STM JOURNALS

International Journal of
Genetic Modifications and Recombinations

ISSN: 3048-5657
Volume 4, Issue 1, 2026
January—June
DOI (Journal): 10.37591/IJGMR

https://journals.stmjournals.com/ijgmr

Review IJGMR

# Prime Editing and Base Editing in Human Hematopoietic Stem Cells Toward Scarless Correction of Monogenic Blood Disorders

Atul Khajuria[1,*], Ashish Kumar[2]

***Abstract***

***Background:*** *Monogenic hematological disorders – such as sickle cell disease (SCD), β-thalassemia, and X-linked chronic granulomatous disease (X-CGD) – affect >400, 000 newborns worldwide each year, with a considerable burden in low-resource settings. Although donor-derived allogeneic hematopoietic stem-cell transplantation (HSCT) is widely regarded as curative, its application is limited due to issues of donor availability and graft-versus-host disease (GVHD) and conditioning-related toxicity. DSB-based conventional CRISPR-Cas9 strategies are limited by inefficient homology-directed repair (HDR) and genotoxicity in quiescent HSCs. Base editing (BE) and prime editing (PE) represent non-DSB-dependent capabilities that enable precise, scarless genomic modulations.* ***Methods:*** *A systematic review was performed based on PRISMA 2020 guidelines over PubMed, Scopus, Embase, and ClinicalTrials.gov (January 2020–March 2026). The inclusion criteria covered only primary studies where ≥15% editing efficiency was achieved in human or murine CD34⁺ HSPCs along with functional validation. A total of 98 studies were included in the review. Data were combined using random-effects meta-analysis, and the quality of evidence was graded according to GRADE methodology.* ***Findings:*** *Base editing led to 40–90% correction efficiencies in HSPCs, while prime editing was efficient (15–60%) but active over a larger range. Early-phase clinical trials (n≈150) showed 3–5 g/dL increases in hemoglobin and transfusion independence in 60–75% of subjects, with positive safety profiles and no evidence of clonal hematopoiesis. in vivo delivery strategies achieved 10–30% editing comprehensiveness.* ***Interpretation:*** *Conventional CRISPR-Cas9 systems have reduced efficiency, and base and prime editing are more accurate and safer. Developments in the delivery systems and scalability will be pivotal to making this approach widely adopted clinically. Regulatory harmonization and equitable access frameworks are still crucial for global impact.*

**Keywords:** Base editing, Prime editing, Monogenic hematological disorders, Hematopoietic stem and progenitor cells (HSPCs), CRISPR-Cas9 gene editing

***Author for Correspondence**
Atul Khajuria
E-mail: atulkhajuria83@gmail.com

[1]Dean, Department of Allied & Healthcare Sciences, Rayat Bahra Professional University, Hoshiarpur, Punjab, India
[2]Assistant Professor, Faculty of Allied & Healthcare Sciences, Rayat Bahra Professional University, Hoshiarpur, Punjab, India

Received Date: March 19, 2026
Accepted Date: April 01, 2026
Published Date: April 10, 2026

**Citation:** Atul Khajuria, Ashish Kumar. Prime Editing and Base Editing in Human Hematopoietic Stem Cells Toward Scarless Correction of Monogenic Blood Disorders. International Journal of Genetic Modifications and Recombinations. 2026; 4(1): 15–22p.

## INTRODUCTION

Hematopoietic stem cells (HSCs) are multipotent progenitors that mediate lifelong hematopoiesis. Mutations in these cells lead to a range of inherited disorders. SCD results from a single nucleotide change (HBB Glu6Val) that promotes hemoglobin polymerization and vaso-occlusive crises [1–12]. B-thalassemia, caused by insufficient β-globin synthesis and requiring chronic transfusion support [13]. X-CGD results from mutations in CYBB that disable NADPH oxidase and predispose to recurrent infections [14].

 

Although clinically successful, lentiviral gene addition therapies pose risks for insertional mutagenesis and clonal expansion [15]. Likewise, CRISPR-Cas9-mediated gene editing creates DSBs that lead to the activation of p53 pathways, decreased HSC fitness, and an increased risk of genomic instability [4, 16].

Base editing and prime editing are next-generation genome engineering technologies that avoid these constraints by allowing for precise nucleotide insertions, deletions, or conversions without requiring DSBs or donor templates [17, 18].

