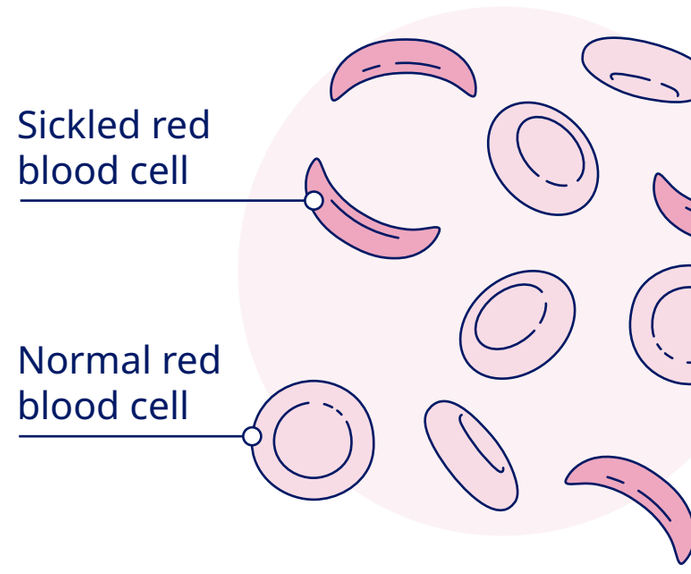
PKR activators are investigational. Safety and efficacy are not established. There is no guarantee that investigational PKR activators will become commercially available for the use(s) under investigation.

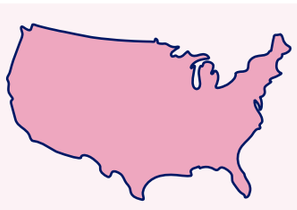
The distinct actions of HbS polymerization inhibitors and PKR activators for treating sickle cell disease

What happens to your red blood cells in sickle cell disease?[1,2]

Sickle cell disease is a genetic condition that changes the shape of red blood cells, which carry oxygen through the body. Unaffected red blood cells are round and soft, but in people with this disease, they become rigid and shaped like a "C", half moon, or “sickle”-shaped. Sickle cells can get stuck in blood vessels and cause complications such as fatigue, pain, swelling in the hands and feet, infections, and other complications in your organs like lungs, heart or brain.

Sickle cell disease happens because of a switch in a gene that helps make hemoglobin—the part of the red blood cell that carries oxygen. This abnormal gene must be passed on by both parents for the child to develop the disease.





In the United States, sickle cell disease mostly affects people of African, Mediterranean, Middle Eastern, and Hispanic descent

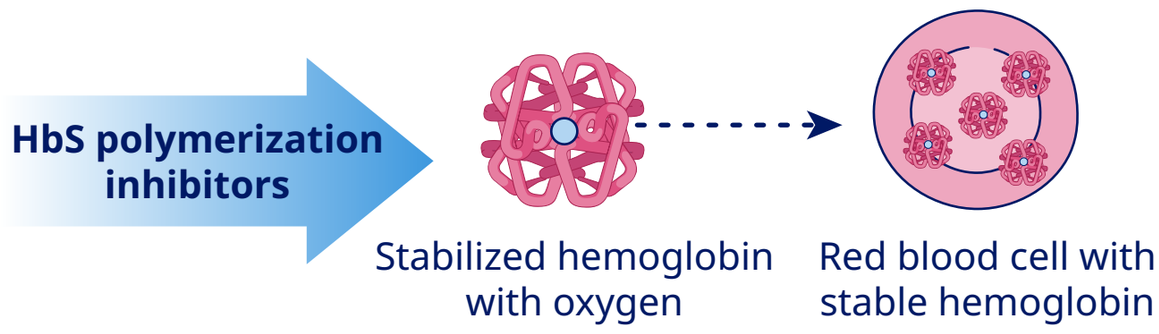
Over 100,000
people have sickle cell disease

90%
African descent

What are HbS polymerization inhibitors and PKR activators, and how do they work to manage sickle cell disease?[3,4]

Both of these drug classes have been developed as potential therapies for sickle cell disease and aim to work by helping sickled red blood cells carry more oxygen around your body; however, they do this in different ways.

