A versatile platform for ADAR-mediated RNA editing *in vivo* in preclinical models

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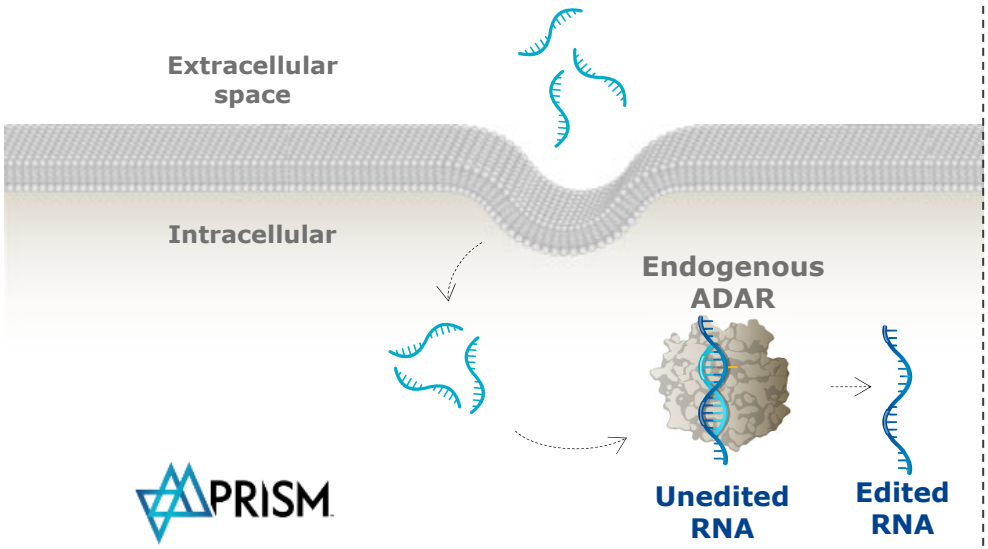
PRISM enables practical approach to RNA editing without need for viruses or exogenous protein

Wave ADAR-editing oligonucleotides



PRISM

- ✓No delivery vehicle required
- ✓No exogenous proteins necessary
- ✓Potential for reduced off-target effects

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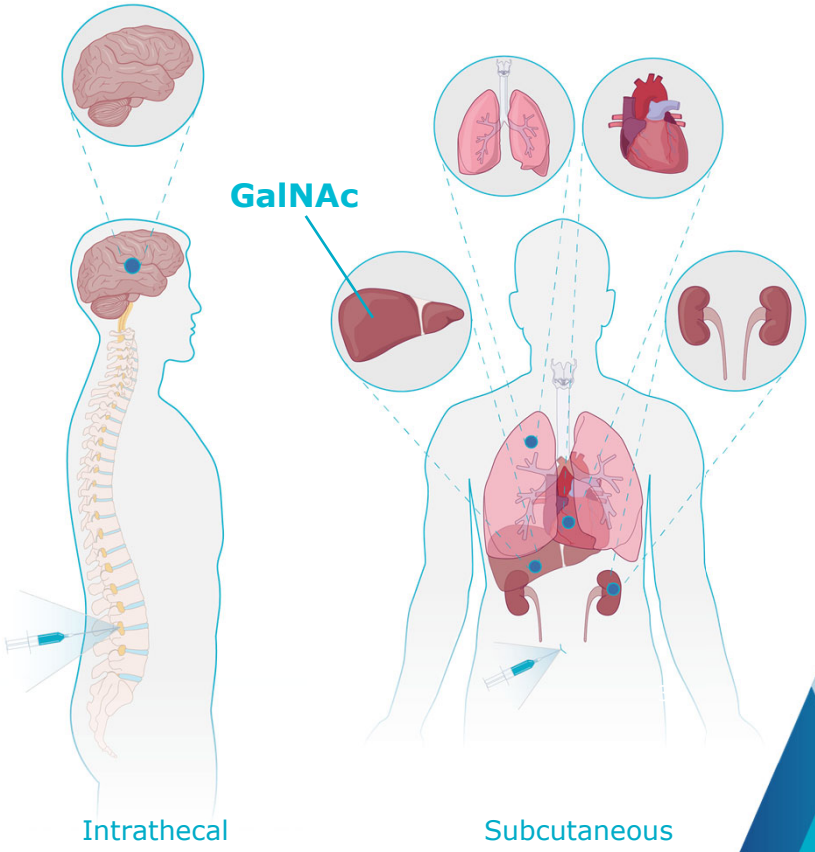
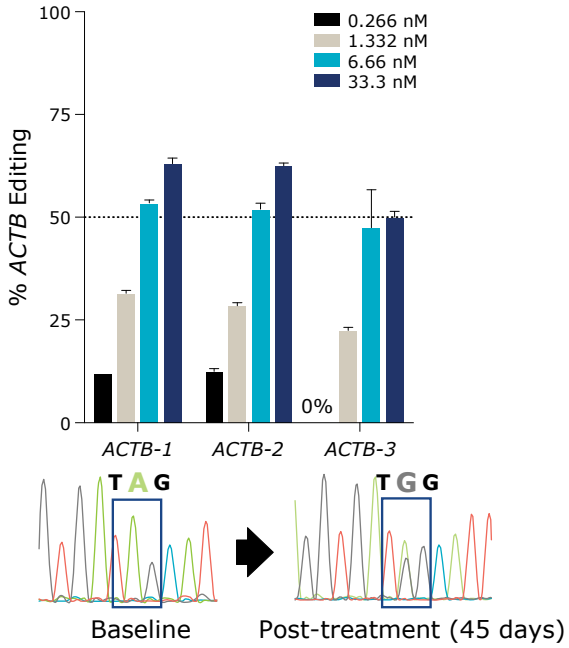


