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What we can learn from the first personalized CRISPR-treated baby to tackle genetic brain disorders

Yang Yang[1,2,*]
[1]Borch Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, IN, USA
[2]Purdue Institute for Integrative Neuroscience, Purdue University, West Lafayette, IN, USA
*Correspondence: yangyang@purdue.edu
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The landmark report on personalized CRISPR genome editing to treat an infant (baby KJ) with a life-threatening liver disease sparked widespread attention,[1] ushering in a new era of precision genetic intervention. This piece discusses the key challenges and opportunities in translating this milestone into treatments for genetic brain disorders.

Introduction

The dream to directly correct the root cause of monogenic disorders through precision genome editing is rapidly transitioning from concept to clinical reality. The first personalized CRISPR intervention, used to treat an infant (KJ) with carbamoyl phosphate synthetase 1 (*CPS1*) deficiency, marks a historic milestone in precision gene correction therapy.[1] *CPS1* catalyzes the initial step of the urea cycle, converting ammonia into carbamoyl phosphate. *CPS1* deficiency causes hyperammonemia, a severe urea cycle disorder associated with high infant mortality rates (30%–50%), with liver transplantation being the preferred treatment option. The condition's severity and urgency made it a compelling candidate for experimental therapy.

CRISPR, a Nobel Prize-winning technology, has revolutionized the genome editing field.[2] Within a decade, CRISPR has evolved from a basic research tool to a therapeutic platform, culminating in a US Food and Drug Administration (FDA)-approved therapy for sickle cell disease. Additionally, there are multiple CRISPR-based therapies in clinical trials. However, traditional CRISPR-Cas9 produces double-stranded DNA breaks (DSBs), which can lead to unpredictable insertions and deletions (indels) through non-homologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ), limiting its utility for precise gene correction to repair point mutations.

Base editing (BE) addresses the limitations of traditional CRISPR-Cas9 by utilizing a Cas9 nickase fused to a DNA deaminase, enabling targeted single-base conversions without DSBs, which enhances its safety profile. Off-target activity of BE is also considered low. Currently, two main classes of BE exist: cytosine base editors (CBEs) mediate C→T transitions (equivalent to G→A on the opposite strand), and adenine base editors (ABEs) mediate A→G transitions (equivalent to T→C on the opposite strand).[3,4] While BE offers high efficiency and a favorable safety profile, it is restricted to four of the twelve possible base substitutions and can introduce unintended bystander edits within the editing window of the guide RNA. Nevertheless, BE is a powerful technology, and its clinical utility was exemplified by KJ's case, marking the arrival of personalized genome editing therapies.

In neuroscience, a wide range of devastating conditions are mediated by genetic mutations, including monogenic forms of epilepsy and autism, Huntington's disease, amyotrophic lateral sclerosis, genetic prion disease, and familial forms of Alzheimer's disease and Parkinson's disease. Correcting disease-causing mutations through genome editing holds transformative potential to effectively treat, or even cure, many of these brain disorders. The following question naturally arises: what can we learn from KJ's case to chart a course toward treating genetic brain disorders using precision genome editing? This piece examines the scientific, technical, and translational lessons from KJ's case to inform the path forward in advancing gene correction therapies for genetic brain disorders.

A perfect storm

KJ became the first patient to receive personalized CRISPR therapy due to a convergence of tractable biological and logistical factors. The target organ, liver, is well vascularized and naturally accumulates delivery vectors such as lipid nanoparticles (LNPs), enabling effective *in vivo* delivery and the possibility of redosing. The *CPS1* gene, where the mutations occur, encodes a critical liver enzyme involved in the urea cycle. KJ harbored compound heterozygous nonsense mutations in *CPS1*, leading to a complete loss of enzyme function. In this context, even partial restoration of enzymatic activity in a fraction of liver cells was likely to reduce ammonia levels and be clinically beneficial. Importantly, while BE has a notable limitation of potential bystander edits as a side effect, in KJ's case, all predicted bystander edits induced by the base editor were synonymous and would not alter the protein sequence.[1] This is an unusual bystander profile, but a fortuitous circumstance for KJ. Furthermore, thorough off-target analyses did not reveal unintended editing at other genomic loci. This rare combination of permissive factors aligns in a highly desirable manner to eventually make KJ the ideal candidate for the first personalized CRISPR treatment. Given KJ's life-threatening condition, treatment proceeded under FDA expanded access

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(compassionate use) via a single-patient investigational new drug (IND), which facilitated expedited clearance.