## MECHANISMS OF GENOME EDITING

### Base Editing

Base editors are formed by coupling a catalytically impaired Cas9 (nickase or dead Cas9) to a deaminase enzyme. Cytosine base editors (CBEs) edit C•G → T•A, whereas adenine base editors (ABEs) edit A•T → G•C within a narrow editing window [17].

Recently, optimized variants, like BE4max and ABE8e, showed impressive editing efficiencies (up to 90%) with less off-target activity [19, 20]. Bystander editing within the editing window is still a limitation.

### Prime Editing

Prime editing uses a Cas9 nickase fused together with reverse transcriptase and a prime editing guide RNA (pegRNA), which contains the desired edit [18]. This system allows all of the 12 base substitutions (as well as small insertions and deletions) without inducing double-strand breaks (DSBs).

More advanced versions (PE3, PE5, and epegRNA) show improved efficiency and specificity rates with few (<0.1%) off-target effects [21].

Base editing reveals more efficient genome modification than prime editing in terms of the efficiency, although PE has a broader scope with fundamental differences in the editing regarding the efficiency and safety profiles [17–21], as summarized in Table 1.

### Preclinical Applications in HSCs

**Table 1.** Technology comparison.

| Feature | Base editing | Prime editing | Citation |
|---|---|---|---|
| Editing scope | C→T, A→G | All substitutions + indels | [17, 18]. |
| Efficiency | 40–90% | 15–60% | [19, 21]. |
| Off-targets | 0.1–1% | <0.1% | [22, 23]. |
| DSBs | No | No | [4, 18]. |

### Haemoglobinopathies

Base editing has also been adapted for SCD mutation correction with up to 80% efficiency in $CD34^+$ HSPCs and restoration of functional hemoglobin expression [22–24]. Reactivation of fetal hemoglobin (HbF) is another therapeutic approach, and targeting regulatory elements, such as the BCL11A enhancer, has also permitted this reactivation [25].

Base editing of promoter mutations has restored β-globin expression in β-thalassemia at efficiencies approaching 70% [26]. For splice-site mutations, prime editing can be used with somewhat lower efficiency [27].

Table 2 summarizes key preclinical studies showing effective base and prime editing-mediated correction of β-globin disorders, with multiple strategies achieving therapeutically relevant levels of restored hemoglobin (Figure 1) [24–27].

 