GalNAc-conjugated oligonucleotides support efficient and durable ADAR editing in NHPs

PRISM
ADAR
Systemic
Liver

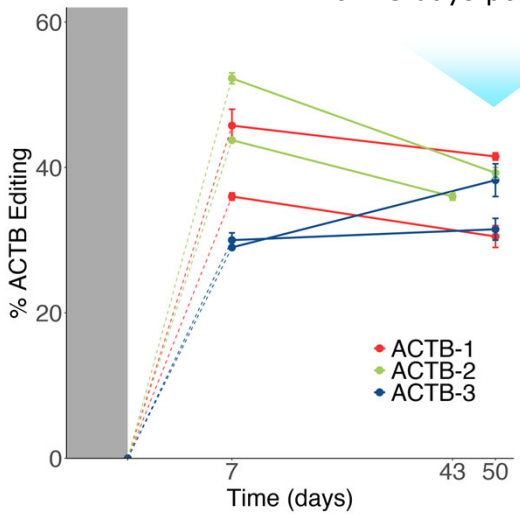
In vitro dose-response in NHP hepatocytes



Substantial and durable editing *in vivo* in NHP liver

(multiple 5 mpk, SC doses)

RNA editing out to **at least day 50**, or 45 days post-last dose



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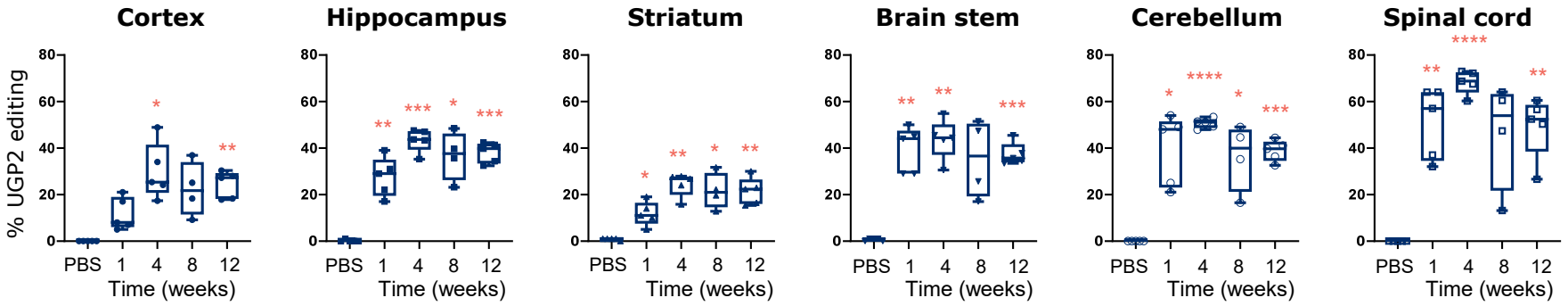
Left: Primary hepatocytes (NHP) were treated with GalNAc-conjugated oligo. Middle: GalNAc-conjugated oligo was administered once daily on days 1-5. Liver biopsies were collected on days 7 and 50. Right: Unconjugated oligo was administered once on day 1. Tissue biopsies were collected on day 8.
NHP nonhuman primate; ACTB β-actin; mpk mg/kg; SC subcutaneous; oligo A-to-I editing oligonucleotide
Stats: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; all comparisons to PBS-treated group by t test

