Bristol Myers Squibb

Increasing fetal hemoglobin in sickle cell disease

What is sickle cell disease?

Sickle cell disease is a group of blood disorders affecting **hemoglobin**, a protein responsible for transporting oxygen in red blood cells. In individuals with the condition, dysfunctional hemoglobin causes red blood cells to become deformed (sickle-shaped). This creates blood flow blockages throughout the body and related serious symptoms, including pain, anemia, and infections. The condition also causes damage to organs, including the bones, spleen, liver, brain, lungs, kidneys and joints.[1-3]

Sickle cell disease is an **inherited condition** caused by a **mutation** in the adult hemoglobin gene (HbS), which causes the production of hemoglobin that does not function properly.[4]

Typical red blood cells

'Sickle' shaped red blood cells

Understanding the impact

People with sickle cell disease experience **sudden and severe episodes of pain** as a result of blocked blood flow, which can require medical attention.[1,4-6]

Nearly all patients will visit the emergency department at least **2-3 times per year** and be hospitalized **at least once a year**

About **30% of patients** report experiencing pain every day, while **more than 50%** report experiencing pain half of the time

The frequency of pain crises varies widely; some individuals can have **6 or more each year**

Sickle cell disease affects about **100,000 individuals in the US** and nearly **8 million globally**; it is most common in people of African, Middle Eastern, Mediterranean, Central and South American and South Asian descent.[2,7]

In the US, life expectancy of those with sickle cell disease is **more than 20 years lower than average**.[2]

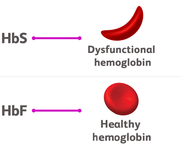
The condition significantly affects **quality of life** and patients often have trouble receiving medical care due to stigma and bias.[1,4]

Widely available treatment strategies focus only on **managing pain and preventing complications**.[1,4]

As a result, a significant need exists for new, effective disease-modifying therapies.

What is fetal hemoglobin (HbF)?

The body produces a different form of **hemoglobin** during fetal development and in the first 6 months of life outside the womb, called **fetal hemoglobin (HbF)**. After birth, HbF declines significantly, with the switch being made to **adult hemoglobin (HbS)** through activation of certain genes. HbS then makes up almost all of the body's hemoglobin going forward.[8]



In patients with sickle cell disease, only the HbS form of hemoglobin is dysfunctional. While the HbF form of hemoglobin is unaffected, it is no longer produced in most cases.[9]

Increasing HbF

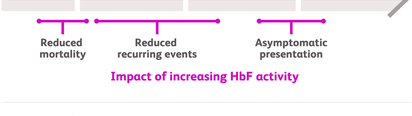
Researchers are investigating ways to revert the body's production of hemoglobin back to HbF, ultimately increasing the percentage of functional hemoglobin in the body.

This research approach is based on **causal human biology**[8,10]:

- Some individuals with sickle cell disease naturally continue to produce HbF into adulthood
- These individuals with a higher proportion of HbF generally have milder disease, experiencing less severe symptoms

Genetic and clinical data from certain populations of people with sickle cell disease have shown that achieving at least 30% of hemoglobin production from HbF could eliminate symptoms for patients.[11]

Percent of hemoglobin produced by HbF



Impact of increasing HbF activity

Researchers at Bristol Myers Squibb are investigating the ability of targeted protein degraders, specifically **molecular glue degraders**, to eliminate key genetic regulators that traditionally turn down production of hemoglobin from HbF. This could increase HbF levels into a range that may alleviate symptoms, associated organ damage and early mortality in people with sickle cell disease.

Protein degraders harness the cell's own degradation machinery to break down therapeutically relevant proteins that were previously considered "undruggable".

Bristol Myers Squibb is building on decades of unique research and clinical experience in protein degradation to discover and develop innovative medicines that could transform patient outcomes in some of the most complex diseases of our time, such as sickle cell disease.

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