Extra, Extra read all about it, pinball wizard in a miracle cure
The Who's Rock Opera, Tommy

OK, OK, so he may not be a pinball wizard, although I guess I don't know this for sure since I never asked him, and maybe it's not a miracle cure for DBA; but this literary trope seems an appropriate introduction to a paper hot off the e-presses from Harvey Lodish and coworkers[1]. This manuscript describes work in the Lodish laboratory directed at identifying molecules that work together with glucocorticoids in promoting erythropoiesis. Such molecules, should they exist, could potentially be used in combination with glucocorticoids in treating various anemias that are glucocorticoid responsive. Further, it might be possible to lower the amount of glucocorticoids used in such combination therapy, which could in principle reduce the overall toxicity of these drugs. Studies such as these are of obvious relevance to the DBA community, and the work by the Lodish group was supported in part by funds provided by the Diamond Blackfan Anemia Foundation and Diamond Blackfan Anemia Canada. (link to website article - http://dbafoundation.org/update-on-dr-lodishs-project-dbaf-and-dbac-provide-95000/).

The current manuscript reports on a class of drugs the Lodish group identified that work together with corticosteroids to promote erythropoiesis. More importantly, one of these molecules is already used clinically in treating hypercholesterolemia and hypertriglyceridemia. This, in turn, could potentially speed up the process by which the drug could be tested together with glucocorticoids in clinical trials for DBA patients.

Let's take a step back however, and look at some of the details of the Lodish paper. In previous work the Lodish laboratory showed that glucocorticoids had their effect in erythropoiesis in part by increasing the number of burst-forming units erythroid (BFU-E)[2], the same erythroid progenitors affected in DBA. In the current manuscript they examined genes induced when BFU-E self-renewal was stimulated by glucocorticoids. One of the genes stimulated under these conditions was a receptor that belongs to a family of nuclear receptors that also includes the glucocorticoid receptor. Both of these receptors bind their ligands and upon binding their respective ligands bind to DNA and stimulate the transcription of subsets of genes controlling various cellular processes. This other receptor is known as the peroxisome proliferator-activated receptor α (PPAR-α). In contrast to the glucocorticoid receptor, which has been known for some time to stimulate erythropoiesis, PPAR-α has not been previously shown to influence erythropoiesis.

The Lodish laboratory tested two drugs known to activate PPAR-α (PPAR-α agonists), fenofibrate which is FDA approved for HC and HT and a experimental drug GW7647 which binds more tightly to the PPAR-α receptor. Neither of these drugs stimulates erythropoiesis on their own in the mouse fetal liver system used for screening purposes in this study. In contrast, when used together with glucocorticoids, the PPAR-α agonists significantly enhance BFU-E self-renewal beyond that seen with glucocorticoids alone. Importantly, when used together with PPAR-α agonists, it was possible to lower the amounts of glucocorticoids needed to achieve the typical BFU-E response observed at much higher concentrations of glucocorticoids alone.

In a more physiological setting of chemically induced hemolysis in mice, GW7647 increases hemoglobin and other red cell parameters as the mice recover from the chemical insult. The effect of the PPAR-α agonist under these conditions is presumably a result of its cooperation with elevated levels of glucocorticoids present in the mice during stress erythropoiesis. Even more exciting is the observation that GW7647 increases BFU-E and CFU-E production from human $CD34^+$ cells where expression of the RPS19 gene is reduced. The effect of the PPAR-α agonist in this cellular model of DBA has already begun discussions about moving forward in testing these drugs in clinical trials with DBA patients.

A question that I'm sure will be of interest to transfusion-dependent DBA patients is whether a person already has to be steroid responsive to gain benefit from a PPAR-α agonist. At present this question

remains unanswered, although there is no reason *a priori* to say they cannot work in this subset of patients. Questions like this will be best answered in clinical trials on DBA patients.

The good news in this regard is many of the effects of a drug fenofibrate in humans are already known because of its use for treating hypercholesterolemia and hypertriglyceridemia. While there can certainly be unanticipated adverse effects when repurposing a known drug to a new patient population, the wealth of knowledge already known about a drug like fenofibrate will hopefully streamline the process of taking these drugs to trial for DBA.

1) Lee, H-Y., Gao, X., Barrasa, M.I., Li, H., Elmes, R.R, Peters, L.L and Lodish, H.F. PPAR-α and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal. Pre-publication web release doi:10.1038/nature14326

2) Flygare, J., Rayon Estrada,V., Shin,C., Gupta,S. & Lodish, H.F. HIF1alpha synergizes with glucocorticoids to promote BFU-E progenitor self-renewal. Blood 117, 3435–3444 (2011).