Intellia THERAPEUTICS

CRISPR/Cas9-Mediated Gene Knockout to Address Primary Hyperoxaluria

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Disclosure: Employee of Intellia Therapeutics, Inc.

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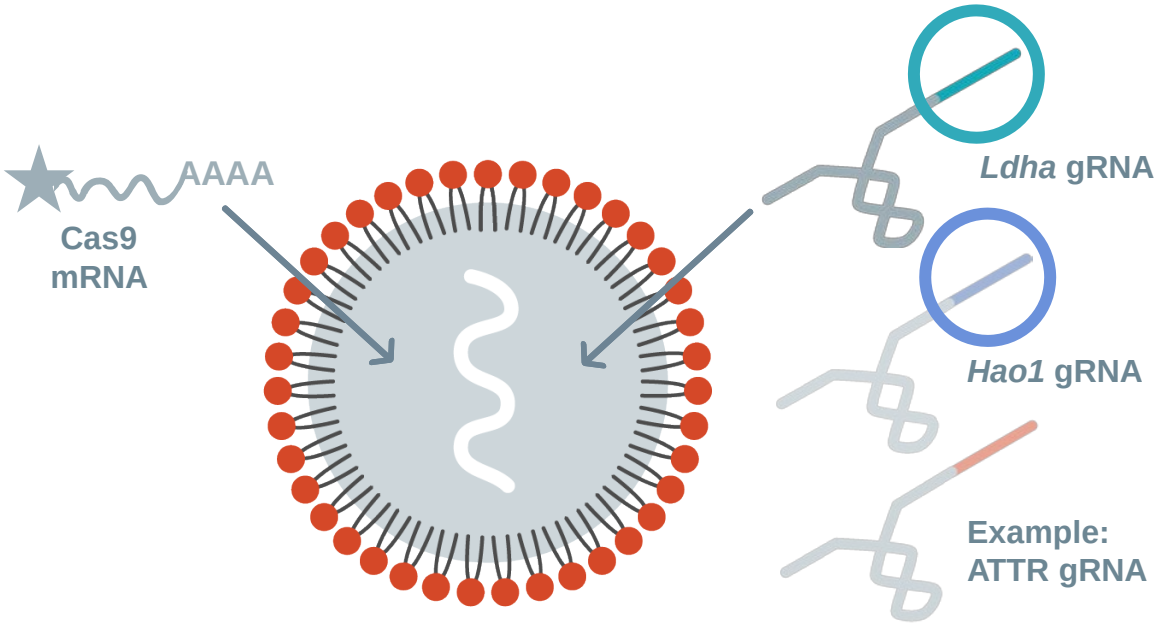
Intellia's Modular Non-Viral Delivery of CRISPR/Cas9 Addresses Disease at the Genetic Level

Lipid Nanoparticles (LNPs)



Variable portion of Intellia's modular LNP-based liver knockout approach limited to 20mer of gRNA

Key Advantages of LNP Delivery

- Large cargo capacity for CRISPR/Cas9
- Transient expression
- Scalable synthetic manufacturing
- Redosing capability
- Low immunogenicity
- Well-tolerated
- Biodegradable
- Adjustable range of tissue tropism

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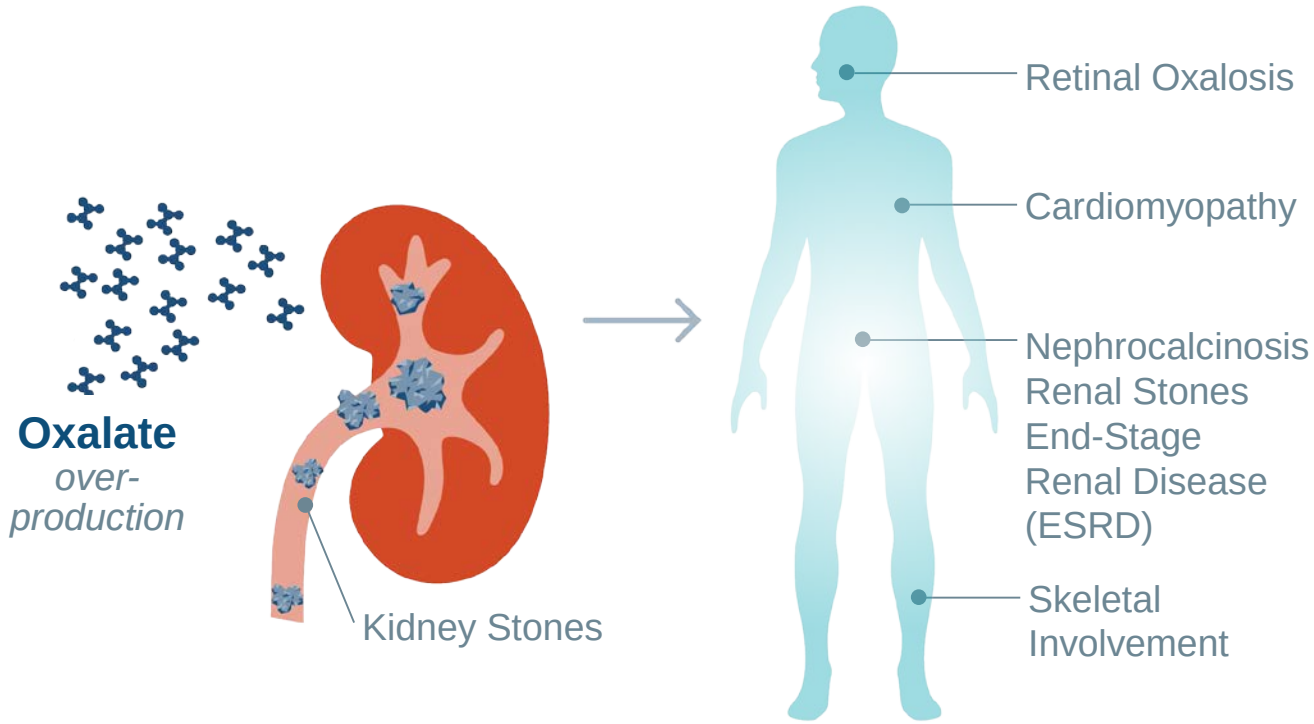
Renal Failure and Systemic Disease[1] Often Result from Oxalate Overproduction Associated with Primary Hyperoxaluria Type 1 (PH1)

