Primary hyperoxaluria (PH) is a rare genetic disease caused by mutations in one of three genes (AGXT, GRHPR and HOGA1) involved in the glyoxylate detoxification pathway, giving rise to PH types 1, 2, and 3, respectively. PH is characterized by excessive accumulation of the toxic waste product oxalate, which leads to formation of insoluble deposits in the kidney and other organs, resulting in renal failure and systemic oxalosis. Currently, the treatment of late-stage disease is limited to combined liver-kidney transplantation. Here, we tested the hypothesis that non-viral CRISPR/Cas9-mediated editing of two genes involved in oxalate formation, Ldha and Hao1, could significantly lower urinary oxalate in a mouse model of PH1, providing proof-of-concept for a one-time treatment approach for the disease.

**INTRODUCTION**

**RESULTS**

Potential to treat PH1 with either:
1. CRISPR/Cas9-mediated knockout of LDHA or
2. CRISPR/Cas9-mediated knockout of HAO1

**TARGETING LDHA WITH CRISPR/Cas9**

- Lead Guide Achieved Robust Editing and Protein Reduction*
- Targeting LDHA with CRISPR/Cas9
- Editing of LdhA Gene Reduces Liver LDH Enzyme Activity*
- Increased Editing and Reduction in Urinary Oxalate are Dose-Responsive*

**TARGETING HAO1 WITH CRISPR/Cas9**

- HAO1 Protein Reduction Correlates with Indel Frequency*
- LdhA Knockout Results in Sustained Oxalate Reduction*
- Lactate Disposition is Preserved in Wild Type and 5/6th Nephrectomy Mice with Edited LdhA

**CONCLUSIONS**

- Modular LNP-based CRISPR system enables efficient knockout of genes involved in oxalate production
- Single treatment targeting either Hao1 or LdhA leads to a dose-dependent and persistent reduction of urinary oxalate levels in the Agxt-/- mouse model of PH1
- LdhA gene disruption decreased LDH enzyme activity in the liver, yet did not impair the disposition of lactate in either wild type or renally-impaired mice
- These results suggest the promise of LNP-delivered CRISPR for treating genetic forms of hyperoxaluria using a single-course treatment paradigm

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*Agxt-/- mouse*