

## Scientists reverse sickle cell anemia by turning on fetal hemoglobin

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Not long after birth, human babies transition from producing blood containing oxygen-rich fetal hemoglobin to blood bearing the adult hemoglobin protein. For children with sickle cell disease, the transition from the fetal to adult form of hemoglobin – the oxygen-carrying protein in blood -- marks the onset of anemia and painful symptoms of the disorder.

Now, new research led by Howard Hughes Medical Institute (HHMI) investigator Stuart H. Orkin of Children's Hospital Boston, Dana Farber Cancer Institute, and Harvard Medical School shows that silencing a protein known as BCL11A can reactivate fetal hemoglobin production in adult mice and effectively reverses sickle cell disease. The new finding, reported October 13, 2011, in [Science Express](#), reveals that BCL11A is one of the primary factors involved in turning off fetal hemoglobin production.

"I think we've demonstrated that a single protein in the cells is a target that, if interfered with, would provide enough fetal hemoglobin to make patients better," says Orkin. "It's been hypothesized for three decades that fetal hemoglobin could be turned on once we understood the mechanism of hemoglobin switching, and this is the first evidence of a target to do that."

BCL11A is likely one of a suite of up to a dozen factors that influence fetal hemoglobin levels, Orkin says, but the new study provides hard evidence that it is one of the key players in regulating the production of

fetal hemoglobin. BCL11A works as a repressor by binding to DNA and regulating gene expression.

[Sickle cell anemia](#) is a genetic disease that affects hemoglobin production. It is estimated that as many as 100,000 people in the United States and many more in other parts of the world, Africa in particular, have the disease. A single nucleotide change in the hemoglobin gene causes an amino acid substitution in the hemoglobin protein from glutamic acid to valine. The resulting proteins stick together to form long fibers and cause the development of irregular, crescent-shaped red blood cells.

It is no secret to scientists or clinicians that elevating fetal hemoglobin in human sickle cell patients can help alleviate the pain-fraught episodes of fatigue and abdominal and bone pain that are hallmarks of the condition. Though a few drugs have been found that can increase fetal hemoglobin, biomedical researchers have spent decades trolling for the basic molecular mechanisms that control the shift from fetal to adult hemoglobin. Recent genome-wide association studies helped narrow the search to a few genes and now, in a critical "proof of principle" test in transgenic mice, the team led by Orkin identified the critical role of BCL11A in tamping down the production of fetal hemoglobin.

Fetal hemoglobin differs from the adult form of the protein in its affinity for oxygen. Production of fetal hemoglobin begins about two months into gestation and helps deliver [oxygen](#) from the mother's bloodstream to the developing fetus. By about 3-6 months after birth, fetal hemoglobin is almost completely replaced by adult hemoglobin. The timing, notes Orkin, explains why sickle cell patients don't experience symptoms of the disease until several months after birth.

Drug therapy with the agent hydroxyurea helps ramp up fetal hemoglobin in some patients and reduces the number of painful episodes

characteristic of sickle cell. But the drug is not uniformly effective, has several side effects and its mode of action is unknown.

Orkin notes that sickle cell was the first congenital disease for which scientists determined the single amino acid change in hemoglobin that sparks the condition. That work was done 60 years ago, he says, but that knowledge has never informed therapy for the disease.

Elevating the amount of fetal hemoglobin, says Orkin, emerged as a desirable strategy for treating sickle cell as clinicians and researchers noted long ago that levels of fetal hemoglobin naturally vary among individuals and that those sickle cell patients who express more of the fetal form of the protein experience fewer episodes of pain. "The more fetal hemoglobin you have, the better," says Orkin, noting that elevating levels of the fetal protein seems to have no toxic side effects. "The cell doesn't care if it's producing fetal hemoglobin or not."

The new study was done through genetic manipulation of a mouse model of sickle cell disease, demonstrating that in the future, gene therapy may be feasible. Knowing the target protein also means the search for new drugs to govern the production of [fetal hemoglobin](#) can shift to a higher gear. Finally, the new work holds promise for devising new treatments for a other congenital blood disorders known as thalassemias, which are also caused by an underproduction of adult hemoglobin.

Now that this key switch has been identified, Orkin asserts, the chances of powerful new therapies for sickle cell and other hemoglobin disorders will become more evident: "For the last 20 years we've been shooting arrows in the dark in hopes of hitting the target. Now we can see the target and it is a meaningful one."

Provided by Howard Hughes Medical Institute

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