Primary Hyperoxaluria Type 1 (PH1)

Rare disease with prevalence of ~1-3 per million;[1]
Potentially ~1,000 patients in U.S.*

Significant proportion of pediatric patients given
median age at onset of 5.5 years[2]

Liver transplant is only curative option[1]



[1]J Am Soc Nephrol. 2015; 26:2559-2570. [2]N Engl J Med. 2013; 369:649-658. * Assumes prevalence numbers in U.S. are similar to Europe

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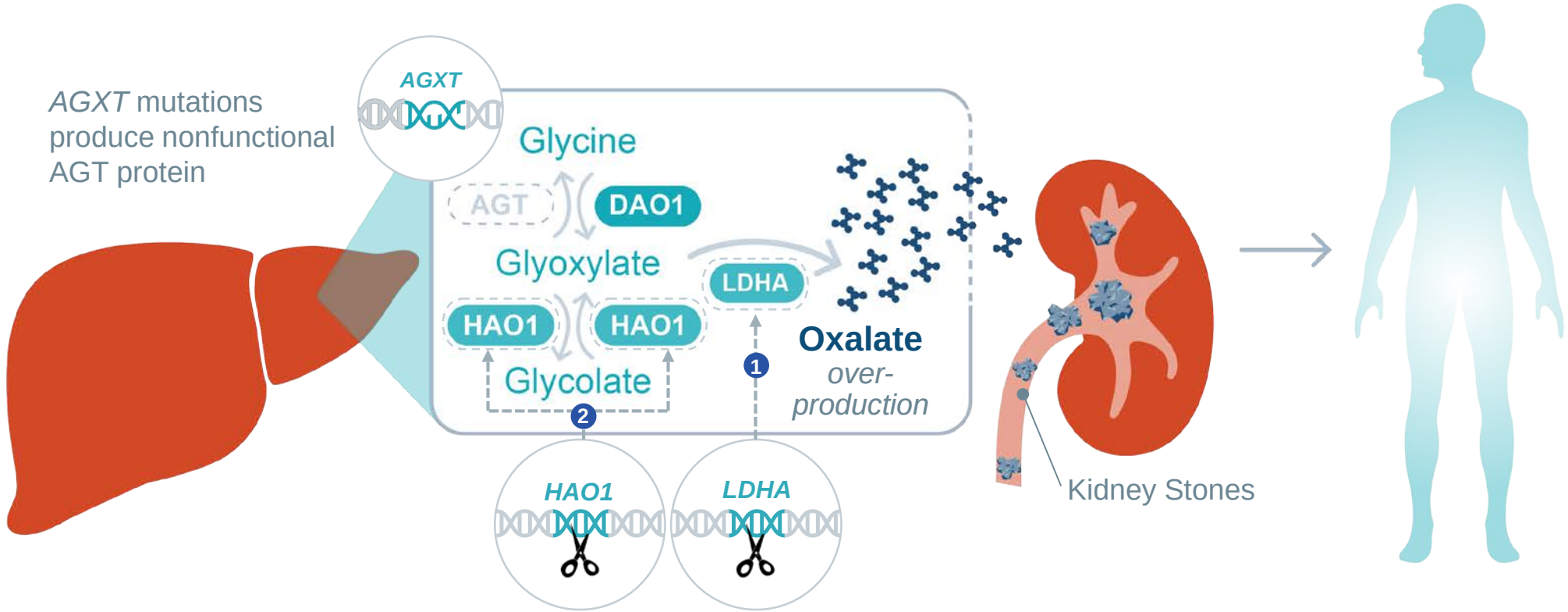
In People with PH1, the Production of Surplus Oxalate Combines with Calcium to Form Insoluble Deposits



Potential to treat PH1 with either:

1. CRISPR/Cas9-mediated knockout of *LDHA or**

2. CRISPR/Cas9-mediated knockout of *HAO1**

* Gene symbols for humans, non-human primates and other domestic species are italicized and all in upper-case. Gene symbols for mice and rats are italicized, with only the first letter in upper-case.

