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Letters to the Editor
https://doi.org/10.63501/ephy8993

CRISPR-Cas9 as a Targeted Therapeutic Strategy for Primary Hyperoxaluria: A New Frontier in Gene-Based Nephrology

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ABSTRACT:

Primary hyperoxaluria (PH), most commonly caused by mutations in the AGXT gene (type 1), is a rare inherited metabolic disorder leading to oxalate overproduction and progressive renal damage. Current treatments, including pyridoxine supplementation and RNA interference therapies, are supportive but not curative, with liver–kidney transplantation remaining the definitive option. CRISPR-Cas9 gene-editing technology offers a potential one-time curative solution by directly correcting pathogenic mutations or silencing disease-related genes. Recent preclinical studies and early clinical trials, such as those investigating YOLT-203, have shown promising reductions in urinary oxalate with minimal toxicity. However, challenges related to long-term safety, delivery, cost, and ethical concerns must be addressed. With further research and responsible innovation, CRISPR-Cas9 could revolutionize the treatment landscape of primary hyperoxaluria.

Dear Editor,

Most often caused by AGXT gene mutations (type 1), primary hyperoxaluria (PH) is a rare inherited metabolic condition that results from the liver's overproduction of oxalate. Recurrent nephrolithiasis, nephrocalcinosis, and increasing renal failure are triggered by the ensuing oxalate buildup in the kidneys. Treatment is supportive and includes high fluid consumption, crystallizing inhibitors, and pyridoxine supplementation. Though intrusive, combined liver–kidney transplant is still the only cure choice for patients with advanced disease since it results in better survival and quality of life. Effective at reducing oxalate levels, lumasiran and other RNA interference treatments have recently become available but are not curative and present questions regarding their long-term safety and effectiveness [1].

CRISPR-Cas9 is a groundbreaking gene-editing technology that allows precise editing of specific DNA sequences within living cells. CRISPR is derived from bacterial immune systems and has been well-studied for treating monogenic diseases by either correcting or silencing the mutated gene. CRISPR has tremendous therapeutic potential and is being used in clinical settings for patients with sickle cell disease, β-thalassemia, and congenital blindness [2]. Because CRISPR allows permanent repair of the disease-causing mutations at the DNA level, it offers possible lasting cures with a single intervention. CRISPR has the potential to be used in similar fashion to correct metabolic defects in rare kidney diseases like primary hyperoxaluria.

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Recent gene editing advances have provided encouraging results for Primary Hyperoxaluria Type 1 (PH1). A preclinical study in 2025 showed that CRISPR-Cas9 targeting the HAO1 gene through lipid nanoparticle delivery significantly reduced glycolate oxidase expression and lowered urinary oxalate levels in mouse models of PH1 with long-lasting effects and minimal toxicity [3]. After these results, YolTech Therapeutics developed YOLT-203, a first-in-human in vivo CRISPR-based therapy for PH1. Phase I trials showed that a single YOLT-203 dose resulted in a nearly 70% reduction of 24-hour urinary oxalate levels, and there were no serious adverse effects during the 16-week follow-up period [4–6]. These exciting results suggest that targeted gene editing can and will be developed into a potential curative approach for PH1 that reduces the need for lifetime therapies and ultimately, repeated dialysis.

Despite its potential therapeutic advances, there are a variety of limitations to using CRISPR-Cas9 as a treatment for PH1. The majority of studies have short-term follow-up periods; therefore, the long-term efficacy and safety of this technique are unknown. Additionally, there are still considerable barriers to widespread clinical use, mainly in the areas of large-scale delivery, cost, and regulatory approvals. While preclinical animal studies may illustrate good results, solid in vivo human studies are lacking. Ethical issues include consent in the pediatric population, equitable access, and germline modifications [7]. New evidence suggests that CRISPR-Cas9 is capable of potentially introducing undesirable alterations to the genome, including large deletions and chromosomal rearrangements, which can lead to genomic instability [8].

CRISPR-Cas9 offers a promising advancement in the treatment of PH. Gene-editing therapies using CRISPR have the potential for one-time curative treatments. However, the clinical implementation of CRISPR will require solving the challenges of rigorous long-term safety assessment, ethics, and regulation. Before the safe use of CRISPR-Cas9 becomes the norm, further research and larger and more robust human trials will be required. With responsible innovation, CRISPR could help revolutionize the management of rare kidney disease.

Funding Declaration

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper on Long-Term Evolution (LTE) technology.

All research activities, data analyses, and conclusions presented in this study were conducted independently and without any external influence from commercial entities, equipment vendors, or service providers associated with LTE networks.

REFERENCES:

1- Garrelfs, S. F., Frishberg, Y., Hulton, S. A., Koren, M. J., O'Riordan, W. D., Cochat, P., Deschênes, G., Shasha-Lavsky, H., Saland, J. M., van't Hoff, W. G., Fuster, D. G., Magen, D., Moochhala, S. H., Schalk,

G., Simkova, E., Groothoff, J. W., Sas, D. J., Meliambro, K. A., Lu, J., … Lieske, J. C. (2021). Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1. *New England Journal of Medicine*, *384*(13), 1216–1226. https://doi.org/10.1056/nejmoa2021712

2- Doudna, J. A. (2020). The promise and challenge of therapeutic genome editing. In *Nature* (Vol. 578, Issue 7794, pp. 229–236). Nature Research. https://doi.org/10.1038/s41586-020-1978-5

3- Jiang, Y., Chen, S., Hsiao, S., Zhang, H., Xie, D., Wang, Z. J., Ren, W., Liu, M., Liao, J., & Wu, Y. (2025). Efficient and safe in vivo treatment of primary hyperoxaluria type 1 via LNP-CRISPR-Cas9-mediated glycolate oxidase disruption. *Molecular Therapy*, *33*(1), 104–118. https://doi.org/10.1016/j.ymthe.2024.10.003

4- YolTech Therapeutics. (2025, February 25). *YolTech Therapeutics Announces Positive Clinical Data for YOLT-203, an In Vivo Gene Editing Therapy for Primary Hyperoxaluria Type 1 (PH1)*. YolTech Therapeutics. https://www.yoltx.com/news/press-release/74

5- ClinicalTrials.gov. (2024, December 19). *Clinical exploration study of YOLT-203 in the treatment of type 1 primary hyperoxaluria (PH1)*. ClinicalTrials.Gov. https://clinicaltrials.gov/study/NCT06511349

6- ClinicalTrials.gov. (2024, December 19). *Clinical exploration study of YOLT-203 in the treatment of type 1 primary hyperoxaluria (PH1)*. ClinicalTrials.Gov. https://clinicaltrials.gov/study/NCT06511349

7- YolTech Therapeutics. (2024, August 22). *YolTech Therapeutics administers first patient dose in IIT of YOLT-203, the world's first in vivo gene editing therapy for PH1*. YolTech Therapeutics. https://www.yoltx.com/news/press-release/67

8- Jiang, Y., Chen, S., Hsiao, S., Zhang, H., Xie, D., Wang, Z. J., Ren, W., Liu, M., Liao, J., & Wu, Y. (2025). Efficient and safe in vivo treatment of primary hyperoxaluria type 1 via LNP-CRISPR-Cas9-mediated glycolate oxidase disruption. *Molecular Therapy*, *33*(1), 104–118. https://doi.org/10.1016/j.ymthe.2024.10.003