Base editors flex sights on sickle-cell disease

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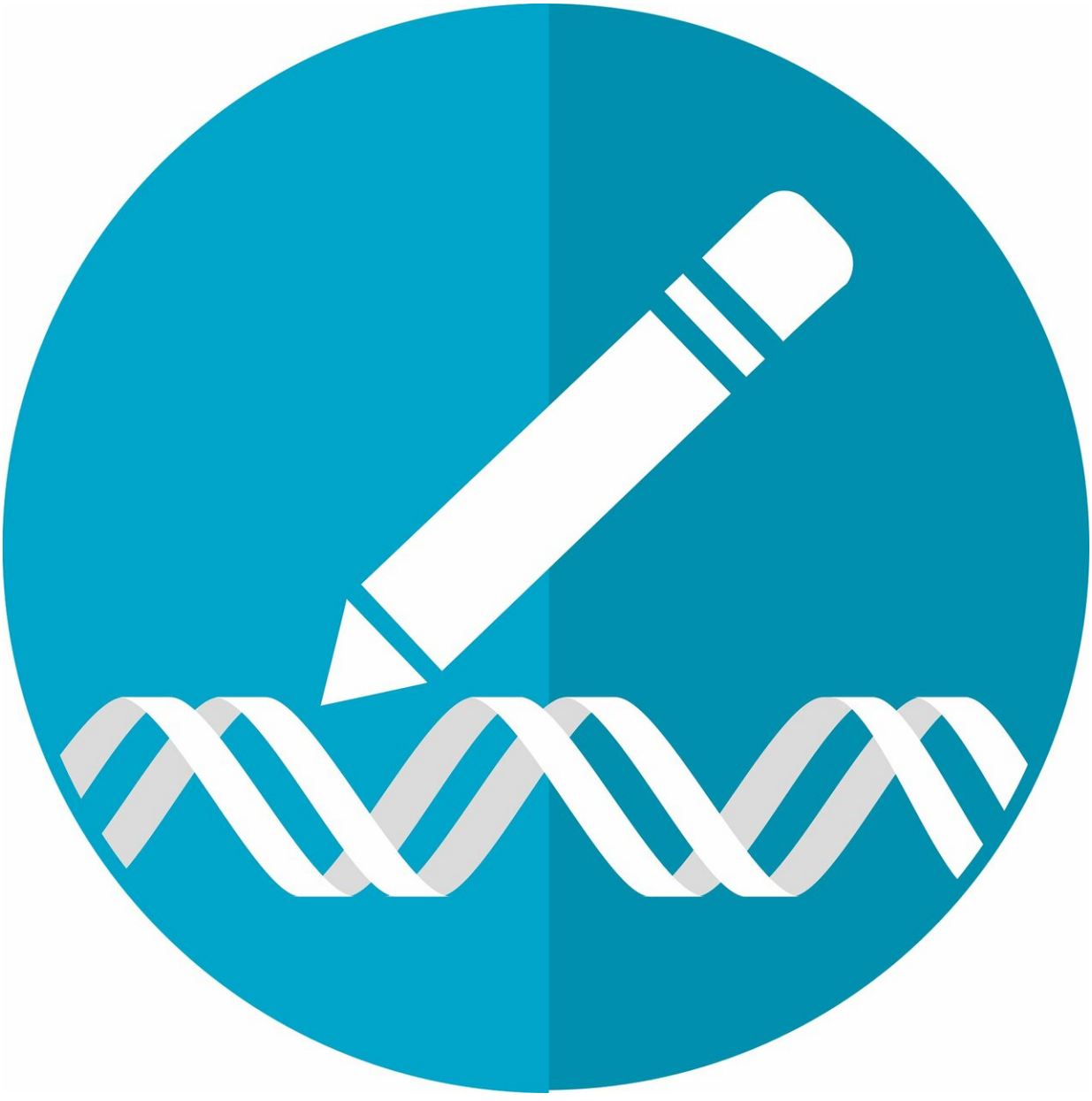

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Researchers at Beam Therapeutics have developed a redesigned base editor that shows considerable promise in directly repairing the single-base mutation that causes sickle-cell disease (SCD). Many strategies are being pursued to harness genome editing approaches including CRISPR to treat patients with SCD and related hemoglobinopathies. The most advanced method in the clinic involves targeting an upstream regulatory pathway to switch on expression of the fetal hemoglobin gene but does not target the SCD mutation directly.

Writing in the April issue of *The CRISPR Journal,* a team at Beam Therapeutics, led by Ian Slaymaker and Giuseppe Ciaramella, describe the successful repair of the SCD point mutation by using a redesigned base editor. The group developed a series of inlaid base editors (IBEs) by taking the deaminase portion of the base editor and inserting it into different parts of the Cas9 protein. This architecture provided a more flexible editing "window" that allowed the researchers to target the key mutation.

SCD is caused by an A-to-T mutation in the beta-globin gene resulting in a Glu-to-Val substitution. Base editing cannot reverse the SCD mutation back to the normal gene sequence but in this case, a substitution from T to G gives rise to a rare benign variant called HbG-Makassar (first described in 1970 in a young male living in Makassar, Sulawesi.)

"This paper is a great illustration of the power of CRISPR, combining the base-editing toolbox development aspect and showcasing the therapeutic potential of this modality for a broadly relevant genetic disease," commented Rodolphe Barrangou, Ph.D., Editor-in-Chief of *The CRISPR Journal.*

The study is discussed in an accompanying "First Cut" co-authored by

Anna Cereseto, T.J. Cradick (Excision Therapeutics), and *The CRISPR Journal* Executive Editor Kevin Davies.

More information: S. Haihua Chu et al. Rationally Designed Base Editors for Precise Editing of the Sickle Cell Disease Mutation. *The CRISPR Journal*
Online: 01 Apr 2021 doi.org/10.1089/crispr.2020.0144