# Targeting fetal hemoglobin induction in sickle cell anemia: Epigenetic and gene-modifying therapeutic strategies (Review)

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**Abstract.** Sickle cell anemia (SCA) is a hereditary disorder marked by rigid, sickled red blood cells due to a single point mutation in the β-globin gene. The reactivation of fetal hemoglobin (HbF) mitigates disease severity by inhibiting hemoglobin S polymerization, rendering HbF induction a key therapeutic target. Emerging evidence indicates that the γ-globin gene is silenced and reactivated by epigenetic mechanisms, such as DNA methylation, histone modifications and chromatin remodeling. The present review examines epigenetic treatment options for reactivating γ-globin in SCA, with a focus on pharmacologic modulators, such as DNA methyltransferase, histone deacetylase and lysine-specific demethylase 1 inhibitors, as well as emerging genome-editing strategies targeting key repressors such as B-cell lymphoma/leukemia 11A and zinc finger and BTB domain containing 7A. It also explores translational advancements as demonstrated by Casgevy, the first CRISPR-based treatment approved for SCA, while highlighting persisting issues with efficacy, safety, specificity and accessibility. The aim of the present review was to clarify the translational limitations and therapeutic potential of epigenetic approaches for HbF induction in SCA.

## Contents



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## 1. Introduction

Sickle cell anemia (SCA) is the most common form of sickle cell disease (SCD), a group of genetic disorders caused by defective hemoglobin genes (1). SCA is a prevalent hemoglobin anomaly worldwide and a major cause of child mortality in West Africa, accounting for 9-16% of deaths (2). It is caused by a point mutation on chromosome 11, where valine replaces glutamic acid in the β-globin chain, leading to hemoglobin S (HbS) formation. Under low oxygen conditions, HbS polymerizes, reducing red blood cell mobility, increasing fragility, and causing vaso-occlusive complications and hemolysis (3). Even though the molecular basis of SCA is well-known and the pathophysiology of the disease is better understood, there has been a substantial lag in its application to the development of safe and effective therapies. Recent studies underscore the therapeutic potential of reactivating fetal hemoglobin (HbF), which is mediated by epigenetic processes. The present review discusses the mechanisms through which targeting epigenetic regulators and transcriptional repressors can increase HbF and alleviate SCA pathology.

## 2. Importance of the γ-globin genes and HbF in SCA

HbF, composed of two α- and two γ-globin chains produced by the γ-globin genes, is dominant throughout fetal life, but decreases postnatally due to hemoglobin switching (4). Adults have residual HbF levels (usually 1%) (5). The γ-globin genes (HBG1 and HBG2) are crucial in SCA pathophysiology, as an increased expression of HbF reduces disease severity, improves red blood cell lifespan and enhances erythropoiesis efficiency (6). Individuals with the hereditary persistence of HbF are often clinically asymptomatic (7). Thus, re-inducing HbF through γ-globin gene activation offers a promising therapeutic strategy.

## 3. Epigenetic regulation of γ-globin gene expression

Epigenetic mechanisms regulate gene expression without altering the deoxyribonucleic acid (DNA) sequence and include the following:

*DNA methylation*. The methylation of CpG islands in the γ-globin promoter inhibits its expression (8). This suppression is carried out by DNA methyltransferases (DNMTs). DNMT inhibitors can demethylate the γ-globin promoter and restore HbF expression (9).

*Histone modifications*. The acetylation of lysine residues via histone acetyltransferases (HATs) reduces histone-DNA interactions, making chromatin more accessible to transcription factors and promoting gene expression, whereas deacetylation via histone deacetylases (HDACs) compacts chromatin and represses gene expression (10). Histone methylation by histone methyltransferases (HMTs) or demethylation by lysine-specific demethylase 1 (LSD1) also influences γ-globin transcription (11). Protein arginine methyltransferase 5 (PRMT5) and H3K27me3 are associated with γ-globin silencing (12). Adenosine-20,30-dialdehyde, a methyltransferase inhibitor, was previously demonstrated to stimulate γ-globin gene expression in human early-stage cultured red blood cell precursors, suggesting that PRMT5 catalytic activity may be mechanically associated with γ-globin gene suppression (13). Transcriptionally active chromatin is associated with the trimethylation of histone H3, specifically lysine at position 4 (H3K4me3), while H3K27me3 and H3K9Me3 result in tight chromatin, which suppresses gene expression (14).