Efficient editing up to 12-weeks post-ICV dose in transgenic human ADAR mouse CNS

PRISM
ADAR
CNS

Peak editing observed 4-weeks post-single dose across tissues



	Cortex	Hippocampus	Striatum	Brain stem	Cerebellum	Spinal cord
Peak editing	30%	>40%	25%	>40%	50%	>65%
Editing at 3 mos	25%	~40%	>20%	>35%	>35%	~50%

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Transgenic huADAR mice were administered 100 μg editing oligo or PBS on day 0 and evaluated for UGP2 editing across CNS tissues at 1, 4, 8, and 12-weeks post dose. Percentage UGP2 editing determined by Sanger sequencing. Stats: 2-way ANOVA compared to PBS (n=5 per time point per treatment) *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. ICV intracerebroventricular; PBS phosphate buffered saline

UGP2 oligonucleotide distributes throughout CNS and persists for at least 3 months

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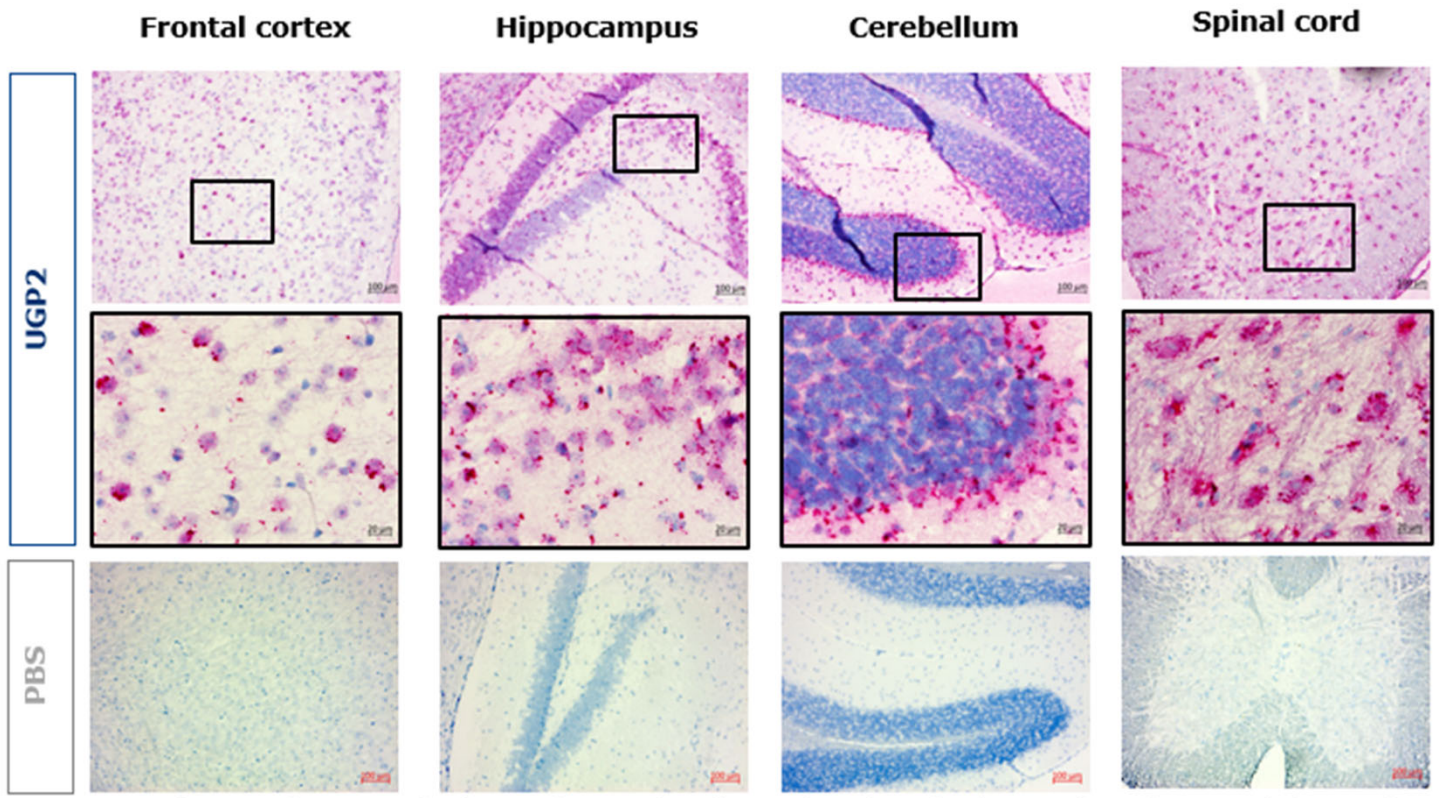
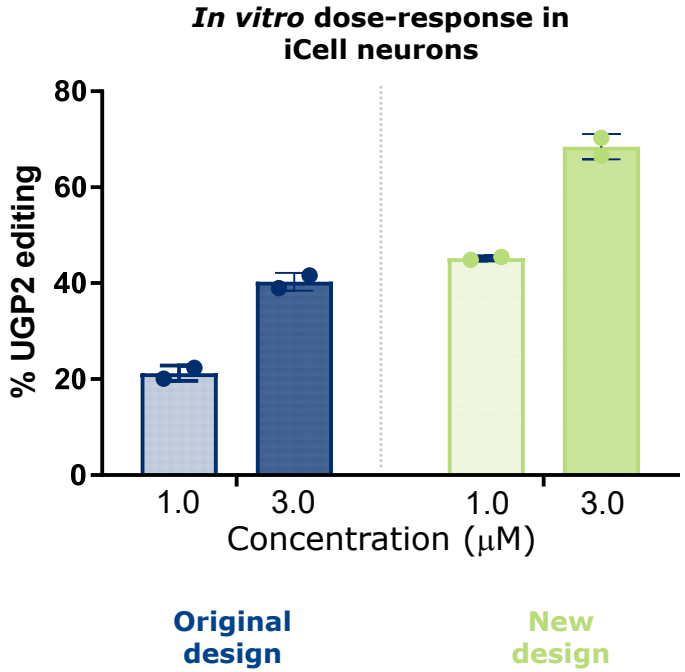
ADAR
CNS



Sections from treated mice 12-weeks after a single 100 µg dose of UGP2-editing oligonucleotide or PBS (bottom). ViewRNA (red, Fast red) was used to detect oligonucleotides; sections are counterstained with hematoxylin (blue nuclei). Magnification 10X (top & bottom), 40X (middle, oil)

Ongoing chemical optimization drives potency gains

PRISM
ADAR
CNS



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iCell neurons treated with 1 or 3 μM UGP2 editing oligonucleotide with old (left, blue) or new (right, green) chemistry. Data are mean ± sd, n=2.

Summary & future directions

- Stereopure oligonucleotides, generated with PRISM, promote RNA editing with endogenous ADAR enzymes in cellular and animal models
- Robust editing observed in liver of NHP and throughout CNS of huADAR mouse
- Editing activity is durable, persisting for at least 3 months throughout CNS of huADAR mouse after a single dose
- Chemical optimization to maximize RNA editing for clinical translation is ongoing

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