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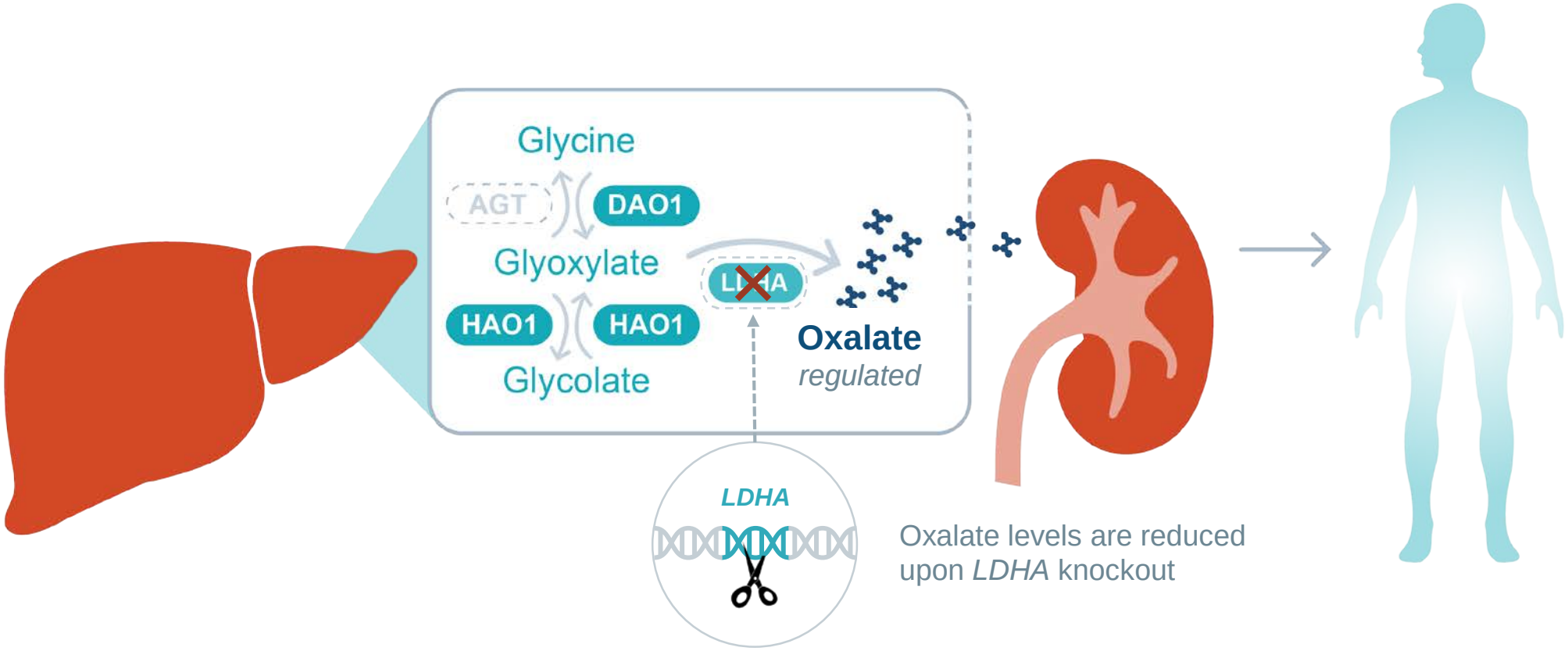
CRISPR-Mediated Knockout of *LDHA* Disrupts LDHA Protein Production

