Weill Cornell Medicine

Platform for Aptamer-Mediated Cellular Regulation using Circular RNA Nanodevices

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Background & Unmet Need

- RNA aptamers are small RNAs capable of folding into complex structures, allowing them to bind to metabolites, proteins, or other molecules and thereby regulate cellular functions
- Various aptamers have been successfully selected against different targets and show promise as a diagnostic, prognostic and therapeutic
- Efficient RNA circularization has led to the development of aptamers resistant to exonucleases, making them highly stable and abundant within cells
- However, their constitutive binding can lead to toxicity
- Allosteric control by theophylline and tetracycline binding aptamers is possible but leads to unwanted biological effects, such as increased cyclic AMP and altered microbiomes and antibiotic resistance
- **Unmet Need:** Reliable method to control the activity of RNA aptamers in a reversible and tunable manner with minimal off-target effects

Technology Overview

- **The Technology:** A platform for generating acyclovir-controlled RNA nanodevices that can be used for controlling cell physiology
- The nanodevice incorporates two aptamers: the first aptamer (input) exhibits a conformational change upon binding acyclovir, which stabilizes the second aptamer (output) in a folded conformation that binds to an effector or performs an effector function
- **PoC Data:** Engineered an RNA nanodevice that successfully demonstrated acyclovir-dependent control of Broccoli, a fluorogenic aptamer
- Engineered an RNA nanodevice containing an iron response element (IRE), an aptamer that binds to the major undruggable iron-regulatory proteins (IRPs), enabling tunable repression of free iron levels and thus the inhibition of ferroptosis
- Compared to samples without acyclovir, those with acyclovir exhibited up to a 126% increase in FTH levels and up to a 22% decrease in TfR expression

Inventors:
Samie Jaffrey
Timo Hagen

Patents:
PCT Application Filed

Publications:
Hagen et al. *Cell Chem Biol* 2024.

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Cornell Reference:
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FTH: ferritin
TfR: transferrin receptor

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Technology Applications

- A platform for developing RNA-based therapeutics, particularly for controlling iron homeostasis and preventing ferroptosis
- Integrated into existing gene therapy platforms to enhance the control of gene expression
- As a tool in for studying cellular processes and pathway regulations

Technology Advantages

- Reversible and tunable control of aptamer function through external activators, allows for precise modulation and reset of expression
- Activation by specific, non-toxic small molecules like acyclovir ensures targeted action with minimal side effects
- Applicable to various cellular functions including mRNA cleavage, splicing, and polyadenylation

Supporting Data / Figures

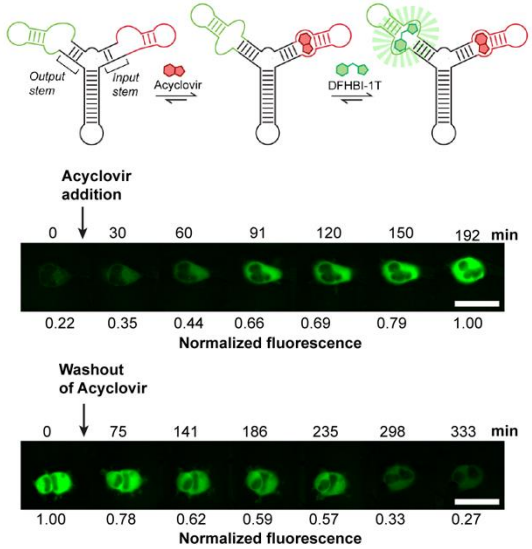

Figure 1: Top: Design of RNA nanodevice that enables acyclovir-regulated fluorescence. **Bottom:** Following acyclovir treatment, cells expressing the RNA nanodevice exhibited a progressive increase in fluorescence over time, which was reversed upon removing acyclovir.

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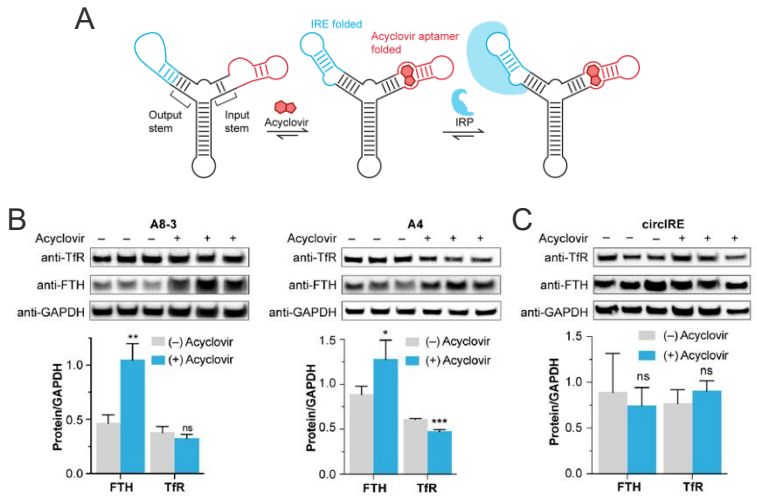

Figure 2: A: Design of RNA nanodevices that exhibit acyclovir-dependent regulation of IRE folding for controllable sequestration of endogenous IRP. **B:** RNA nanodevices shows acyclovir-dependent modulation of FTH and TfR expression. **C:** CircIRE, a constitutively folded IRE, shows no response to acyclovir.

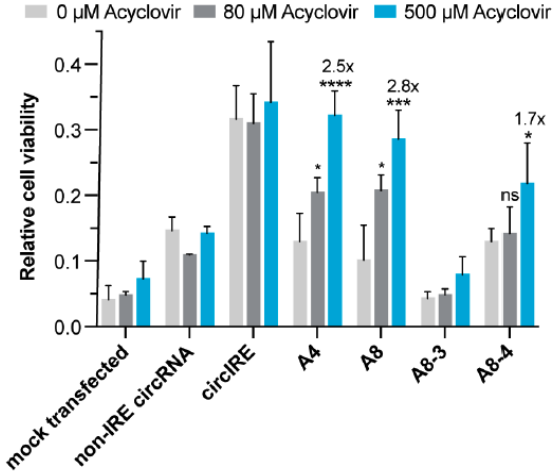

Figure 3: Acyclovir-sensitive RNA nanodevices enable tunable control of ferroptosis inhibition, not exhibited in control or circIRE.

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