Lightning speed

As *CPS1* deficiency is a life-threatening disease with a high mortality rate in infants, therapy development for it is a race against time. In KJ's case, the lightning speed of therapy development was made possible by the rapid genetic diagnosis, strong expertise of the team in liver and metabolic disorders, an established CRISPR genome editing platform, as well as committed industry partnerships and swift FDA authorization.[1] This effort clearly demonstrates that bespoke therapies can be developed and deployed expeditiously for time-sensitive medical conditions in 7–8 months. Within this time frame, an immortalized cell line and a mouse model with the human *CPS1* gene cassette were generated, enabling the evaluation of editing efficiency both *in vitro* and *in vivo* for a large array of different base editors. This systematic approach led to the identification of a lead editor that achieved ~40% effective editing in the mouse liver, which was subsequently selected for therapeutic use in KJ. Due to the urgency, functional rescue was not tested in a preclinical setting, which would have required advanced disease models capable of robustly recapitulating *CPS1* deficiency phenotypes. Assessing functional rescue is generally a laborious and time-consuming process. In KJ's case, bypassing the demonstration of phenotype reversal in preclinical disease models did not prevent the translation of the therapy into the clinic. The strategic decision to forgo functional rescue, and only use molecular correction and predicted benefit to seek regulatory clearance, also greatly shortened the timeline from preclinical validation to human intervention.

Challenges for treating genetic brain disorders

While KJ's treatment marks a groundbreaking moment, translating this success into the treatment of genetic brain disorders would be a winding journey. Here, I outline the key challenges and opportunities ahead (Figure 1).

Delivery, delivery, delivery

The primary hurdle for translating KJ's success to genetic brain disorders is delivery. The liver, which has a major function in clearing foreign materials from the blood and process them for elimination, readily uptakes LNPs and most other delivery vectors. In contrast, the brain is tightly protected by the blood-brain barrier (BBB) and is considered immune privileged, complicating the safe and effective delivery of any exogenous editors.[5] Direct injections into the brain's ventricles (intracerebroventricular), spinal fluid (intrathecal), or brain tissue (intraparenchymal) are possible, particularly in infants, but each approach carries surgical risks and allows only limited diffusion of the therapy. To overcome these limitations, strategies to transiently and safely open the BBB for drug delivery are being explored.

Among available vectors, adeno-associated viruses (AAVs) are the most widely used both in preclinical models and in clinical applications for brain disorders. However, they face cargo size limits (~4.7 kb), potential immunogenicity issues, and possible liver toxicity. Most genome editors, unless specifically engineered to be compact, exceed the packaging capacity of a single AAV vector, necessitating dual-AAV delivery systems. Moreover, editor expression via viral vectors often persists long after editing is complete, which is suboptimal for gene correction therapies that require only transient expression. Technologies such as self-limiting expression systems for editors and guide RNAs are being developed to mitigate risks associated with prolonged Cas9 expression. Recent advances in AAV engineering that exploit transferrin receptors and other cell-surface markers to cross the BBB are expected to make systemic intravenous (i.v.) delivery feasible. These engineered AAVs are expected to offer more uniform brain-wide exposure and broad neuronal transduction while reducing dosing requirements and enhancing safety. Despite many challenges, AAVs currently represent the most practical near-term vector for brain delivery. Accordingly, efforts to engineer smaller editors that fit within a single AAV vector, reduce its immunogenicity, and improve manufacturing efficiency warrant sustained attention.