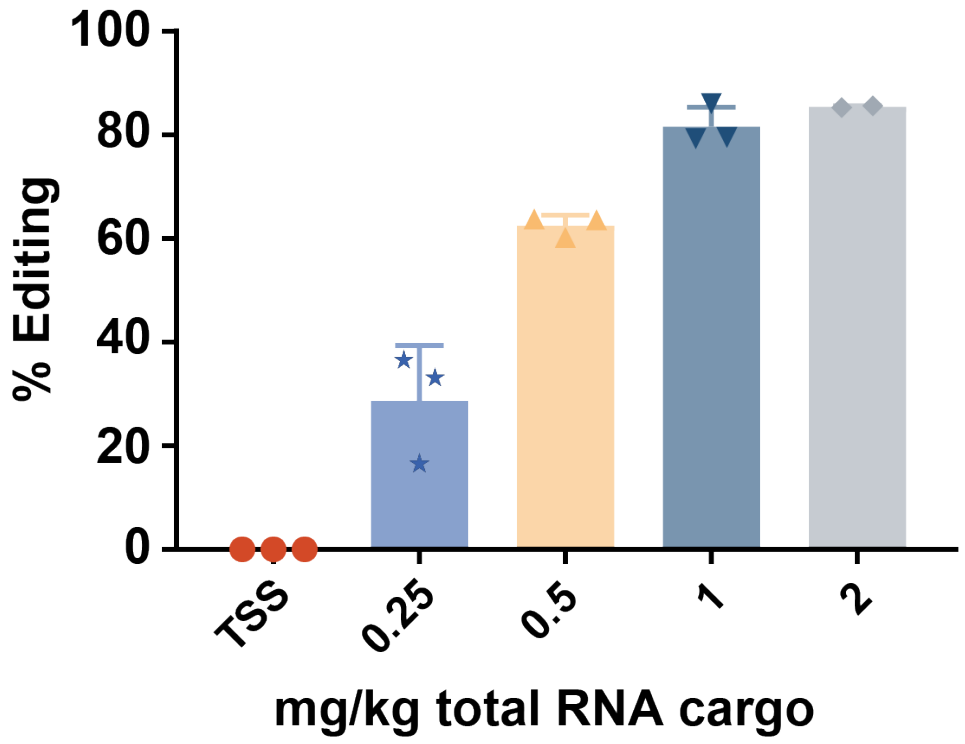


Treatment Hypothesis 1 for PH1 Patient*

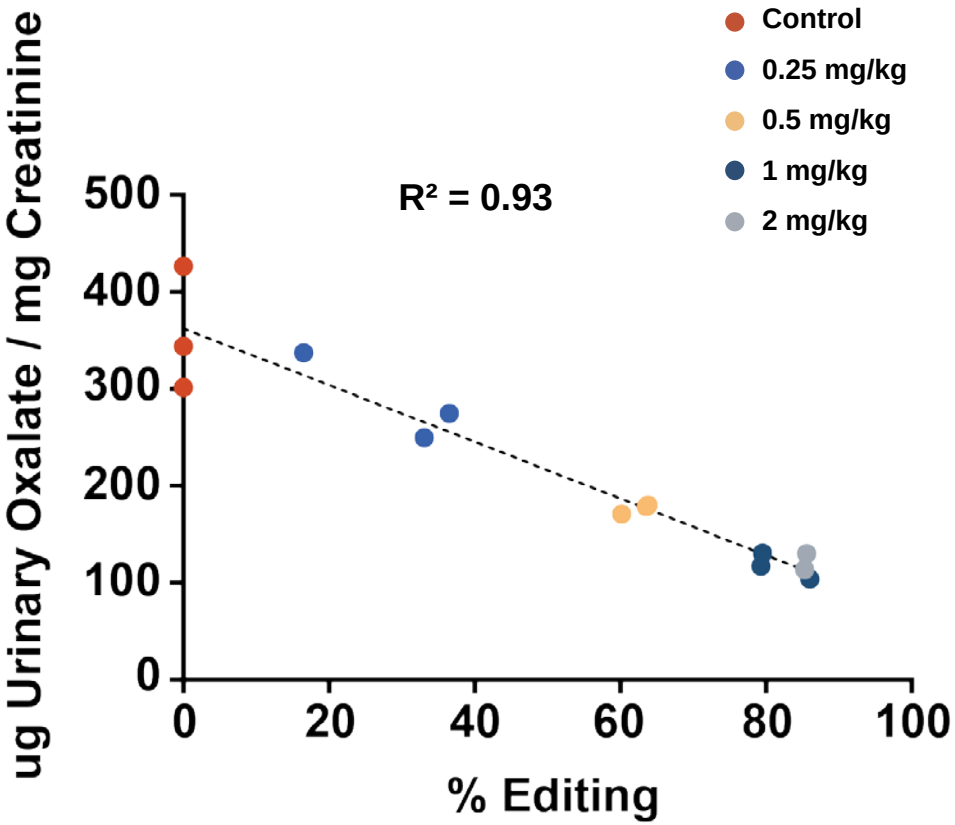
*Graphic depicts CRISPR-mediated *LDHA* knockout in PH1 patient only, although this treatment approach addresses all three forms of PH (PH1, PH2 and PH3)

In Vivo Ldha Gene Editing Levels Following Single Dose of CRISPR/Cas9 LNPs Correlate with Urinary Oxalate Decrease in PH1 Mouse Model[1]

