Review Form 3

Journal Name:	**Asian Journal of Biochemistry, Genetics and Molecular Biology**
Manuscript Number:	**Ms_AJBGMB_130454**
Title of the Manuscript:	**Sickle Cell Disease in Sub-Saharan Africa: Is CRISPR-Cas9 the Breakthrough We've Been Waiting For?**
Type of the Article	**Review Article**

PART 1: Comments

	Reviewer's comment	**Author's Feedback** *(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.	**The manuscript provides a detailed and technically rich discussion on CRISPR-Cas9 and its application to sickle cell disease. However, certain sections, such as the description of CRISPR-Cas9 mechanisms, are dense and may not be easily accessible to readers without a strong molecular biology background. Simplifying the technical language or including diagrams to visually explain complex processes could enhance readability.**	Noted
Is the title of the article suitable? (If not please suggest an alternative title)	**Yes**	Thanks
Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.	**The abstract is comprehensive and provides a clear overview of the topic. However, I suggest to briefly mention the clinical outcomes or effectiveness of CASGEVY™ (Numbers if available)**	Ok
Is the manuscript scientifically, correct? Please write here.	Yes	Thanks
Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.	yes	

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Is the language/English quality of the article suitable for scholarly communications?	yes	
Optional/General comments	**Major revision:** • The text discusses both NHEJ and HDR repair pathways but does not elaborate on the challenges of achieving efficient HDR in primary hematopoietic stem cells (HSCs). Including recent advancements to enhance HDR efficiency (e.g., small molecules or alternative repair templates) would provide more depth. • The issue of off-target effects is highlighted, but specific techniques to minimize these, such as the use of high-fidelity Cas9 variants (e.g., Cas9-HF1 or eSpCas9), are not discussed. **Minor revisions:** • Some sentences, particularly those explaining mechanisms (e.g., "Disrupting the promoter regions of the HGB1 and HGB2 genes…"), are dense and could be simplified for clarity. Breaking these into shorter sentences would improve readability. • Some sections rely heavily on a limited number of references (e.g., the discussion on HPFH mutations and their potential). Including more diverse and recent references would strengthen the credibility of the analysis and provide a more comprehensive view of ongoing research in the field. • The transition between correcting HBB mutations and promoting HbF production could be smoother. Consider adding a brief introductory sentence to explain why both approaches are complementary yet distinct. • Authors explain how HbF repressors like BCL11A are targeted. However, it could discuss whether transient gene-editing approaches (e.g., epigenetic editing using dCas9 fused to transcriptional activators) are viable alternatives for upregulating HbF without permanent genetic changes. Authors must discuss the long-term safety, ethical concerns, or potential risks associated with CRISPR-Cas9 therapies for SCD more explicitly	

PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)*	

Reviewer Details:

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