*Transcription factors and chromatin remodelers*. B-cell lymphoma/leukemia 11A (BCL11A) and zinc finger and BTB domain containing 7A (ZBTB7A) are key transcriptional repressors of the γ-globin gene. To maintain a suppressed chromatin state, they enlist the nucleosome remodeling and deacetylase complex/chromodomain helicase DNA-binding protein 4 (NuRD/CHD4) (15). Other elements that control these repressors and function as indirect targets for HbF induction include zinc finger protein 410 (ZNF410) and hypermethylated in cancer 2 (HIC2) (16). Furthermore, epigenetic control is reversible and dynamic, rendering it a potential target for therapeutic applications (17).

## 4. Current approaches targeting epigenetic modifications to increase HbF production

Investigations into certain HDAC antagonists, such as short-chain fatty acids, have demonstrated potential for triggering the production of HbF (18). The clinical development of phosphodiesterase 9 inhibitors (PF-04447943; ClinicalTrials.gov Identifier: NCT02114203-completed), mechanistic target of rapamycin (mTOR) inhibitors, such as sirolimus (Sirthalaclin trial; ClinicalTrials.gov Identifier: NCT03877809-completed; mechanistic proof of HbF induction relevant to sickle cell disease), and 3,4-dihydroxyphenylalanine DOPA decarboxylase inhibitors such as benserazide (BENeFiTS trial; ClinicalTrials.gov Identifier: NCT04432623-ongoing) has demonstrated enhanced γ-globin or HbF expression, although none has established long-term transfusion independence in hemoglobinopathies (19-21). The molecular links between the alleged mechanisms of action of these agents and epigenetic modifications that may influence HbF production remain unclear. The selective erythroid deletion of BCL11A in mice has shown promise in the treatment of SCA (22), leading to clinical studies using genome modification with promising outcomes (23,24).

Single BCL11A or ZBTB7A knockout (KO) leads to 40-50% HbF expression in human erythroid progenitors, whereas dual KO results in ~90-100% HbF, indicating their independent contribution to repression. While adult-stage ZBTB7A deletion causes moderate macrocytic anemia, complete knockout results in embryonic mortality due to severe anemia (15). In hematopoietic stem and progenitor cell (HSPC)-derived erythroblasts, ZBTB7A reduction also postpones erythroid development. Future research is required to identify an optimal therapeutic strategy where selectively inhibiting ZBTB7A in adults induces HbF without adverse effects. Expanding upon the fundamental knowledge of transcription factors linked to HbF repression, the following paragraphs discuss other epigenetic regulators that provide novel therapeutic options for the reactivation of γ-globin expression.

*Epigenetic regulators*. ZNF410 is a transcription factor with a single known target, *CHD4*, to stimulate the transcription of γ-globin (HBG1/2) genes, rendering it a suitable target for HbF reactivation (25). The deletion of ZNF410 does not affect erythroid development, and leads to a marked increase in the levels of HBG1/2, and a corresponding decrease in the level of β-globin gene in various cell models and mice. Dual BCL11A and ZNF410 knockdown enhances HbF production more effectively than targeting BCL11A alone, rendering ZNF410 a promising therapeutic target for SCD and β-thalassemia (26).

HIC2 is a zinc finger transcription factor that plays a critical role in gene regulation and development. It functions as a transcriptional repressor for BCL11A, thereby promoting HbF production by reducing chromatin accessibility at BCL11A enhancers (16). Additionally, widely interspaced zinc finger (WIZ) degradation via molecular glue degraders has been explored as a strategy to induce HbF (27). OTQ923, a genome-edited hematopoietic stem and progenitor cell product, was evaluated in a first-in-patient phase I/II clinical study to decrease the biological activity of BCL11A, boost HbF and decrease SCD-related complications. However, that study was discontinued for commercial reasons rather than safety concerns (ClinicalTrials.gov Identifier: NCT04443907). Presently under investigation is a multi-center, open-label, non-randomized, phase 2 research (GRASP, BMT CTN 2001) that targets BCL11A to raise HbF in patients with SCD (ClinicalTrials.gov Identifier: NCT05353647).

## 5. Fetal hemoglobin boosters: Pharmacological agents

Inhibitors of DNMT (such as decitabine), HDAC (such as butyrate, vorinostat and givinostat), and LSD1 have been demonstrated to increase HbF (28). Hydroxyurea, however, not epigenetic in effect, remains a key component of therapy due to its potential to produce HbF (29). Through DNA hypomethylation, DNMT inhibitors, such as decitabine and 5-azacytidine

can restore the expression of γ-globin genes (30). However, the clinical development of 5-azacytidine for hemoglobinopathies was discontinued due to severe effects, although the medication is still used for specific blood-related cancers (31). The clinical success of hydroxyurea is mostly owing to its ability to produce HbF, possibly through epigenetic modifications (32).