Lead Guide[2] Achieved Robust Editing



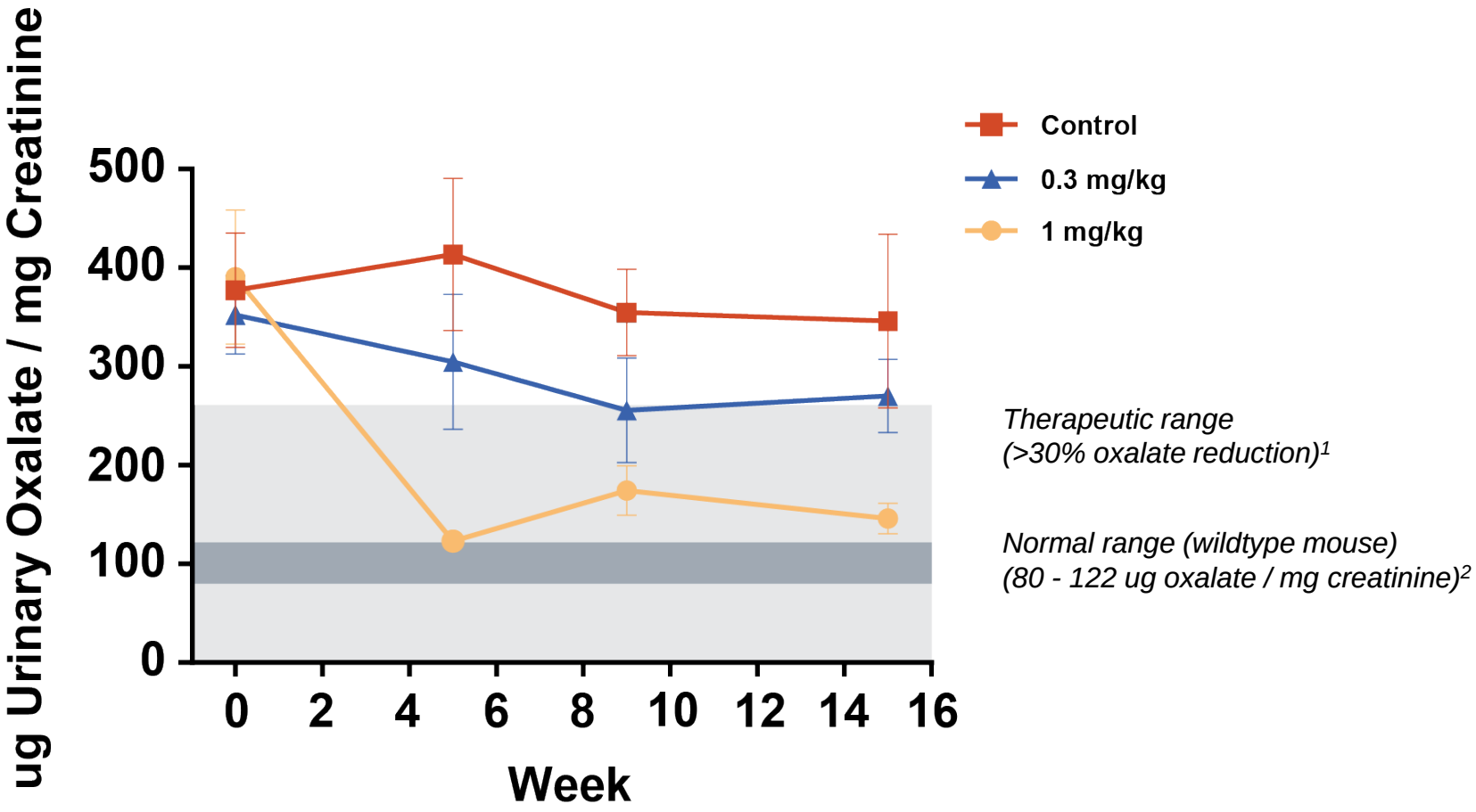
Increased Editing and Reduction in Urinary Oxalate Are Dose-Responsive[3]



[1]PNAS. 2006; 103 (48):18249-18254. [2]Intellia designed and screened guides [3]University of Alabama at Birmingham tested best guide in the *Agxt* KO mouse model for efficacy

63% Oxalate Reduction Sustained for at Least 15 Weeks, Following Single Dose of CRISPR/Cas9 LNPs at 1 mg/kg in PH1 Mouse Model

Ldha Knockout Results in Sustained Oxalate Reduction



[1]Nephrology Dialysis Transplantation 1999; 14:2556-2558.

[2]Biochim Biophys Acta 2016; 1862(2):233-239.

