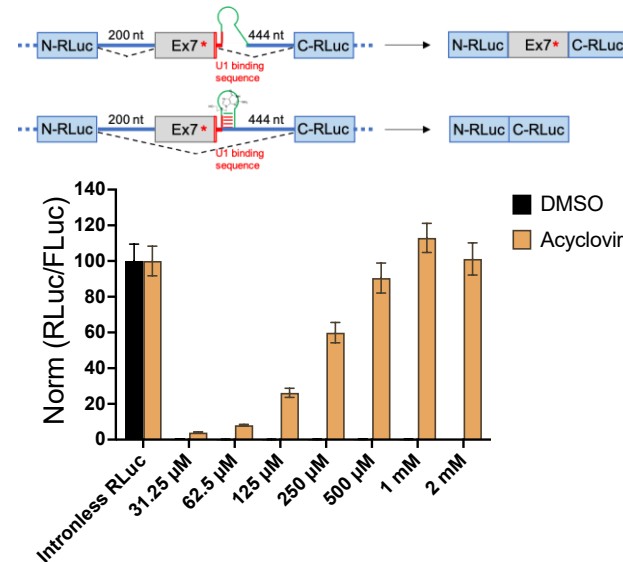


Figure 1: Schematic showing how splicing cassette regulates gene expression (**top**). Acyclovir-induced activation of the luciferase reporter gene correlated with dosage (**bottom**).

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