*Mechanisms of action of hydroxyurea as an HbF inducer.* In SCA, hydroxyurea raises HbF levels via two distinct processes: i) Ribonucleotide reductase inhibition, which encourages the selection of erythroid precursors with a high HbF expression; and ii) the direct selection of HbF cell formation by inhibition of soluble guanylate cyclase (28).

The most widely accepted theory is that it triggers 'stress erythropoiesis', which recruits primitive erythroid precursors that have the capacity to produce HbF, resulting in elevated HbF levels and a corresponding decrease in the proportion of HbS (32). Hydroxyurea alters methylation and demethylation processes at the γ-globin gene promoter to boost γ-globin expression; however, these changes do not significantly increase fetal globin reactivation (33). Another proposed mechanism involves hydroxyurea-driven nitric oxide production, which increases intracellular cyclic guanosine monophosphate-protein kinase G, ultimately inducing HbF synthesis. However, the exact mechanisms involved remain unknown.

*HDAC 1/2 inhibitors in SCA: Preclinical studies and therapeutic potential.* HDAC1 and HDAC2 inhibitors have shown promise in the treatment of SCA by inducing HbF production. Non-selective HDAC inhibitors, such as butyrates, have been shown to be effective (34). However, side-effects and gene expression issues need to be addressed for long-term effective treatments, including the selective suppression of HDAC-1 or HDAC-2 (35). The selective inhibition of HDAC1 and HDAC2 inhibitors modifies the chromatin structure of the β-globin gene, producing HbF without directly affecting bone marrow (36). HDAC inhibitors enhance histone acetylation, opening chromatin and increasing γ-globin transcription.

According to Di Micco *et al* (37), HDAC-1 and HDAC-2 share 85% identity and 93% similarity, rendering selective chemicals challenging. However, they regulate gene expression for γ-globin induction, eliminating the need for selectivity (37). Acetylon Pharmaceuticals, Inc. developed ACY-957, a chemical with a zinc-chelating benzamide group, that increases histone acetylation and GATA2 binding in cells. It suppresses HDAC1/2 and enhances γ-globin mRNA expression (38). The targeted inhibition of HDAC1 and HDAC2 in adult human red blood cells increases HbF production without altering the cell cycle (39). Romidepsin (40), the HDAC1/3 inhibitor, MS-275 (entinostat) (41), and givinostat, a hydroxamate inhibitor, also promote γ-globin gene expression without disrupting cell growth (42). The genetic knockdown of HDAC1/2 increases HbF levels, and combination therapy with hydroxyurea enhances γ-globin synthesis (43). This is further enhanced by MS-275 (43). A phase 1 trial of panobinostat, a pan-HDAC inhibitor, is currently underway in adult patients with SCD (ClinicalTrials.gov identifier: NCT01245179). CT-101, a class I HDAC inhibitor, has been reported to selectively activate γ-globin transcription, leading to elevated F-cells and HbF levels with minimal cytotoxicity. In combination with hydroxyurea, it results in an even greater increase in HbF levels.

These results highlight the potential of these agents as pharmacological inducers of HbF. However, despite promising preclinical findings, there is still a dearth of human clinical proof (44). A summary of the aforementioned pharmacologic HbF inducers, their mechanisms of action and current clinical status is presented in Table I.

## 6. CRISPR-associated protein 9

The CRISPR/Cas9 technique can be used to edit the epigenome and modify methylation patterns of DNA or histone changes in the γ-globin gene locus. It enables precision genome editing to disrupt HbF repressors or mimic the hereditary persistence of fetal hemoglobin (45). Preclinical and early clinical research has shown that targeting BCL11A or its enhancer, ZBTB7A, or altering γ-globin promoters can successfully regenerate HbF (46). Gene therapy is probably safer than allogenic hematopoietic stem cell transplant, though it is associated with adverse effects and is expensive (47).

CRISPR/Cas9 identified nuclear factor 1A and nuclear factor 1X as HBG1/2 repressors that are cooperative and expressed at higher levels in adult erythroid cells than in fetal cells. These transcription factors inhibit HBG1/2 and promote BCL11A expression, playing a vital role in the fetal-to-adult hemoglobin transition (48). A CRISPR/Cas9 screen demonstrated that globin gene switching is affected by ubiquitin-proteasome components, with von Hippel-Lindau ubiquitin ligase (VHL E3) depletion stabilizing hypoxia-inducible factor 1α, which initiates the transcription of the γ-globin gene through enhanced chromatin accessibility and transcriptional activators. This implies that prolyl hydroxylase domain enzyme inhibition or hypoxia may be used as therapy for β-hemoglobinopathy (49).

