

**Talk delivered at the annual meeting of the Society for Free Radical Biology and Medicine**, at the Washington Renaissance Hotel, Washington, D.C., November 15, 2007.

**Ferritin Heavy Chain is a Hemoglobin Switching Factor and a Probable Treatment for Sickle Cell Disease and Beta-Thalassemias**

**Robert H. Broyles**<sup>1</sup>, Robert A. Floyd<sup>2</sup>, Visar Belegu<sup>3</sup>, Emily J. Clarkson (Curry)<sup>2</sup>, Kelly S. Williamson<sup>2</sup>, Charles A. Stewart<sup>2</sup>, Quentin N. Pye<sup>2</sup>, Paolo Santambrogio<sup>4</sup>, Sonia Levi<sup>5</sup>, Paolo Arosio<sup>6</sup>, and Marie Trudel<sup>7</sup>

<sup>1</sup>University of Oklahoma Health Sciences Center, <sup>2</sup>Oklahoma Medical Research Foundation, <sup>3</sup>Johns Hopkins University School of Medicine, <sup>4</sup>University of Milan, <sup>5</sup>San Raffaele Scientific Institute, <sup>6</sup>University of Brescia, <sup>7</sup>Institut de recherches cliniques de Montréal

We have found that ferritin heavy chain (FtH), an antioxidant/stress response/iron-storage protein, localizes to the nucleus in K562 cells and represses the human adult beta-globin promoter in transient assays in primate cells (Broyles et al., *PNAS* **98**: 9145, 2001) as well as in transgenic mice that express human FtH in the definitive erythroid cells that emanate from the fetal liver at mid-gestation. Recently, we have found that FtH also activates the gamma-globin genes in erythroid precursor cells from sickle cell patients, producing high amounts of fetal hemoglobin (HbF) which is known to prevent sickling and extend the circulating lifetime of the red blood cell (RBC). With erythroid precursor cells from pediatric SCD patients, under an IRB-approved protocol, we have used a two-phase culture system for in vitro maturation of erythroid cells in the presence of FtH, delivered to the cells as pure protein, as an expression plasmid, or as a priority inducer compound that activates the endogenous FtH gene. HPLC with a PolyCAT A column was used to separate and quantify human Hbs. With each mode of delivery, FtH stimulated a complete switch from HbS to HbF. This result was repeatable in five experiments using erythroid precursor cells from three different SCD donors. Antibodies to HbF and HbS have been used to confirm the results with HPLC. FITC-labeled recombinant human FtH protein was taken into red cell precursors in culture, suggesting that the purified protein can be directly delivered without gene therapy. This method of producing a phenotypic cure in SCD patients should be easy and inexpensive to deliver in vivo, and should provide effective treatment for the beta-thalassemias as well. We thank **The Sickle Cell Cure Foundation, Inc.**, for partial support of this research.

**Free Radical Biology & Medicine** **43**: S67/#148 (2007).