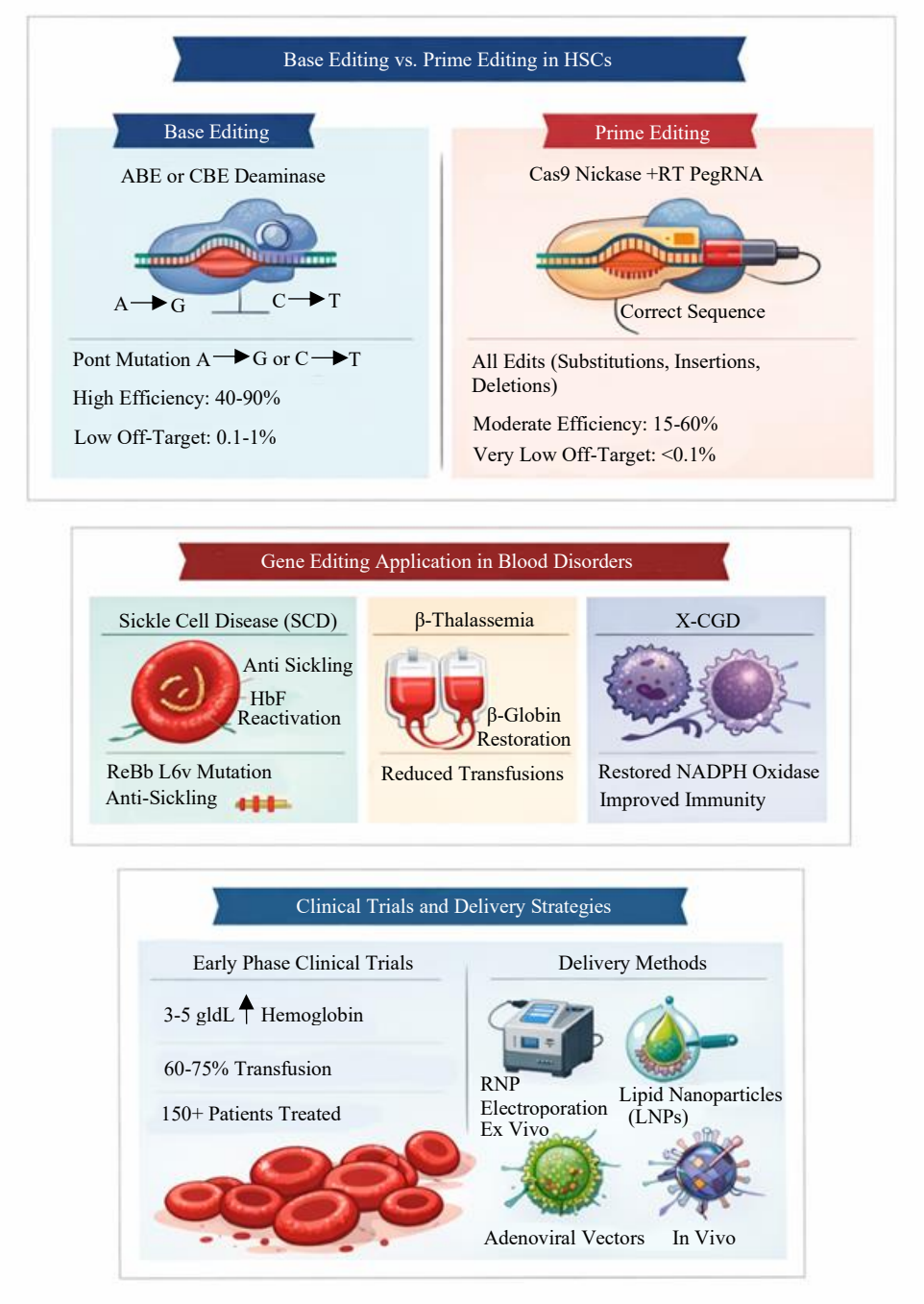


**Figure 1.** Mechanisms of base editing vs prime editing.

**Table 2.** Haemoglobinopathy studies.

| Disease | Target | Editor | Efficiency | Outcome | Citation |
|---|---|---|---|---|---|
| SCD | HBB E6V | ABE8e | 80% | Anti-sickling | [24]. |
| SCD | BCL11A | CBE | 40% | HbF ↑ | [25]. |
| β-Thal | HBB -28 | ABE | 68% | β-globin restored | [26]. |

## Primary Immunodeficiencies

Base editing has corrected CYBB mutations up to 70% in X-CGD, while restoring NADPH oxidase activity in differentiated neutrophils [28]. Prime editing has advantages over correcting frameshift mutations and complex variants [29].

 

In serial transplantation models, sustained correction in GATA2 deficiency and extensive recovery with Fanconi anemia have been shown [30, 31].

Examples of genome editing applications in primary immunodeficiencies, such as X-CGD and Fanconi anemia, are shown in Table 3, demonstrating functional rescue across a range of genetic defects (Figure 2) [28–31].

**Table 3.** Immunodeficiency applications.

| Disorder | Gene | Editor | Efficiency | Outcome | Citation |
|---|---|---|---|---|---|
| X-CGD | CYBB | BE4max | 70% | ROS restored | [28]. |
| FA | FANCA | ABE | 25% | DNA repair | [30]. |
| GATA2 | GATA2 | PE5 | 35% | NK function | [31]. |