Beyond AAVs, emerging alternatives such as engineered virus-like particles (eVLPs), extracellular vesicles (EVs), and next-generation LNPs capable of crossing the BBB and having optimal diffusion properties to target neurons are under active development. These emerging vectors represent future aspirations for minimizing immune responses as well as enabling widespread brain transduction and preferential targeting of specific brain cell types. It is also worth distinguishing diseases for which localized delivery may be sufficient (e.g., focal seizures) from those that require broad brain-wide delivery (e.g., genetic prion disease). Recognizing this distinction is essential for selecting the most suitable delivery vector. Developing optimal delivery systems that effectively balance safety, expression kinetics, transduction efficiency, and cell-type specificity remains a major research priority for translating genome editing therapies to the human brain.

Functional rescue in preclinical models

While many brain disorders stem from point mutations, their pathophysiology is often more complex. For example, in the case of Rett syndrome or fragile X syndrome, the affected genes (e.g., *MECP2* and *FMR1*) are involved in the regulation of the expression of many genes. For ion-channel-related brain disorders (e.g., *SCN1A*-related Dravet syndrome or *SCN2A*-related autism and epilepsy), these channels are expressed in specific neuron types and participate in diverse neuronal functions. Because of the complexity of brain disorders, multiple synergistic models should be employed to study the functional rescue. For instance, rodent models may display informative behavioral deficits but lack a human cell context. Human induced pluripotent stem cell (hiPSC)-derived neurons or brain organoids/assembloids offer a complementary approach,[6] enabling mutation-specific mechanistic studies and preclinical testing of interventions in human cells. However, these *in vitro* systems lack the intricacy of the *in vivo* brain environment. Human-mouse chimeric brain models may bridge this gap by allowing the assessment of genome editing strategies targeting human genetic sequences within human cells integrated into a living brain *in vivo*.[7] While the aspirational goal of prioritizing human-based research technologies to reduce animal use is admirable, it is worth emphasizing that animal models will remain indispensable for the foreseeable future,

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particularly in neuroscience research involving brain circuits, behaviors, and other *in vivo* processes. The combination of these models is more likely to provide a holistic view of functional rescue.

Moreover, due to the nonlinear dynamics and interconnectivity of neuronal networks, a minimum threshold of gene correction may be necessary for restoring functional outcomes. This threshold should be carefully defined using preclinical disease models. Would achieving 30% editing efficiency across the entire brain be sufficient, or would high-efficiency correction within a specific brain region or cell type be more effective? It is worth noting that, in KJ's case, editing efficiency in human liver cells was not directly quantified due to ethical considerations. Measuring editing efficiency in the human brain will pose even greater challenges, owing to the inaccessibility of neural tissue. Given these obstacles, for the majority of debilitating yet non-lethal brain disorders, demonstrating functional rescue in preclinical models will likely be a prerequisite for clinical translation, a process that inherently requires time. While the pace of development in KJ's case was extraordinary, such rapid intervention may only be feasible for a limited subset of genetic brain disorders.

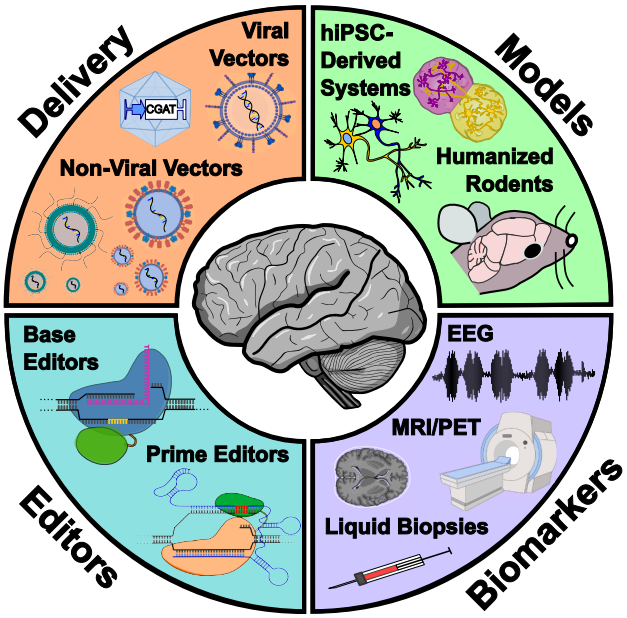

Figure 1. Key pillars for translating gene correction therapies to the brain

This figure summarizes the major translational components shaping the adaptation of CRISPR-based gene correction strategies for genetic brain disorders, spanning four interconnected domains. Continued innovation and integration across these pillars will be essential to bring precision genome editing therapies to patients with genetic brain disorders.

