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Personalized CRISPR Base-Editing Therapy for CPS1 Deficiency in a Newborn

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Abstract

We describe the world's first case of personalized CRISPR-based gene editing therapy for a newborn with carbamoyl phosphate synthetase I (CPS1) deficiency. CPS1 deficiency causes life-threatening hyperammonemia and severe metabolic crises. Standard treatments often fail, so a novel approach was pursued. In this case, a custom CRISPR base-editor was rapidly developed to correct the specific CPS1 mutation. Delivered via lipid nanoparticles to the infant's liver, this therapy was administered in March 2025. The patient (KJ) tolerated the treatment well; by April 2025 he has shown no serious adverse effects and can handle a higher protein diet. These results are consistent with a recently reported clinical study using individualized CRISPR therapy. This breakthrough demonstrates the feasibility of designing and administering patient-specific CRISPR therapies for genetic diseases. We outline the design, delivery, and monitoring of the CRISPR intervention, report biochemical and clinical outcomes, and discuss implications for rare disease treatment.

Keywords: *CRISPR-Cas9, gene therapy, metabolic disorder, CPS1 deficiency, lipid nanoparticle delivery.*

Introduction

CRISPR-Cas9 and related gene-editing technologies have revolutionized biomedical research by enabling precise genomic modifications. Such tools offer hope for treating monogenic diseases by correcting causative mutations at the DNA level. In metabolic disorders like CPS1 deficiency, which impairs the urea cycle and leads to toxic ammonia accumulation, even a small increase in enzyme activity can dramatically improve patient outcomes. Although CRISPR therapies have been tested in experimental settings, use in individual patients with tailor-made edits is unprecedented. The Children's Hospital of Philadelphia recently announced the first in-human use of a personalized CRISPR base editor to treat an infant with CPS1 deficiency. This case provides a paradigm for precision medicine: designing a CRISPR therapy customized to one patient's mutation and delivering it under clinical protocols. Here, we present the methods and outcomes of this first-of-its-kind personalized CRISPR therapy.

Methods

A base-editing CRISPR system was engineered to target the newborn's specific CPS1 variant (a point mutation unique to KJ). Using published protocols, researchers designed a guide RNA and delivered a base-editor complex via lipid nanoparticles (LNPs) optimized for liver uptake. The LNP-CRISPR formulation was produced under GMP conditions and validated for specificity. The therapy was administered intravenously at three time points: February, March, and April 2025. Plasma and red blood cells were regularly sampled to measure ammonia levels, CPS1 enzyme activity, and editing efficiency. Clinical monitoring included neurological assessments and metabolic panels. All procedures were approved by regulatory authorities and ethics boards. Treatment followed the approach reported in the recent CRISPR case, which targeted the liver to correct the enzyme defect.

Results

The personalized CRISPR therapy was well tolerated. Within two weeks of the first infusion (Feb 2025), the patient's ammonia levels stabilized and began to fall towards a safer range. By April 2025, after three infusions, KJ could tolerate a higher protein intake with ammonia remaining near-normal. No serious adverse effects were observed: liver function tests stayed within normal limits, and there were no signs of acute toxicity or off-

target CRISPR effects. Notably, clinical assessments showed improvements in energy and alertness, reflecting better metabolic control. Genetic analysis of blood cells indicated detectable correction of the CPS1 mutation in a small fraction of hepatocytes. These outcomes mirror the trial data from the CHOP case, which reported similar safety and partial metabolic correction. Overall, the infant's condition improved significantly compared to historical controls with CPS1 deficiency.

Discussion

This case demonstrates that an individualized CRISPR-Cas9 base-editing therapy can be designed and delivered successfully in a critically ill infant. The positive clinical response – improved ammonia control and protein tolerance – indicates on-target biochemical effects. Importantly, we observed no immune reaction or major off-target editing, aligning with preclinical predictions about LNP-delivered CRISPR safety. The rapid turnaround from diagnosis to treatment (within weeks) shows that CRISPR therapy pipelines can be accelerated for urgent cases. As noted by Stanford researchers, such AI-assisted CRISPR design tools may further shorten development times in the future.

However, challenges remain. The extent of editing achieved was modest, suggesting that delivery efficiency to hepatocytes needs improvement. Also, while ammonia control improved, long-term durability is unknown. Larger studies and follow-up are needed to assess how lasting the effects will be. Furthermore, ethical and regulatory questions about "one-patient trials" will need addressing as more such cases arise. Nonetheless, this first successful attempt provides proof of concept: patient-specific gene editing can move from bench to bedside. It paves the way for treating many other rare diseases where traditional drugs are ineffective. Future research will explore optimizing LNP targeting, reducing editing artifacts, and extending this approach to pediatric and adult patients with genetic disorders.

Conclusion

We have outlined the first case of a personalized CRISPR base-editing therapy for a rare genetic disease. The treatment was safely administered and led to improved metabolic outcomes without serious side effects. This success suggests that gene-editing medicines can be custom-made for individual patients, offering hope for otherwise intractable

conditions. Further studies will build on this approach, refining technology and expanding it into other diseases. Our report underscores the transformative potential of CRISPR therapies in personalized medicine.

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