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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 Filed](#)
[US Application Filed](#)

Publications:

[Hagen et al.](#) *Cell Chem Biol.* 2024.

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Cornell Reference:

D-11080, D-10197



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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

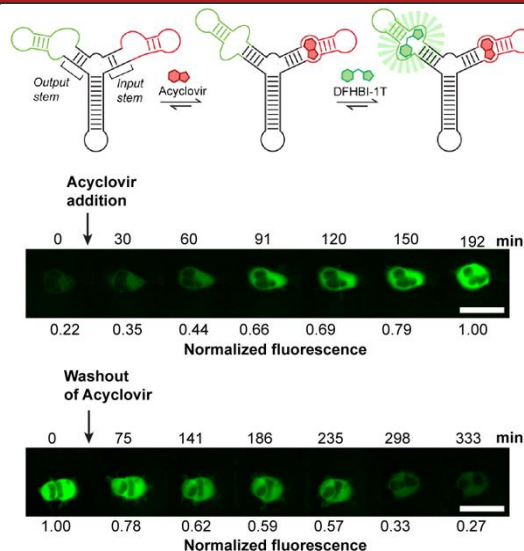


Figure 1: Top: Design of RNA nanodevice that enables acyclovir-regulated fluorescence. **Bottom:** Following acyclovir treatment, cells expressing the RNA nanodevice exhibited a progressive increase in fluorescence over time, which was reversed upon removing acyclovir.

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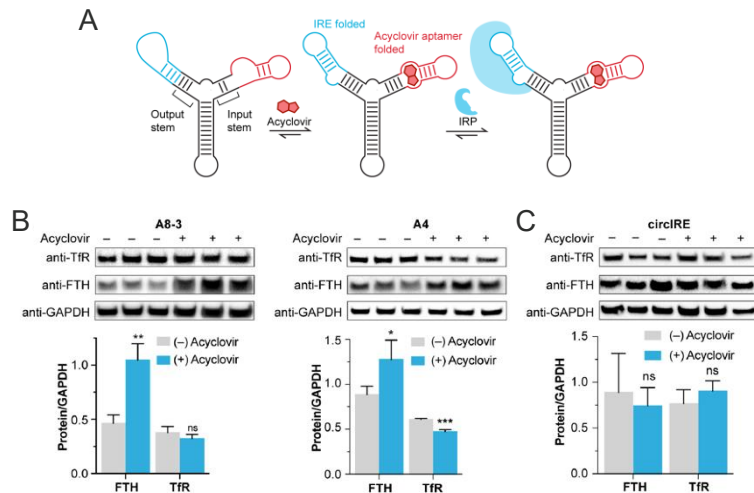


Figure 2: A: Design of RNA nanodevices that exhibit acyclovir-dependent regulation of IRE folding for controllable sequestration of endogenous IRP. **B:** RNA nanodevices shows acyclovir-dependent modulation of FTH and TfR expression. **C:** CircIRE, a constitutively folded IRE, shows no response to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

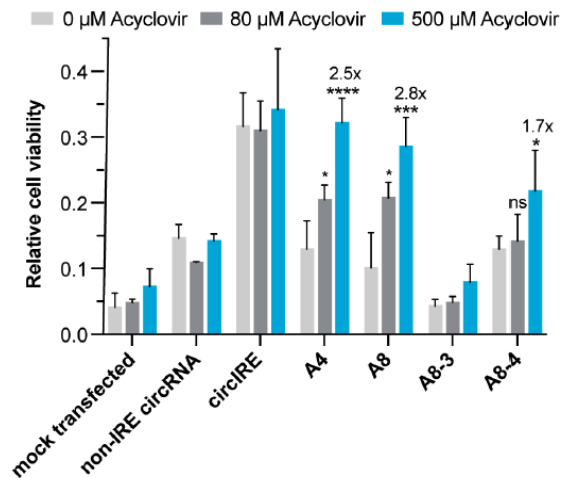


Figure 3: Acyclovir-sensitive RNA nanodevices enable tunable control of ferroptosis inhibition, not exhibited in control or circIRE.