Delivery: achieving safe and efficient delivery to the brain remains a major challenge. Current approaches include viral vectors (e.g., adeno-associated virus [AAV] and canine adenovirus [CAV-2]) and emerging non-viral platforms such as lipid nanoparticles (LNPs), engineered virus-like particles (eVLPs), and extracellular vesicles (EVs).

Models: translational success depends on human-relevant preclinical models, including human induced pluripotent stem cell (hiPSC)-derived neural cultures, brain organoids, and genetically engineered or humanized rodents, such as human-mouse chimeric brain models.

Biomarkers: functional and molecular biomarkers are instrumental for assessing therapeutic efficacy. These include electrophysiological measures (e.g., electroencephalogram [EEG]), advanced neuroimaging modalities (e.g., magnetic resonance imaging [MRI] and positron emission tomography [PET]), and minimally invasive liquid biopsies.

Editors: genome editing technologies have expanded to include base editors and prime editors, enabling precise correction of mutations with enhanced safety profiles.

Evaluating therapeutic efficacy clinically

In KJ's case, ammonia and its metabolic byproduct levels served as clear biomarkers of therapeutic efficacy. In contrast, most genetic brain disorders lack minimally invasive liquid biomarkers that can reliably reflect treatment response. Accessing cerebrospinal fluid is significantly more invasive than collecting blood or urine. For certain developmental brain disorders involving seizures, electroencephalography (EEG) can be used to assess therapeutic efficacy by quantifying seizure reduction. In Alzheimer's disease, positron emission tomography (PET) enables longitudinal tracking of amyloid and tau pathology. In mental disorders, outcome measures often rely on neuropsychological test batteries in combination with other clinical parameters. While advanced neural recording technologies and functional imaging have expanded our ability to monitor brain activity, these tools often function as surrogate measures and may be most interpretable when analyzed in the context of a control group. However, a control group is often not available in rare disease trials. Thus, translating these new recording technologies from preclinical settings to clinical endpoints is challenging.

For many rare genetic diseases, well-curated natural history data with diverse measurement outcomes become essential for defining disease trajectories and establishing meaningful parameters for therapeutic evaluation. For a subset of rare diseases, however, the collection of natural history data is either not feasible or confounded by substantial heterogeneity (either across genotypes or within subgroups of the same genotype differing in severity). In such cases, functional improvements measured in "*N*-of-1" trial design, where each patient effectively serves as their own control, may represent the most practical path toward meaningful gene therapy advances.[8] Progress in quantitative EEG beyond seizure detection, as well as advances in functional imaging, ultrasound, digital biomarkers, and liquid biopsy, could revolutionize the way therapeutic efficacy is evaluated by permitting robust within-subject "before-versus-after" comparisons. Developing and validating such translational biomarkers remains an urgent priority, as they will be essential to reliably measure treatment benefit and accelerate the development of therapies for rare and heterogeneous brain disorders.

Expanding the landscape of treatable mutations

KJ's case leveraged the precision of BE to correct a specific *CPS1* mutation, resulting in a favorable clinical outcome. BE is a powerful tool: although it is limited to four of the twelve possible base substitutions and may introduce unintended bystander edits, it can actually correct a

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far greater fraction of pathogenic variants than the theoretical 33%, because transition mutations (A↔G or C↔T substitutions) occur much more frequently than transversions do (A↔C, A↔T, G↔C, or G↔T).[3,4] As a case in point, our analysis of more than 100 disease-causing *SCN2A* point mutations associated with epilepsy or autism revealed that roughly two-thirds are, in principle, correctable by BE. However, our *in silico* analysis also indicates that only a subset may be practical candidates, considering the risk of bystander edits. At present, without experimental validation, it remains challenging to predict which mutations are likely to yield high editing efficiency with an acceptable bystander profile. Therefore, more versatile and precise genome editing technologies will be pivotal to realizing the full therapeutic potential of gene correction therapy.