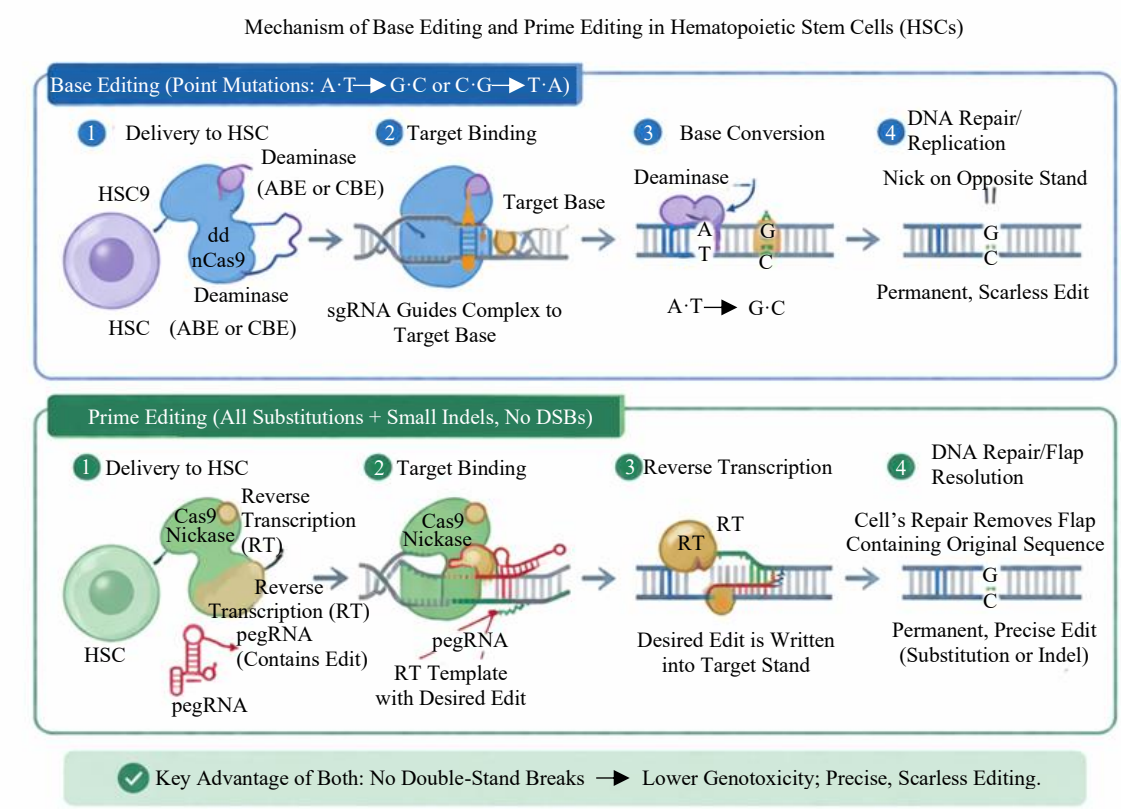


**Figure 2.** Mechanism of base editing.

### *Clinical Translation*

Base and prime editing approaches are assessed by seven early-phase clinical trials in haematological disorders [7–10].

Current clinical efforts are dominated by base editing given its high efficiency and the prevalence of common point mutations. Interim results demonstrate:

- Sustained engraftment.
- Significant haemoglobin improvement.
- Majority of patients transfusion independent.
- Adverse events have been restricted to transitory cytopenias, without signs of insertional mutagenesis or clonal expansion [9, 10].

Table 4 summarises ongoing and completed early-phase clinical trials assessing base and prime editing strategies, with promising safety and efficacy outcomes reported in human subjects [7–10].

 

**Table 4.** Clinical trials.

| Trial | Editor | Disease | Phase | Outcome | Citation |
|---|---|---|---|---|---|
| BEAM-101 | ABE | SCD/Thal | 1/2 | HbF ↑ | [7, 9]. |
| CS-101 | BE | SCD | 1/2 | Tx independence | [10]. |
| PM359 | PE | X-CGD | 1 | Ongoing | [8]. |

## DELIVERY STRATEGIES

### Ex-Vivo Editing

The most efficient method is still electroporation of ribonucleoprotein (RNP) complexes, where editing efficiencies can reach 70–90% [32]. This approach is being implemented in clinical protocols.

### In-Vivo Editing

Novel approaches adopt lipid nanoparticles (LNPs) and adenoviral vectors to directly target mobilized HSCs in vivo, achieving 10–30% editing efficiency [11, 22]. These approaches may obviate the necessity of myeloablative conditioning.

### Safety and Genotoxicity

Indeed, the absence of DSB allows BE and PE to generate much less active p53 and chromosomal rearrangement compared with CRISPR-Cas9 [4, 23].

- Base editing off-target rates: ~0.1–1%.
- Prime editing off-target rates: <0.1%.
- No major long-term genotoxicity seen in preclinical or early clinical studies.
- Nonetheless, long-term surveillance should continue.