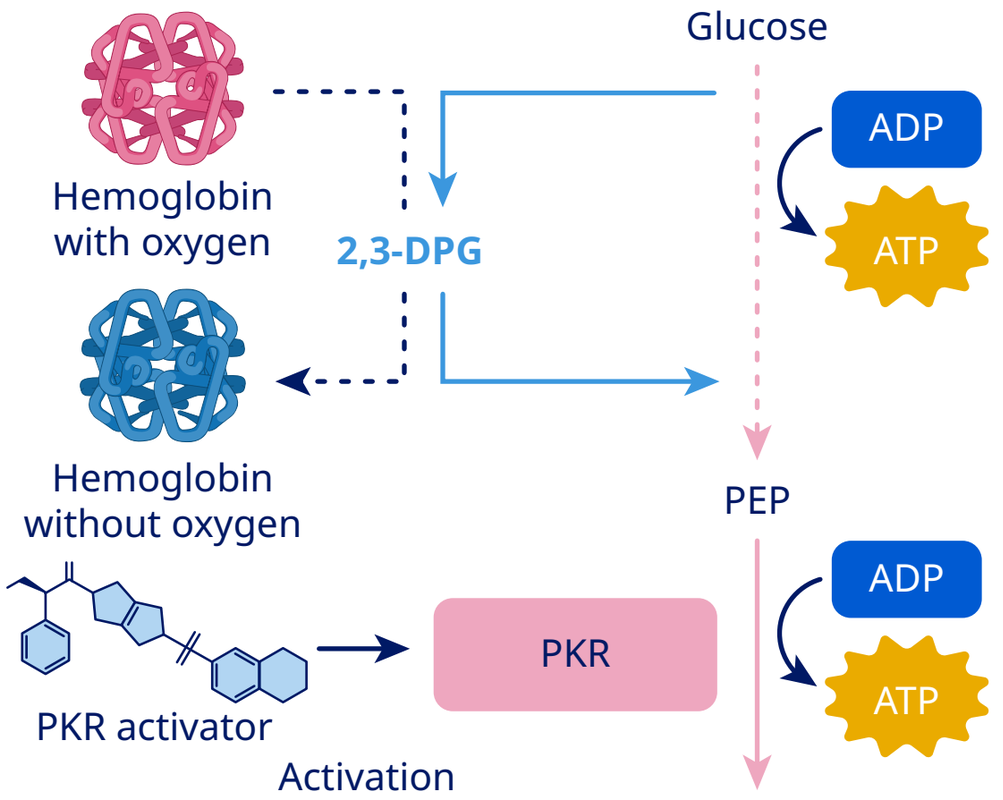
HbS polymerization inhibitors attach directly to the affected hemoglobin in sickled cells and help prevent the abnormal hemoglobin from clumping together. This clumping is what causes the cells to become sickle-shaped and block blood flow.



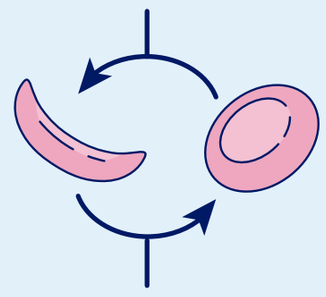
PKR activators enhance an existing pathway in the body to help manage sickle cells in two different ways. It does this by activating a protein in red blood cells called PKR, which

1. Increases cell energy (ATP) and
2. Lowers levels of a molecule called 2,3-DPG.

This helps hemoglobin hold on better to oxygen to reduce cell sickling and helping red blood cells stay healthy and live longer.



The process of activating PKR decreases 2,3-DPG and hemoglobin sickling



PKR activation increases energy and repairs red blood cells

What makes these two drug classes different from each other?[4-6]

Both classes present approaches to managing sickle cell disease but act on different biological pathways to improve red blood cell performance and reduce disease complications.

There are 2 key differences between these classes:

1. HbS polymerization inhibitors bind directly to the hemoglobin, whereas PKR activators use an energy-generating pathway that already exists in the body. This allows for the hemoglobin to function normally. Since HbS polymerization inhibitors bind tightly and directly to the part of the hemoglobin, it has the potential to interfere with oxygen reaching your tissues properly.

2. PKR activators have a dual action to manage sickle cell disease, and work without binding to red blood cells directly. In addition to increasing energy in red blood cells, it also helps hemoglobin hold on to oxygen to reduce cell sickling.

Key Takeaways

- Both HbA polymerization inhibitors and PKR activators are potential therapies for sickle cell disease and work to improve red blood cell’s ability to carry oxygen throughout the body
- HbS polymerization inhibitors work by directly binding to the hemoglobin protein and preventing it from forming clumps in the blood
- PKR activators have dual action by both preventing the sickle cell clump formation through a naturally occurring pathway and increasing energy to aid in red blood cell repair and health

1. What is Sickle Cell Disease? NIH National Heart, Lung, and Blood Institute. Sept 30, 2024. Accessed from: https://www.nhlbi.nih.gov/health/sickle-cell-disease; 2. Sickle cell anemia. Mayo Clinic: Diseases & Conditions. May 17th, 2025. Accessed from: https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876;
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