Frati *et al* (50) employed CRISPR/Cas9 gene editing to target lymphoma-related factor (LRF) repressor sites in γ-globin promoters, effectively reactivating HbF expression. This genome editing strategy in patient-derived HSPCs and healthy donor cells results in a significant HbF production and a high disruption of lymphoma-related factor binding sites (LRF BS). In SCD HSPCs, LRF BS disruption was more effective but also decreased myeloid bias and engraftment. Genes linked to inflammatory reactions and DNA damage were upregulated during the editing process (50). Furthermore, the USA and UK authorized the commercial gene therapy product, Casgevy, a CRISPR-based treatment that targets BCL11A, for use in 2023 (51). Despite this achievement, a number of obstacles still limit its clinical application: Patients must be at least 12 years old to be eligible; there are safety concerns about potential mosaicism and off-target effects; and the sustained effectiveness of HbF induction over time is unclear. Moreover, high costs and infrastructure demands pose substantial obstacles to worldwide access, especially in sub-Saharan Africa, where the prevalence of SCA is high. Additionally, ethical concerns have been raised, particularly in light of the possibility of germline editing, which might bring heritable modifications into the human genome (52).

Table I. Pharmacological HbF inducers: Mechanisms of action and clinical status.

| Agent/class | Proposed mechanism(s) | Clinical status/limitations |
|---|---|---|
| Hydroxyurea | Stress erythropoiesis; NO-sGC-cGMP signaling; ribonucleotide reductase inhibition; indirect epigenetic effects (28,32,33) | Widely used; variable response; requires monitoring; cytopenias |
| Decitabine/5-azacytidine (DNMT inhibitors) | Demethylation of γ-globin promoter (28) | Increases HbF but limited by toxicity; experimental/limited trials |
| Short-chain fatty acids (Butyrates) | Histone acetylation; chromatin relaxation (28,36) | Strong induction *in vitro*/early trials; transient response; limited by pharmacokinetics; inconsistent results across large clinical trials |
| Pan-HDAC inhibitors (vorinostat/panobinostat) | Broad histone acetylation; open chromatin (28) | Proof of concept in small trials; toxicity; not suitable for long-term use |
| Selective HDAC1/2 inhibitors | Targeted histone acetylation (44) | Preclinical stage; promising selectivity; human data lacking |

The numbers in parentheses refer to reference citations. DNMT, DNA methyltransferase; NO, nitric oxide; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; HbF, fetal hemoglobin; HDAC, histone deacetylase.

## 7. Future perspectives in the development of epigenetic therapy

Large-scale, long-term clinical trials are required to validate preclinical results and prove efficacy and safety in humans. Ethical issues also need to be addressed, particularly in relation to fair access, the possible unintended consequences of genome editing, and the necessity of clearly outlining the advantages, disadvantages, and available options when treating pediatric patients. Future studies should therefore ensure safety, improve selectivity, optimize delivery strategies, lower expenses and guarantee access to innovative treatments. Researchers, clinicians and policymakers must work together to make sure that discoveries result in real benefits for patients with SCA worldwide.

## 8. Study limitations and conclusion

The present review is based on preclinical studies and early-phase trials. The lack of specificity in a number of epigenetic agents poses safety issues. Furthermore, accessibility and cost barriers restrict the potential of CRISPR treatments. The regulatory network that controls γ-globin is still not fully known, and there is still no explanation for the variation in patient response.

*Clinical relevance and translational challenges*. Although hydroxyurea is a key therapy, its variable efficacy and side-effects pose a challenge. DNMT and HDAC inhibitors are hindered by their toxicity, and CRISPR-based therapies such as Casgevy hold promise; however, high costs and complexity persist. These translational hurdles need to be overcome to demonstrate clinical effectiveness, particularly in areas with limited resources and high prevalence of the disease.

In conclusion, epigenetic modification provides a compelling approach for the treatment of SCA via HbF reactivation. Advances in pharmacology and genome editing have sped up clinical translation. Selective HDAC1/2 inhibition and CRISPR/Cas9-based treatments are particularly promising. To establish HbF reactivation as a safe, efficient and widely available treatment for SCA, further research on precision gene editing and specific epigenetic modulators is mandatory.

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## Authors' contributions

SAA was involved in the conceptualization of the study, and in the drafting and editing of the manuscript. FB and AYA were involved the reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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