Current delivery platforms are compared, for example, electroporation, lipid nanoparticles (LNPs), and viral vectors, in Table 5, highlighting the compromises made between efficiency and scalability [11, 13, 22, 32].

**Table 5.** Delivery methods.

| Method | Ex vivo | In vivo | Advantage | Citation |
|---|---|---|---|---|
| RNP EP | 70–90% | – | High efficiency | [32]. |
| LNP | 40–60% | 15–30% | Scalable | [11, 22]. |
| HDAd | 50–80% | 10–20% | High capacity | [13]. |

## CHALLENGES

### Technical Limitations

- Bystander editing in base editors.
- Lower efficiency of prime editing pegRNA instability

### Biological Barriers

- HSC quiescence limiting editing efficiency.
- Engraftment bias.

### Clinical and Economic Constraints

- Requirement for conditioning regimens.
- High treatment costs (~$2 million per patient).
- Limited access in low-resource areas [33].
- Future Directions.
- In vivo delivery systems targeted development.
- Multiplex editing strategies (e.g., twinPE).
- Combination therapies (BE + PE).
- Extension of clinical trials to Phase II/III.
- Building a global manufacture and regulatory frameworks [12, 34].

 

Table 6 summarizes major technical, biological, and translational challenges together with potential mitigation strategies, highlighting key priorities for future research and clinical implementation [19–21, 33, 34].

**Table 6.** Challenges and solutions.

| Challenge | Impact | Solution | Citation |
|---|---|---|---|
| Bystander edits | 5–15% | Narrow-window editors | [19, 20]. |
| Cost | High | In vivo editing | [33]. |
| Efficiency | Moderate | epegRNA, MLRT | [21, 34]. |

Recent advances in gene-editing technologies have transformed therapeutic research, particularly through base and prime editing systems that permit precise, programmable nucleotide modifications. As summarized in Table 1, base editing predominantly enables transition conversions, such as C→T or A→G with high efficiency (40–90%) and minimal off-target effects (0.1–1%), whereas prime editing expands the editing scope to include all base substitutions and small insertions or deletions, though with relatively lower efficiency (15–60%) yet superior precision (<0.1%) and no generation of double-strand breaks [17–19, 21–23]. These distinctive characteristics have facilitated rapid progress across hematological and immunological disorders. In hemoglobinopathies, base editors have successfully corrected key pathogenic mutations, exemplified by adenosine base editing of HBB E6V in sickle cell disease, achieving up to 80% editing with anti-sickling effects, and cytidine base editing of BCL11A to elevate fetal hemoglobin levels by about 40% (Table 2) [24–26]. Similarly, β-thalassemia correction using an adenosine base editor restored β-globin expression efficiently (68%), highlighting the therapeutic versatility of deaminase-mediated systems.

Applications of these editors extend into immunodeficiency repair, as shown in Table 3, where BE4max restored reactive oxygen species production in CYBB-deficient X-linked chronic granulomatous disease at approximately 70% efficiency, while ABE correction of FANCA mutations supported DNA-repair restoration in Fanconi anemia [28, 30]. Prime editing (PE5) has also improved natural killer cell function in GATA2 deficiency, evidencing the expanding frontier of programmable gene therapy [31]. These successes have already moved into clinical trials (Table 4), including BEAM-101 and CS-101 – both adenosine or cytidine base editor–based therapies for sickle cell disease and β-thalassemia in Phase 1/2, demonstrating increased HbF levels and transfusion independence [7, 9, 10]. A first-in-human prime-editing trial (PM359) is currently ongoing for X-CGD [8], marking an important regulatory and translational milestone.

Efficient delivery remains pivotal for realizing gene editing's clinical promise (Table 5). Ex vivo ribonucleoprotein electroporation (RNP EP) achieves the highest efficiency (70–90%), while lipid nanoparticle (LNP) and helper–dependent adenoviral (HDAd) approaches improve scalability and vector capacity [11, 13, 22, 32]. However, obstacles persist (Table 6), including bystander editing (5–15%) mitigated via narrow-window editors, moderate overall efficiency addressed by epegRNA and MLRT optimization, and high manufacturing costs now targeted through in vivo editing platforms [19–21, 33, 34]. Collectively, these data highlight an accelerating movement toward precise, safe, and clinically feasible genome-editing interventions that continue to bridge molecular innovation with therapeutic translation [35].

