

# Emerging drug class may enhance red blood cell production in anemic patients

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By determining how corticosteroids act to promote red blood cell progenitor formation, Whitehead Institute researchers have identified a class of drugs that may be beneficial in anemias, including those resulting from trauma, sepsis, malaria, kidney dialysis, and chemotherapy.

Anemia occurs due to a breakdown in erythropoiesis, the multi-step process that creates [red blood cells](#). Some common anemias can be treated with a recombinant form of the hormone erythropoietin (EPO), which normally stimulates red blood-cell production at a fairly early stage of erythropoiesis.

However, certain anemias fail to respond to EPO, creating a large unmet medical need. In the case of Diamond Blackfan anemia (DBA), patients lack a sufficient number of EPO-responsive cells. Instead, [corticosteroids](#) such as prednisone or prednisolone are used to treat DBA, although it has been unclear exactly how these agents affect erythropoiesis.

To see how corticosteroids are able to increase red blood cell counts, Johan Flygare, a postdoctoral researcher in the lab of Whitehead Institute Founding Member Harvey Lodish, purified two [progenitors](#) of red blood cells, called burst forming unit-erythroids (BFU-Es) and colony forming unit-erythroids (CFU-Es), from mouse fetal [liver cells](#). During erythropoiesis, BFU-Es produce CFU-Es, which are then stimulated by EPO to generate the pro-erythroblasts that eventually

become red blood cells. By dividing numerous times before maturing, both BFU-Es and CFU-Es have a limited ability to self-renew. When Flygare exposed BFU-Es and CFU-Es in vitro to a corticosteroid, only the BFU-Es responded--dividing 13 times instead of the usual 9 times before maturing into CFU-Es. These additional cell divisions ultimately led to a 13-fold increase in red blood-cell production.

Flygare identified 83 genes in BFU-Es that are stimulated by the corticosteroid, and he examined the promoters that facilitate those genes' transcription. The promoters appeared to have binding sites for a transcription factor, called hypoxia-induced factor 1-alpha (HIF1-alpha), that is activated when an organism is deprived of oxygen. To prolong the 83 genes' promotion by HIF1-alpha, Flygare used a class of drugs known as prolyl hydroxylase inhibitors (PHIs), which extends HIF1-alpha's effectiveness. PHIs have also been used in early-stage clinical trials to increase EPO production.

When Flygare added both a corticosteroid and a PHI to BFU-Es in culture, the cells produced 300 times more red blood cells than did cells without exposure to the drugs. Flygare repeated the experiment with adult human BFU-Es, and found that a corticosteroid plus a PHI generated 10 times more red blood cells than BFU-Es exposed to a corticosteroid alone.

Flygare hopes this research eventually leads to improved treatment for DBA patients who currently suffer from a host of corticosteroid-induced side effects, including decreased bone density, immunosuppression, stunted growth, and cataracts.

"If you could lower the dose of steroids so DBA patients would get just a little bit, and then add on this kind of drug, like a PHI, that would boost the effect, maybe you could get around the steroids' side effects," says Flygare. "That would be good."

This new approach to increasing erythropoiesis by extending the self-renewal of BFU-Es-resulting in creation of more EPO-responsive cells-could lead to novel therapies for other anemias.

"There are a number of anemias that are much more prevalent than DBA and that cannot be treated with EPO, either, such as anemias from trauma, sepsis, malaria, and anemia in [kidney dialysis](#) patients," says Lodish, who is also a professor of biology and bioengineering at MIT. "Whether these treatments will work in those conditions remains to be seen."

**More information:** "HIF-1 Alpha synergizes with glucocorticoids to promote BFU-E progenitor self-renewal", *Blood*, published online the week of December 22, 2010

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