



## **Targeting Transcription in Stem Cells: Ferritin Heavy Chain May Be Useful In Gene Therapy and Iron Chelation Therapy for Parkinson's and Other Diseases.**

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The use of stem cells as a therapeutic approach offers potential treatments for incurable diseases such as Parkinson's, Alzheimer's, ALS, cardiovascular disease and others. For this potential to be realized, however, we must be able to manipulate gene expression in stem cells, particularly gene repression, i.e., be able to control the balance between normal cell differentiation versus uncontrolled growth and cancer. Using K562 cells, human erythroleukemia cells with properties of erythroid-megacaryocyte precursor/stem cells, we have shown that nuclear ferritin heavy chain (FH) represses EKLf-activated human  $\beta$ -globin-reporter constructs in co-transfections, and that repression involves very tight FH binding ( $K_d = 10^{-10}$ ) to the -150 CAGTGC promoter motif (*PNAS* **98**:9145;2001). This repression may be stabilized by cooperative interaction between FH and silencer-binding proteins mediated by DNA looping (*FRBM* **33**:S312;2002). Using recombinant human ferritins, we have found that ferritin-H subfamily peptides (H and X) bind the promoter CAGTGC motif in vitro, whereas neither ferritin-L nor mutant (non-iron-binding) ferritin-H bind, indicating that bound iron and/or an active ferroxidase center is/are required for sequence specific binding and repression. Current work is with chemicals that induce FH in NTERA-2 cells, human embryonal carcinoma (EC) stem cells capable of differentiating into neurons. We have found a new potent FH inducer (compound C1) for NTERA-2 and K562 cells that we are testing in a mouse model of Parkinson's disease (PD). Treatment with FH may ameliorate the effects of excess free iron found in PD; and regulated expression of FH may aid in controlling growth and differentiation of transplanted stem cells for Parkinson's and other diseases.

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