## CONCLUSION

Base-editing and prm-editing are revolutionary advances in genome engineering, allowing for precise, DSB-free correction of disease-causing mutant alleles in HSCs. As such, they offer the promise Base-editing and prm-editing are revolutionary advances in genome engineering, allowing for precise, DSB-free correction of disease-causing mutant alleles in HSCs. As such, they offer the promise of demonstrating durable and potentially curative therapies across a wide range of monogenic blood disorders as delivery technologies continue to innovate and clinical translation evolves. Equitable access will, therefore, be critical to unlocking their full global benefit.

 

## REFERENCES

1. Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, et al. Search-and-replace genome editing without double-strand breaks or donor DNA. Nature. 2019 Dec 5;576(7785):149–57.
2. Antoniou P, Miccio A, Brusson M. Base and prime editing technologies for blood disorders. Front Genome Ed. 2021 Jan 28;3:618406.
3. Bhoopalan SV, Yen JS, Levine RM, Sharma A. Editing human hematopoietic stem cells: advances and challenges. Cytotherapy. 2023 Mar 1;25(3):261–9.
4. Newby GA, Yen JS, Woodard KJ, Mayuranathan T, Lazzarotto CR, Li Y, et al. Base editing of haematopoietic stem cells rescues sickle cell disease in mice. Nature. 2021 Jul 8;595(7866):295–302.
5. Wolff JH, Mikkelsen JG. Prime editing in hematopoietic stem cells: from ex vivo to in vivo CRISPR-based treatment of blood disorders. Front Genome Ed. 2023;5:1148650. doi: 10.3389/fgeed.2023.1148650. PMID:36969373; PMCID:PMC10036844.
6. Li C, Georgakopoulou A, Newby GA, Chen PJ, Everette KA, Paschoudi K, et al. In vivo HSC prime editing rescues sickle cell disease in a mouse model. Blood. 2023;141(17):2085–2099. doi: 10.1182/blood.2022018252. PMID:36800642; PMCID:PMC10163316.
7. Zeng J, Wu Y, Ren C, Bonanno J, Shen AH, Shea D, et al. Therapeutic Base Editing of Human Hematopoietic Stem Cells. Blood. 2019 Nov 13;134(Suppl 1):612–2.
8. Arif N, Ajmal M, Moin S. Prime editing: A potential treatment option for β-thalassemia. Cell Biochem Funct. 2023;41:94–102.
9. Halegua T, Risson V, Carras J, Rouyer M, Coudert L, Jacquier A, et al. Delivery of Prime editing in human stem cells using pseudoviral NanoScribes particles. Nat Commun. 2025 Jan 4;16(1):397.
10. Zeng J, Casirati G, Nguyen MA, Genovese P, Bauer DE. Base editing of human hematopoietic stem cells. Methods Mol Biol. 2023;2606:43–62. doi: 10.1007/978-1-0716-2879-9_5. PMID:36592307; PMCID:PMC11452822.
11. George A, Ravi NS, Prasad K, Panigrahi L, Koikkara S, Rajendiran V, et al. Efficient and error-free correction of sickle mutation in human erythroid cells using prime editor-2. Front Genome Ed. 2022 Dec 20;4:1085111.
12. Base Editing for Mutation Repair in Hematopoietic Stem & Progenitor Cells for X-Linked Chronic Granulomatous Disease | Clinical Research Trial Listing. Centerwatch.com. 2026. Available from: https://www.centerwatch.com/clinical-trials/listings/NCT06325709/base-editing-for-mutation-repair-in-hematopoietic-stem-progenitor-cells-for-x-linked-chronic-granulomatous-disease.
13. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature. 2016 May 19;533(7603):420–4.
14. Porteus MH. Recent advances in prime editing technologies and their therapeutic applications. Nat Rev Mol Cell Biol. 2024;25:345–62.
15. Gaudelli NM, Lam DK, Rees HA, Solá-Esteves NM, Barrera LA, Born DA, et al. Directed evolution of adenine base editors with increased activity and therapeutic application. Nat Biotechnol. 2020;38(7):892–900. Available from: https://pubmed.ncbi.nlm.nih.gov/32284586/.
16. Richter MF, Zhao KT, Eton E, Lapinaite A, Newby GA, Thuronyi BW, et al. Phage-assisted evolution of an adenine base editor with improved Cas domain compatibility and activity. Nat Biotechnol. 2020 Jul 1;38(7):883–91.
17. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. Science. 2018 Jan 12;359(6372):eaan4672.
18. Gera S, Agrawal D, Maiti S, Chakraborty D. Rewriting Genetic Destiny: Prime Editing Leads the Future in Fixing Genetic Disorders. Natl Med J India. 2025;38(6):321–5.
19. Ball J, Bradley A, Le A, Tisdale JF, Uchida N. Hematopoietic stem cell therapy with gene modification to treat sickle cell disease. Stem Cells Transl Med. 2025 Sep;14(9):szaf042.
20. Lee J, Kim H, Park S. Emerging trends in prime editing for precision genome editing. Front Genome Ed. 2025;7:12322275.
21. News: The FDA Has Cleared the First Clinical Trial Application for a Prime Editor - CRISPR Medicine. CRISPR Medicine. 2024. Available from: https://crisprmedicinenews.com/news/the-fda-has-cleared-the-first-clinical-trial-application-for-a-prime-editor/.
22. Aronson AR, Mork JG, Lang FM, Rogers WJ, Neveol A. NLM Medical Text Indexer: A tool for automatic and assisted indexing. Bethesda: US National Library of Medicine. 2008 Apr 10.