More recently, CRISPR prime editing (PE) was developed, which fuses a Cas9 nickase with a reverse transcriptase and uses a specialized guide RNA (epegRNA) to introduce desired edits into the genome through reverse transcription.[9] It also only induces a single-strand DNA nick, which has an enhanced safety profile much like BE. PE is capable of correcting all 12 possible single-base substitutions and making small insertions and deletions without the risk of unintended bystander editing. Excitingly, the FDA has granted clearance for the first human trial of PE, marking a major step toward its therapeutic use. Most recently, PE has also been successfully applied in human iPSCs and rodent models of brain disorders.[10] To enhance editing efficiency, PE often employs an additional nicking guide RNA (ngRNA) that induces a second nick on the opposite DNA strand. It is thought that the initial nick introduced by the epegRNA and the subsequent nick from an optimized ngRNA occur in a staggered, sequential manner, thereby avoiding the formation of DSBs and minimizing off-target effects. Nonetheless, on-target insertions or deletions (indels) remain a concern and require further characterization and mitigation. In addition, because of PE's large size, reliance on complex epegRNA/ngRNA, and low compatibility with compact Cas domains, it is viewed by some as more challenging to package and translate for brain applications. Despite these challenges, PE currently represents the most versatile genome editing platform, capable of targeting a broad spectrum of pathogenic mutations with a safety profile expected to improve as the technology evolves.

The first brain case: What might it look like?

Given the risks associated with experimental genetic therapies, the first CRISPR-based treatments for brain disorders will likely focus on life-threatening conditions, such as severe forms of developmental and epileptic encephalopathies (DEEs) associated with drug-resistant seizures and the risk of sudden unexpected death in epilepsy (SUDEP). However, translating such therapies to the clinic still requires overcoming major challenges in delivery and safety. Rigorous preclinical evaluation, particularly of immune responses to both delivery vectors and genome editors, will be essential. Due to limitations in the distribution of current delivery systems across the large and complex human brain, localized injection into specific brain regions may be the most realistic short-term approach. Meanwhile, appropriate preclinical models are likely to be required to demonstrate that partial or regionally restricted correction of a pathogenic mutation can restore cellular function and lead to meaningful rescue in disease phenotypes. Considering these practical limitations, a condition involving focal, life-threatening seizures caused by a single point mutation in a defined brain region may represent the most plausible scenario for the first application of personalized CRISPR-based genome editing in the brain. Establishing proof of principle in such a case would lay the foundation for expanding this approach to a broader range of genetic brain disorders.

Balancing early intervention and technological maturity

For neurodevelopmental disorders, earlier treatment is generally assumed to yield better outcomes by leveraging the plasticity of the developing brain. For fatal neurodegenerative diseases, the benefit of early intervention has been shown, presumably by preventing progressive neuronal loss.[11] However, for devastating but non-fatal conditions, the optimal timing of treatment requires thoughtful consideration. Genome editing technologies continue to evolve at a rapid pace, with newer iterations offering potentially higher editing efficiency and improved safety profiles. Emerging evidence also suggests that the human brain may be more plastic than previously thought. For viral delivery platforms where redosing may not be feasible, initiating treatment too early with suboptimal tools could limit future options. Ideally, preclinical models should define the minimum editing threshold necessary to justify intervention. Yet such quantitative benchmarks are often lacking. Should we proceed with 20% editing efficiency? 50%? 80%? In the absence of clear data, these decisions pose significant ethical and clinical complexities. Therefore, determining the timing of genome editing interventions should involve a multidisciplinary dialogue among scientists, clinicians, bioethicists, and patient advocates. These stakeholders can collaboratively weigh the trade-offs between acting now and waiting for technological advancements.

