Sickle Cell Disease: Gene Therapy, Accessibility, and the Road Ahead

By Lynzie Manson

Ever heard of sickle cell disease? Also referred to as "SCD", this is a tough inherited disease that affects the blood caused by a tiny mistake in our body's instructions. SCD can have a large impact on the quality of life of the individuals who suffer from the disease. Symptoms of SCD include severe vaso-occlusion events (i.e. blood vessel blockages), chronic anemia, organ damage, stroke, and an overall reduced lifespan[2].

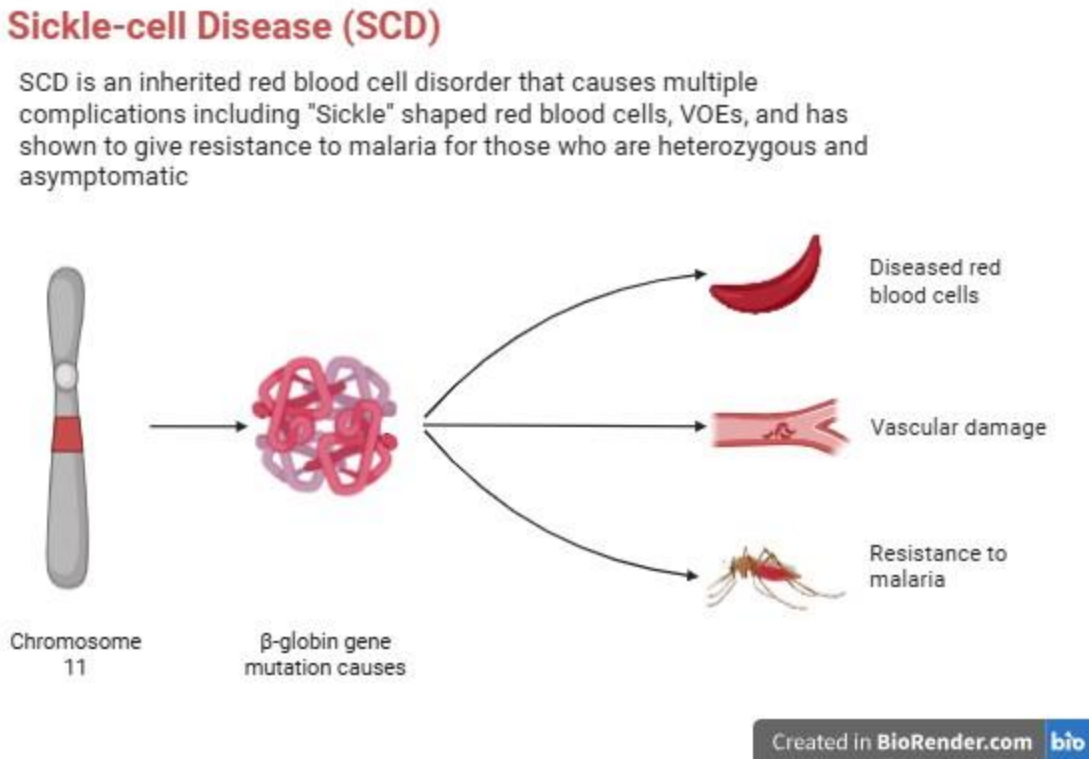
People with SCD have impaired hemoglobin, the protein in red blood cells responsible for carrying oxygen throughout the body. The mutant SCD form of hemoglobin is called hemoglobin S (HbS). In SCD, when oxygen is low, molecules of HbS stick together, or polymerize, and produce firm fibers.

Hemoglobin is a fascinating protein—it is referred to as a *tetramer* because it is composed of four smaller peptide subunits: two alpha-globin and two beta-globin chains. These four subunits assemble in red blood cells to form an efficient oxygen transport system.

In individuals with SCD, the hemoglobin protein (specifically HbS) contains two mutant copies of the beta-globin gene. This mutation makes the protein unusually sticky, leading to the polymerization of hemoglobin molecules—especially when oxygen is low. The polymerization of HbS warps the naturally flexible red blood cells into the characteristic sickle shape of SCD; the distorted cells can no longer fit through capillaries and tiny blood vessels, resulting in obstructions that will heavily disrupt blood flow and lead to a cascade of complications. A blockage of blood flow means reduced oxygen transport throughout the body; both the reduced oxygenation and inflammation following vessel blockages can lead to extensive tissue and organ damage throughout the body.

People with SCD inherit one mutant beta-globin gene from each parent, a condition known as homozygosity (i.e., both gene copies are the same). Interestingly, individuals who inherit only one mutant beta-globin gene and one normal copy—a condition known as heterozygosity—do not typically develop SCD. Instead, they carry what is called the *sickle cell trait*, which provides a remarkable advantage: resistance to malaria.

The heterozygous survival advantage conferred by the sickle cell trait is why the SCD mutant beta-globin gene has been maintained in populations where malaria is common, despite the negative impact on homozygous individuals for the SCD mutation.



Although there is no cure for sickle cell disease (SCD), several treatments—such as hydroxyurea, which helps relieve painful symptoms, and newer gene therapies like Casgevy—can effectively manage the condition and improve outcomes. However, access to these treatments remains a significant challenge.Current treatments

Although there is no cure for SCD, several treatments—including hydroxyurea, which helps relieve painful symptoms, and newer gene therapies like Casgevy—can effectively manage the condition and improve outcomes; however, access to these treatments remains a significant challenge[1,3]. The search for curative options continues, with hematopoietic stem cell transplantation (HSCT) emerging as a promising strategy for genetic correction.[4] HSCT can be performed using either autologous or allogeneic stem cells. In autologous transplantation, a patient's own stem cells are collected, genetically modified—often using gene therapy—and then returned to the body. Because the cells originate from the patient, the risk of immune rejection is significantly reduced. In contrast, allogeneic transplantation involves receiving stem cells from a donor. While autologous HSCT holds promise, it is currently limited by the substantial loss of cells needed to correct the underlying genetic mutation.