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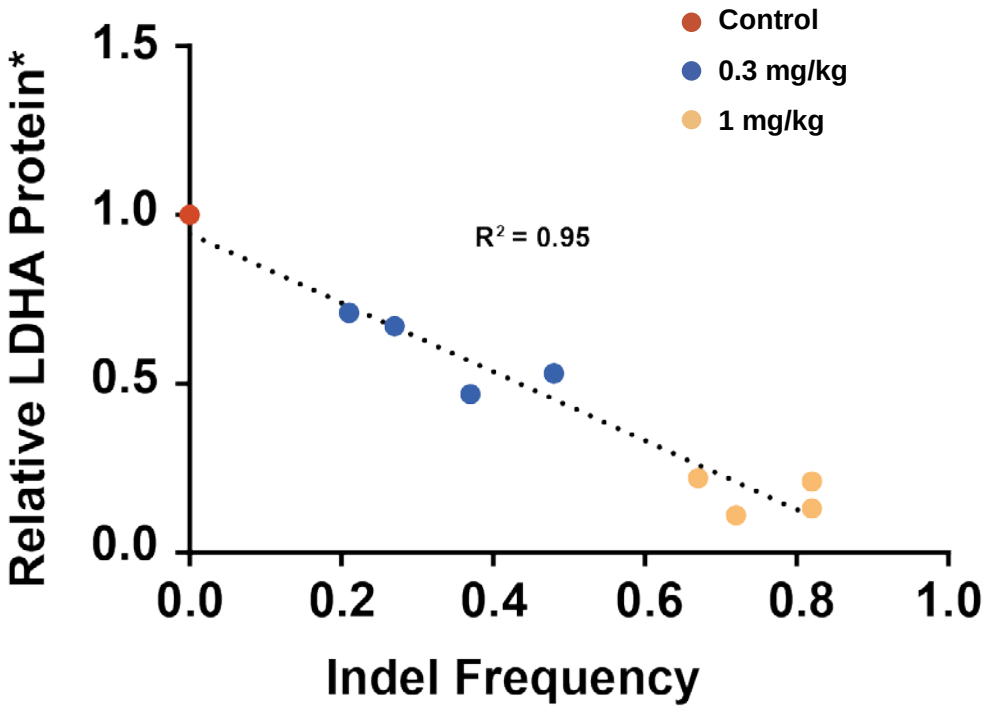
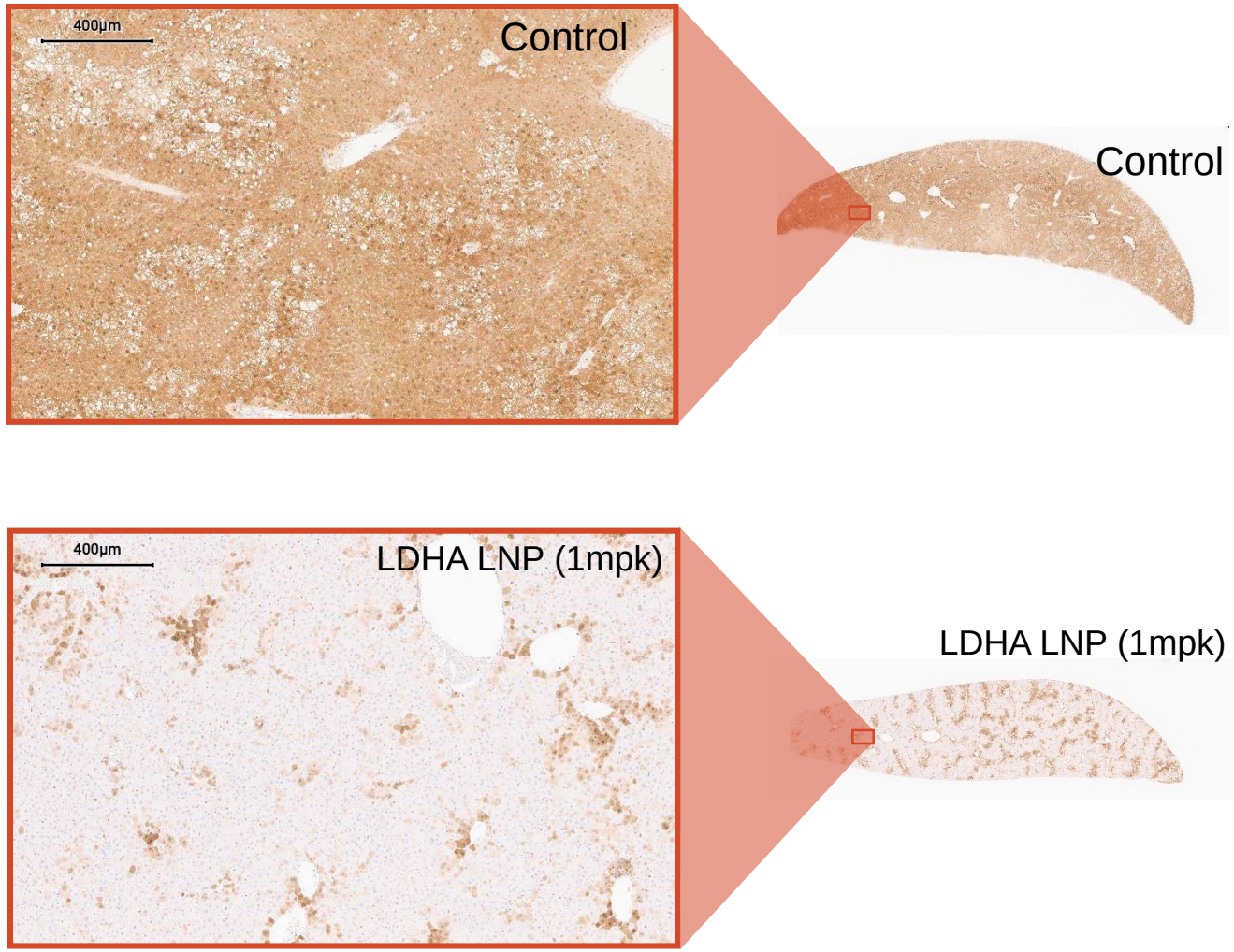
CRISPR-Mediated Knockout of *Ldha* Reduces LDHA Protein Production; Effect Sustained for at Least 15 Weeks in PH1 Mouse Model

