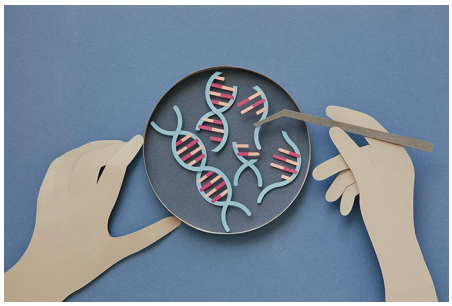
Genome editing

https://doi.org/10.1038/s41576-025-00898-z

A clinical milestone for CRISPR in sickle-cell disease



The haemoglobinopathies transfusion-dependent β-thalassemia (TDT) and sickle-cell disease (SCD) are two globally prevalent and severe monogenic blood disorders. These conditions impose substantial morbidity and mortality, and their burden falls disproportionately on populations in sub-Saharan Africa, the Middle East and parts of Asia, underscoring the global health significance of any curative approach. In 2021, a study by Frangoul et al. marked a defining moment for genomic medicine and global health. Published in *The New England Journal of Medicine*, the authors reported the clinical application of CRISPR–Cas9 genome editing to treat two patients with TDT or SCD.

The ex vivo approach taken by Frangoul et al. involved harvesting $CD34^+$ haematopoietic stem and progenitor cells from the patients, which were edited using CRISPR–Cas9 to disrupt the erythroid enhancer of *BCL11A* — encoding the transcription factor BCL11A that represses fetal haemoglobin (HbF) — and reinfused after myeloablation. Both treated individuals showed striking results, including high levels of allelic editing, pan-cellular HbF induction, transfusion independence and, for the patient with SCD, complete resolution of vaso-occlusive crises. By focusing on the erythroid-specific enhancer, the editing strategy ensured that BCL11A function in other haematopoietic lineages remained intact — an elegant design that maximizes therapeutic benefit while minimizing unintended effects on the patient's immune system.

What made this study so compelling to me was the clear demonstration that CRISPR technology can be applied safely and effectively in humans to modify disease-relevant pathways. This has broad implications, because many diseases have a genetic component, from single-gene disorders to common conditions with genetic predispositions. For SCD and TDT, allogeneic bone marrow transplantation had, for decades, been the only curative therapy, but its feasibility was constrained by human leukocyte antigen (HLA)-matched donor (most often a matched sibling) availability and transplant-related risks. By contrast, the investigators showed that targeted editing of a regulatory element can reactivate endogenous HbF, recapitulating the naturally protective phenotype of hereditary persistence of fetal haemoglobin. Deep sequencing further confirmed the precision of editing, with no detectable off-target effects. The clinical benefits were accompanied by haematological reconstitution consistent with durable engraftment, and safety assessments reported no clonal dominance or concerning genomic alterations during follow-up.

Reading this paper was exhilarating, as it signalled a paradigm shift towards genome editing as a frontline therapy for inherited blood disorders, but also sobering. The therapy, now marketed as exa-cel (exagamglogene autotemcel), carries an estimated price of nearly US$2 million per patient. This raises pressing questions of equity, particularly in sub-Saharan Africa, where the burden of SCD is greatest. The trajectory recalls early antiretroviral therapy for HIV, when treatment was prohibitively expensive and concentrated in high-income countries with lower HIV prevalence, whereas access in Africa lagged for more than a decade. Only after broad coalitions, including the US President's Emergency Plan for AIDS Relief (PEPFAR), the World Health Organization (WHO), national governments, industry and civil society, joined forces to reduce costs and build clinical infrastructure did antiretroviral therapy for HIV become available in the regions most affected.

CRISPR-based cures for SCD require a comparable response: pooled financing and tiered pricing; regional treatment hubs that leverage existing haematopoietic stem cell transplantation capacity; technology transfer and workforce training; and regulatory frameworks aligned with Africa's genomic diversity. Practical considerations matter. CRISPR editing for SCD requires mobilization and apheresis, cell-processing facilities, reliable supply chains for conditioning agents and post-infusion monitoring, all of which can be scarce in resource-limited settings. Lessons from the HIV response show that, with the right mix of global financing, political will and stakeholder coordination, such barriers can be overcome, and life-saving therapies can be made accessible where they are needed most.

> "the true measure of innovation lies not only in technical achievement but also in equitable impact"

Its dual legacy makes the study by Frangoul et al. unforgettable: it is both a triumph of modern science and a call to action for global health. Achieving equitable access will demand sustained commitments in infrastructure, financing and ethical governance, supported by rigorous evidence and partnership. For young scientists, the paper is exemplary because it shows how deep mechanistic insight, in this case HbF regulation, can translate into transformative therapy. It also underscores that scientific breakthroughs carry societal responsibilities, especially the principle of equity and the imperative to deliver new cures where they will save the most lives. As CRISPR applications expand, this study should remain a touchstone, reminding us that the true measure of innovation lies not only in technical achievement but also in equitable impact.

Gerald Mboowa
Broad Institute of MIT and Harvard, Cambridge, MA, USA.
e-mail: gmboowa@broadinstitute.org

Competing interests
The author declares no competing interests.

Original article: Frangoul, H. et al. CRISPR–Cas9 gene editing for sickle cell disease and β-thalassemia. *N. Engl. J. Med.* **384**, 252–260 (2021)

Related article: Mboowa, G. et al. The dawn of a cure for sickle cell disease through CRISPR-based treatment: a critical test of equity in public health genomics. *Ann. Hum. Genet.* **89**, 188–194 (2025)