ELSEVIER

Blood 142 (2023) 5243

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

112.THALASSEMIA AND GLOBIN GENE REGULATION

Development of Best-in-Class Gene Editing Therapy for β-Hemoglobinopathies Using Innovative Transformer Base Editor (tBE)

Lijie Wang[1], *Peixue Li, PhD*[2], *Yichuan Wang*[1], *Kewei Lan*[1], *Huiming Zheng*[1], *Di Zhu*[1], *Yan Zhang*[1], *Runni Guo*[1], *Hongxia Ma*[1], *Jing He*[1], *Qing Su*[1], *Runze Gao*[1], *Lang Zhang*[1], *Zhiwei Bao*[1], *Jianxia Hou*[1], *Letu Ji*[1], *Jian Zhang*[1], *Sijia Wu*[1], *Yaliang Li*[1], *Bei Luo*[1], *Bingbing Wu*[1], *Susan Mou*[1], *Jia Chen, PhD*[3,4]

[1] CorrectSequence Therapeutics, Shanghai, China
[2] CorrectSequence Therapeutics, Shanghai, China
[3] School of Life Science and Technology, ShanghaiTech University, Shanghai, China
[4] Shanghai Clinical Research and Trial Center, Shanghai, China

β-thalassemia and sickle cell disease (SCD) are among the most prevalent monogenic disorders worldwide and both these β-hemoglobinopathies are caused by mutations in the β-globin gene HBB. Reactivating the expression of the γ-globin genes (*HBG1/2*) mimicking the naturally occurring hereditary persistence of HbF (HPFH) is expected to be a universal strategy to treat β-thalassemia and SCD by the induction of fetal hemoglobin (HbF). To achieve this goal, CorrectSequence Therapeutics' first pipeline, CS-101, uses transformer Base Editor (tBE) to precisely edit human hematopoietic stem cells (HSC) *ex vivo* to induce the expression of γ-globin for treatment of β-thalassemia and sickle cell disease. Compared with the commonly used gene editing methods such as CRISPR/Cas nucleases or other base editors, tBE is a base editing system that avoids to cause DNA double strand breaks or off-target mutations. With the safety advantages of tBE, CS-101 targets one of the most potent targets to activate γ-globin expression without causing unexpected off-target mutations. A commercial scale manufacturing process to *ex vivo* edit HSC has been developed and validated with more than 10 batches of commercial scale production, all of which exhibited consistent process performance and product quality. Pre-clinical *in vivo* studies showed that while tBE-mediated editing of HSC induces robust γ-globin expression, tBE did not cause adverse effect on the engraftment or differentiation of the HSC in mice after transplantation. Clinical study for CS-101 is underway and it holds great promise to become the best-in-class gene editing treatment for β-hemoglobinopathies.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-178440