Pharmacological chaperones as a novel therapeutic intervention line for congenital erythropoietic porphyria

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The group of pathologies produced by a lack of activity in some of the enzymes of the heme group biosynthesis is generically known as porphyria. Normally the loss of activity is produced by mutations in the amino acid sequence of said proteins and the type of porphyria depends on the specific enzyme causing the mutation. Specifically, congenital erythropoietic porphyria (CEP), also known as Günther's disease named after the author who described it in 1911, is a hereditary disease and the least frequent of the porphyrias (affecting > 1 in 1000000 people). This disease is a consequence of a malfunction in the uroporphyrinogen III synthase (UROIIIS), which is an enzyme of 260 amino acid residues (in the human isoform) catalyzing the cyclization of the linear tetrapyrrole hydroxymethylbilane to produce macrocycle uroporphyrinogen III (or urogen III), the precursor of the heme groups, siroheme, F340, vitamin B12 and chlorophyll.

Here, we describe a novel putative treatment for congenital erythropoietic porphyria (CEP). In particular, we have demonstrated that a repurposed pharmacological chaperone enhances the catalytic activity of uroporphyrinogen III synthase (UROIIIS) by increasing its stability and intracellular concentration levels. Further, the compound reduces the levels of uroporphyrinogen (UROI) and its derivatives in relevant models of the disease.