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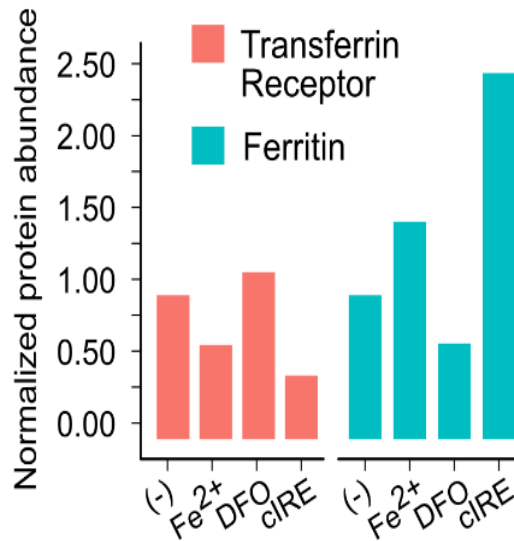
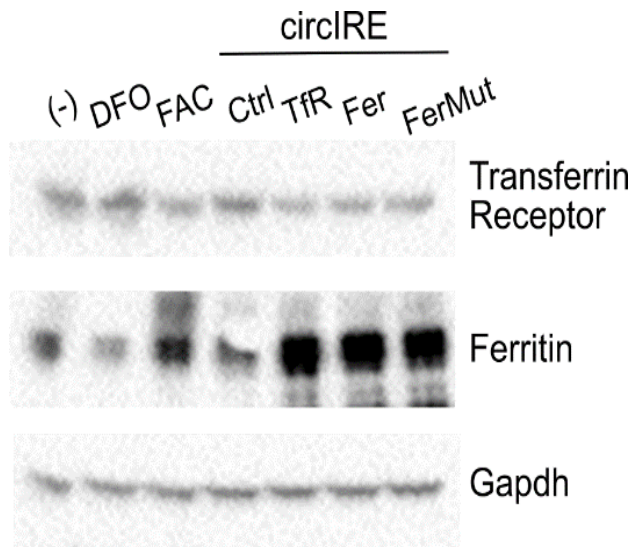


Figure 3: Circular IRE RNA demonstrates therapeutic potential for iron homeostasis control. Western blots and quantification show circIRE significantly increasing ferritin (iron storage) and decreasing transferrin receptor (iron import). These non-acyclovir-regulated circular RNA constructs demonstrate the potential for aptamer nanodevice-based iron metabolism therapeutics.

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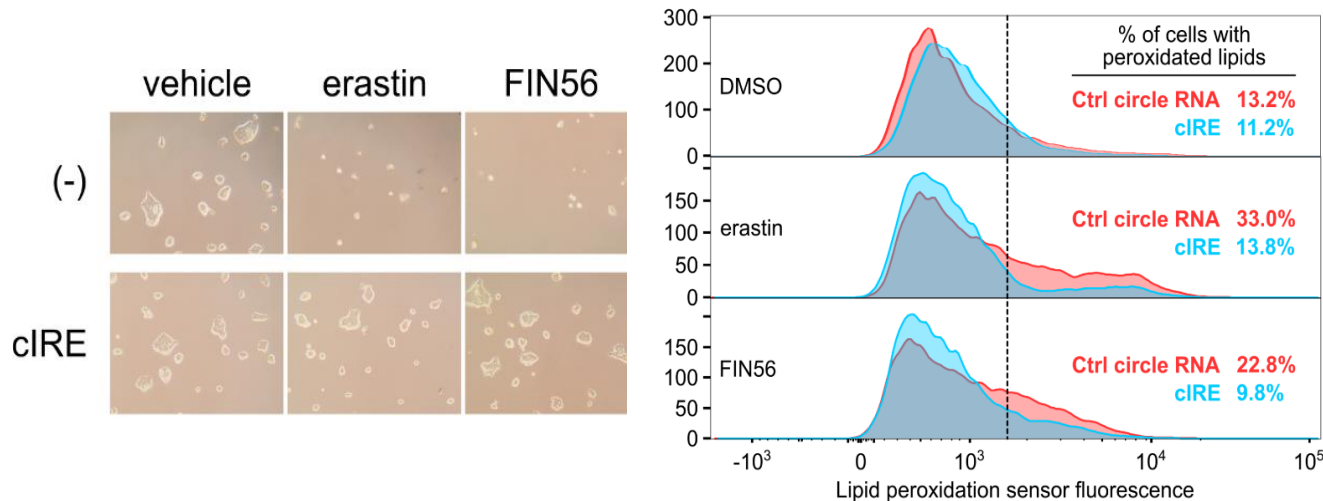


Figure 4: Circular IRE RNA provides robust protection against ferroptosis, highlighting the therapeutic potential of aptamer nanodevices for ferroptosis-related diseases. Cell viability imaging (left) shows that while control cells become nonviable following ferroptosis induction, circular IRE-expressing cells remain viable. Lipid peroxidation measurements (right) demonstrate that these non-acyclovir-regulated cIRE constructs block ferroptosis with minimal lipid oxidation compared to over 2-fold increase in control cells.

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