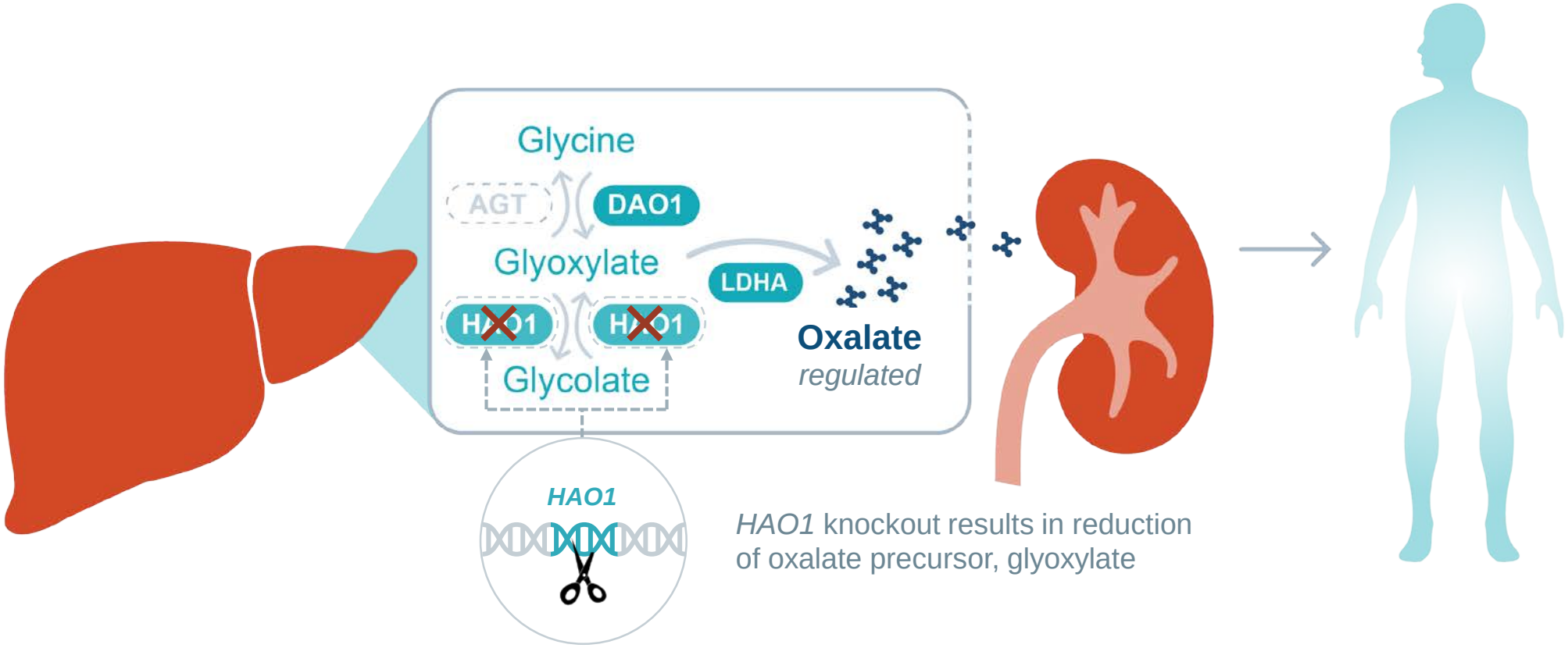
LDHA Protein Reduction Correlates with Indel Frequency





*Western Blot quantification

CRISPR-Mediated Knockout of *HAO1* Disrupts Glycolate-to-Glyoxylate Conversion, Addressing PH1