Cost and accessibility

The bespoke nature of KJ's therapy, designed for a single patient in a true $N = 1$ manner, is undoubtedly costly. Its realization was made possible by large-scale federal NIH funding and generous in-kind contributions from industry partners and research institutions. Future cases of personalized genetic therapies are also expected to remain resource intensive in the near term. However, as with other technological breakthroughs, costs are likely to decline substantially over time due to economies of scale and the continued maturation of the underlying platforms. The dramatic reduction in the cost of whole-genome sequencing, from billions of dollars to under a thousand, provides a compelling precedent. Until similar reductions are realized in genome editing, continued support from federal agencies and private, disease-specific foundations or donors will be essential. Venture philanthropy, exemplified by the Cystic Fibrosis Foundation's highly successful investment in disease-modifying therapies for cystic fibrosis, offers an attractive model for funding early-stage innovation. Strategic early investment by

disease-focused foundations, coupled with partnerships across biotech and philanthropic donors, can help de-risk development and align incentives with patient-centered goals. In the longer term, a promising strategy is the development of a "platform IND," in which standardized components, such as delivery vectors and genome editors, are reused across therapies, with only the guide RNA customized for each patient's variant.[12] However, until editing efficiency becomes consistently high across genomic targets, platform IND remains an aspirational goal, as efficiency by current editors still varies considerably between genomic sites. Nevertheless, by modularizing genome editing systems, "product families" targeting specific disease categories could streamline development, reduce regulatory burden, and accelerate clinical translation. This platform-based approach may emerge as a standard operation that enhances accessibility of genome editing to an ever-expanding patient population and reduces health disparities.

While technological advances will help lower costs over time, regulatory requirements remain a dominant driver of expense in developing *N*-of-1 and other ultra-rare therapies. The need for good laboratory/manufacturing practice (GLP/GMP) compliance, IND-enabling toxicology packages, and other regulatory obligations often imposes costs that can halt programs at an early stage. Moving forward, greater regulatory creativity will be vital. Regulators could adopt more nuanced, patient-informed approaches to risk-benefit assessment, especially in fatal disorders without standard-of-care options. Such changes are essential for building viable models for *N*-of-1, *N*-of-few, and broader rare disease therapies. Beyond regulation, policy measures and economic incentives will also be critical to lowering barriers and expanding access. For example, programs such as priority review vouchers should not be overlooked, which can provide meaningful financial returns to companies investing in rare disease programs. Governments could also encourage greater social responsibility from industry by offering targeted incentives that reinvest resources into rare disease research. Together, these strategies could foster sustainable models that broaden access to therapies for all affected patients.

Collaboration across stakeholders

The personalized nature of CRISPR therapies demands close collaboration among stakeholders. KJ's treatment succeeded largely due to strong partnerships between basic and clinical researchers, physicians, industry partners, the patient's family, and the FDA. For brain disorders, similar coalitions are essential to navigate the complexities of preclinical testing, clinical trial design, and regulatory oversight. Families and advocacy groups play a critical role in defining priorities, facilitating recruitment, and sustaining long-term follow-up. Scientists will focus on developing and optimizing editing tools and delivery systems. Clinicians will play an essential role in identifying suitable patients, administering therapies, and monitoring outcomes. It is also important for regulators to develop flexible pathways to expedite access for rare conditions. Additionally, for these emerging technologies to benefit more patients, data sharing and registries are vital. Functional data, trial design, outcome measures, efficacy, and safety monitoring should be shared across institutions and stakeholders to accelerate intervention development across the board. Additionally, manufacturing infrastructure needs to be considered so that rapid manufacture and validation of bespoke editing reagents can be achieved in GMP-compliant or near-GMP (GMP-lite) facilities capable of small-batch production.

Conclusions

The successful treatment of KJ with personalized CRISPR-based genome editing is a landmark in precision medicine, offering tremendous hope and insights for addressing genetic brain disorders. Advances in genome editing technologies, including BE and PE, coupled with innovative delivery strategies, will make gene correction therapy in brain disorders within reach. Overcoming challenges in therapeutic delivery, demonstrating phenotypic rescue in preclinical models, developing reliable biomarkers, and ensuring accessibility will require coordinated team efforts. Through collaboration from committed basic, translational, and clinical scientists, as well as strong support from the federal government, private foundations/donors, or venture philanthropy, a future where all genetic brain disorders are treatable is not unrealistic. KJ's case provides valuable lessons and inspiration for a transformative new era in treating genetic brain disorders.

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DECLARATION OF INTERESTS

The author declares no competing interests.

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