P1560 IMR-261, A NOVEL, ORAL NRF2 ACTIVATOR, REDUCES IRON OVERLOAD IN AN EXPERIMENTAL MOUSE MODEL BY ACTIVATING BMP6-MEDIATED HEPcidIN SYNTHESIS

**Topic:** 29. Iron metabolism, deficiency and overload

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**Background:** Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates several cellular defense mechanisms, including the oxidative stress response. Recent studies elucidated a protective role for Nrf2 under conditions of iron overload. Accumulation of toxic iron activates Nrf2, which activates Bmp6-mediated synthesis of hepcidin, thereby inhibiting ferroportin and improving iron homeostasis (Lim et al, Nat Metab 2019). IMR-261 is a novel, oral Nrf2 activator which has been tested in Phase 2 clinical trials (previously as CXA-10). Our previous work in mouse models of sickle cell disease and b-thalassemia showed that activation of Nrf2 by IMR-261 increases fetal hemoglobin (HbF) and hemoglobin (Hb), decreases markers of hemolysis and adhesion, reduces VOCs and improves ineffective erythropoiesis.

**Aims:**

The objective of this study was to evaluate the ability of IMR-261 to activate Bmp6-mediated synthesis of hepcidin (encoded by the *Hamp* gene), regulate iron stores and modulate transferrin saturation (TSAT) in a mouse model of iron overload.

**Methods:** b-thalassemic mice (*Hbbth1/th1*) were treated with IMR-261 at 37.5 or 50 mg/kg BID for 4 weeks. To assess activation of the Bmp6-hepcidin pathway, hepatic mRNA and plasma protein levels were measured. Iron concentrations in serum and tissue (liver, kidney and spleen) as well as markers of iron overload were also evaluated, and standard hematologic assessments were performed.

**Results:** IMR-261 showed a significant, dose-dependent increase in hepatic mRNA levels of *Bmp6 and Hamp* (~3-fold increase; high dose vs vehicle) as well as Bmp6 target genes, *Smad7* and *Id1*. A corresponding significant increase in Bmp6 and hepcidin protein levels in plasma was also observed. IMR-261 significantly decreased iron in serum by 32% (high dose vs vehicle) and in all tissues tested (34% in liver, 39% in spleen and 24% in kidney; high dose vs vehicle). Mice treated with IMR-261 also showed a significant decrease in TSAT and ferritin levels (up to 30% and 27%, respectively), as well as a reduction in GDF15 and erythropoietin (up to 72% and 48%, respectively) relative to vehicle. IMR-261 improved hematologic markers including a 30% decrease in reticulocytes and significant increases in RBCs, hemoglobin and hematocrit (consistent with our previous data).

**Image:**
**Summary/Conclusion:** Pharmacologic activation of Nrf2 by IMR-261 in a mouse model of iron overload activates hepcidin synthesis (likely via the Bmp6 signaling pathway) and decreases iron in serum, liver, spleen and kidney. IMR-261 also showed significant reductions in TSAT, ferritin, GDF15 and erythropoietin, which further support its role in iron homeostasis. Induction of hepcidin synthesis via Nrf2 activation is a novel therapeutic approach, and these results support further clinical development of IMR-261 as a treatment for conditions associated with iron dysregulation, including hereditary hemochromatosis.