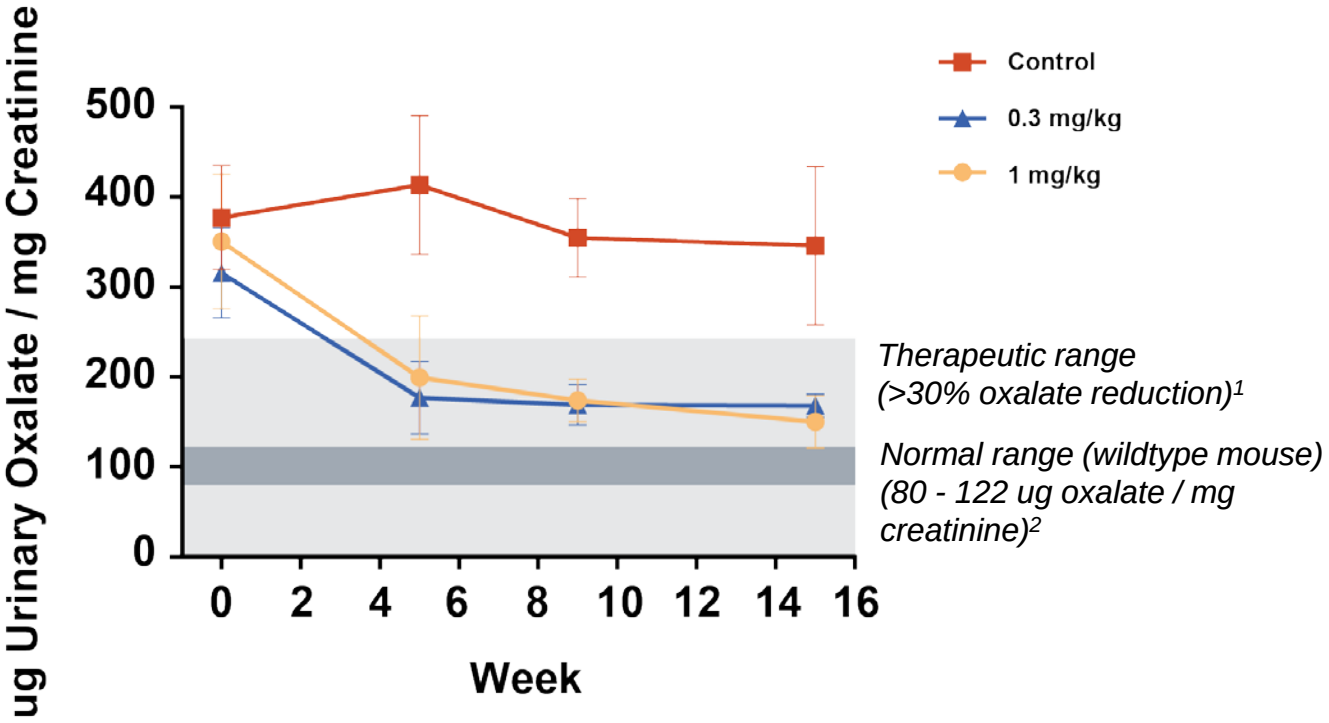


HAO1 knockout results in reduction of oxalate precursor, glyoxylate

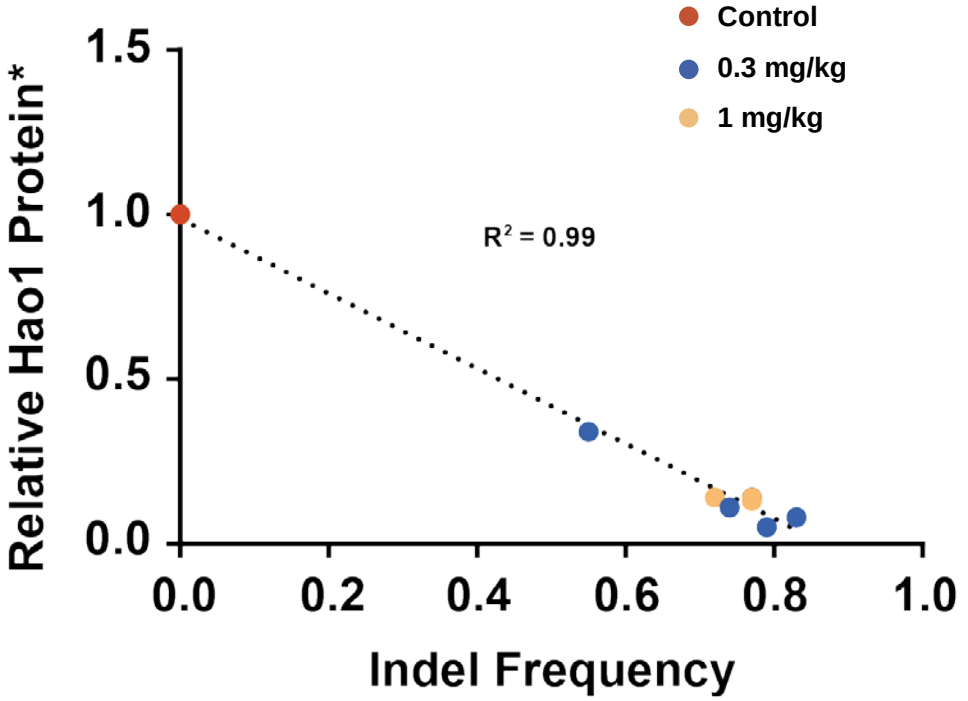
Treatment Hypothesis 2 for PH1 Patient

57% Oxalate Reduction Sustained for at Least 15 Weeks, Following Single Dose of CRISPR/Cas9 LNPs at 1 mg/kg in PH1 Mouse Model

Hao1 Knockout Results in Sustained Oxalate Reduction



HAO1 Protein Reduction Correlates with Indel Frequency



[1]Nephrology Dialysis Transplantation 1999; 14:2556-2558.

[2] Biochim Biophys Acta 2016; 1862(2):233-239.

* Western Blot quantification

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Key Takeaways

- Modularity of Intellia's platform enables independent, one-time therapeutic approaches for PH1 by swapping guide alone

- Editing of *Ldha* or *Hao1* gene each results in therapeutically relevant reduction of oxalate (>30% oxalate reduction[1]) in PH1 mouse model:
  - ***Ldha*** knockout: **63%**
  - ***Hao1*** knockout: **57%**

  Urinary oxalate level reduction

- Urinary oxalate reduction sustained for at least 15 weeks in PH1 mouse model following a single administration

[1]Nephrology Dialysis Transplantation 1999; 14:2556-2558.

Acknowledgements

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