The Future of Gene Therapy for Sickle Cell Disease

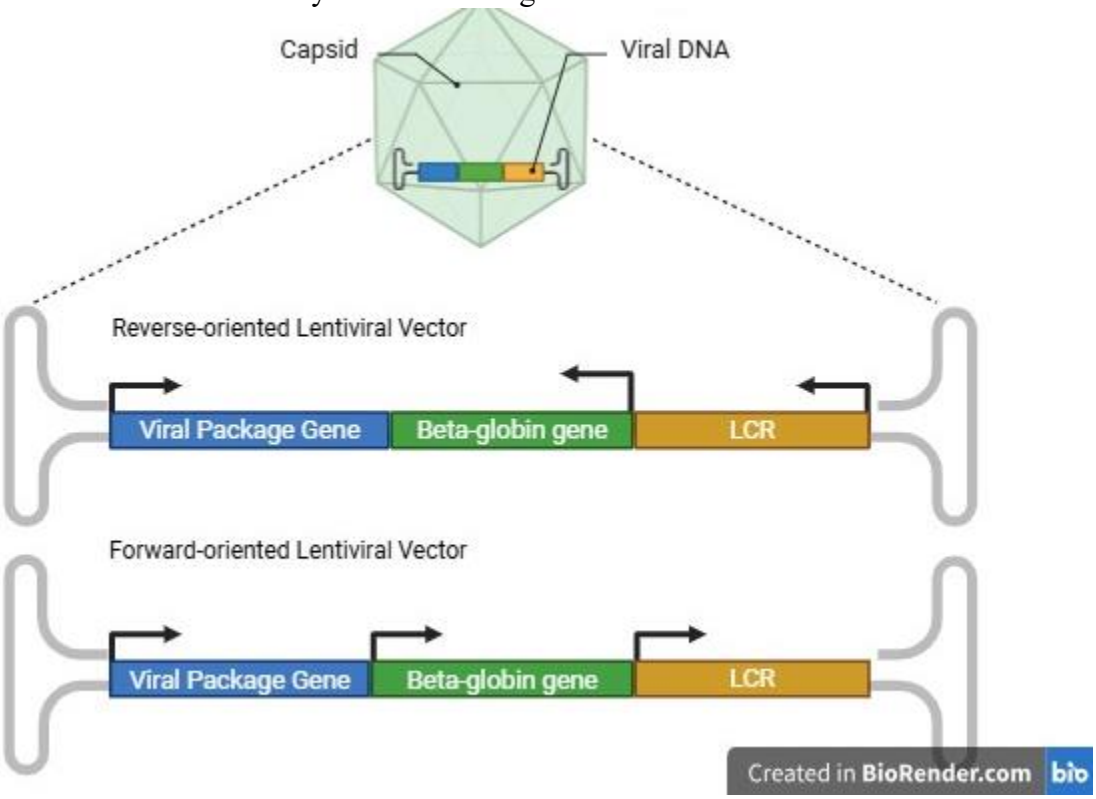
Gene therapy and HSCT are often prohibitively expensive, making them inaccessible to many patients—especially those in low-income communities and regions where SCD is most

prevalent. This financial barrier contributes to significant disparities in access to care and underscores the urgent need for more affordable and widely available treatment options.

Researchers are actively working to improve gene therapy for SCD. One promising strategy involves optimizing the design of lentiviral vectors, which are used to deliver therapeutic genes into cells. One promising approach focuses on improving lentiviral vectors, which are used to deliver therapeutic genes into cells. These vectors, derived from the human immunodeficiency virus (HIV), are engineered to be safe and have shown promise due to their ability to efficiently infect hematopoietic stem cells (HSCs) and sustain long-term gene expression.

A key factor influencing the effectiveness of lentiviral vectors is their orientation. "Forward-oriented" vectors—where the β-globin gene and its regulatory elements are aligned in the same direction—have demonstrated better performance than "reverse-oriented" vectors.[5] Reverse-oriented vectors may partially inactivate themselves, reducing the production of the therapeutic protein due to inefficient gene expression.

SCD is a debilitating disease that disproportionately affects vulnerable populations. While some treatments show promise, they remain accessible to only a limited number of patients. The scientific community is actively working to improve these therapies and expand their availability—particularly for individuals in low-resource settings. Current research is focused on improving gene delivery techniques, with the goal of creating more effective and affordable therapies for those most affected by this debilitating conditions.



1. Agrawal, Rohit Kumar, et al. “Hydroxyurea in Sickle Cell Disease: Drug Review.” *Indian Journal of Hematology & Blood Transfusion*, vol. 30, no. 2, June 2014, pp. 91–96, https://doi.org/10.1007/s12288-013-0261-4.
2. CDC. “Complications of SCD: Pain.” *Sickle Cell Disease (SCD)*, 22 May 2024, https://www.cdc.gov/sickle-cell/complications/pain.html.
3. Commissioner, Office of the. “FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease.” *FDA*, 9 Aug. 2024, https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease.
4. “Hemoglobin Subunit Beta.” *Wikipedia*, 2 Nov. 2024, https://en.wikipedia.org/w/index.php?title=Hemoglobin_subunit_beta&oldid=1255061577.
5. Uchida, Naoya, et al. “Development of a Forward-Oriented Therapeutic Lentiviral Vector for Hemoglobin Disorders.” *Nature Communications*, vol. 10, no. 1, Oct. 2019, p. 4479, https://doi.org/10.1038/s41467-019-12456-3.