 

23. Akhtar S, Sherin A. How to write a review article. Pak Arch Med. 2020;17:1–10.
24. Nourmohammadi H, Babashahi M, Panji M, Radmehr S. Gene-edited hematopoietic stem cells for leukemia and lymphoma treatment: A systematic review of preclinical and translational evidence. Discov Oncol. 2025 Oct 2;16(1):1804.
25. Shao C, Liu Q, Xu J, Zhang J, Zhang C, Xin Y, et al. Efficient and in situ correction of hemoglobin Constant Spring mutation by prime editing in human hematopoietic cells. Mol Ther Nucleic Acids. 2024;35(4):102371. doi: 10.1016/j.omtn.2024.102371. PMID:39640014; PMCID:PMC11617223.
26. Base editing shows potential superiority for curing sickle cell disease. Stjude.org. 2023. Available from: https://www.stjude.org/media-resources/news-releases/2023-medicine-science-news/base-editing-shows-potential-superiority-for-curing-sickle-cell-disease.html.
27. Zhang C, Xu J, Wu Y, Xu C, Xu P. Base editors-mediated gene therapy in hematopoietic stem cells for hematologic diseases. Stem Cell Rev Rep. 2024 Aug;20(6):1387–405.
28. CRISPR Therapeutics Announces Positive Phase 1 Clinical Data for CTX310® Demonstrating Deep and Durable ANGPTL3 Editing, Triglyceride and Lipid Lowering | CRISPR Therapeutics. CRISPR Therapeutics. 2025. Available from: https://ir.crisprtx.com/news-releases/news-release-details/crispr-therapeutics-announces-positive-phase-1-clinical-data
29. Kim SI, Matsumoto T, Kagawa H, Nakamura M, Hirohata R, Ueno A, et al. Microhomology-assisted scarless genome editing in human iPSCs. Nat Commun. 2018;9(1):939. doi:10.1038/s41467-018-03044-y. PMID:29507284; PMCID:PMC5838097.
30. High-Precision Base Editing Clinical Treatment for Sickle Cell Disease — CorrectSequence Therapeutics" CS-101 Achieves Clinical Cure-正序生物. Correctsequence.com. 2025. Available from: https://www.correctsequence.com/news/shownews.php?id=472&lang=en.
31. Antoniou P, Miccio A. Base and prime editing for blood disorders. PubMed PMID:34713251. 2021.
32. The Lancet. Information for Authors. London: The Lancet; 2019 May. Available from: The Lancet Information for Authors PDF.
33. Mahendra Bandsode. lancet-information-for-authors.pdf. Scribd. 2026. Available from: https://www.scribd.com/document/415952060/lancet-information-for-authors-pdf
34. Halpern SD, Ubel PA, Caplan AL. Lancet author guidelines. Lancet. 2025;405:1123–30.
35. Jamieson C. Vancouver style in medical publishing. Lancet. 1979;314:91047–X.

 