Protein “Gene Therapy”: Correcting Juvenile Hemochromatosis Using Targeted Delivery of the BMP Co-receptor HJV

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Iron homeostasis is a vital biological process closely regulated by several signaling systems. One of the most important systems is HJV/BMP6; it regulates the release or sequestration of iron in the liver. The system’s importance in iron homeostasis is demonstrated by key findings in human genetics, where loss-of-function mutations in the Hemojuvelin gene (HJV) result in Juvenile Hemochromatosis (JH), a severe iron overload disorder. HJV protein is GPI-anchored and lacks a signaling domain; however, it is an obligate co-receptor for BMP6 and vital for the formation of the mature receptor complex. This receptor system is similar to other multi-component receptor systems, like those for CNTF and IL6, where non-signaling, yet obligate ‘Receptor alpha’ (Rα) components function as obligate ligand recognition ‘co-receptors’ and participate in the final signaling complex. The soluble forms of these Rαs (sRαs) enable cognate cytokine-initiated signaling in cells that lack the membrane tethered Rα (a process known as ‘transignaling’). This property has been harnessed to generate a “Designer Cytokine” method for cell-selective targeting of sRαs to enable signaling in otherwise unresponsive cells. I hereby propose to adapt this approach to the HJV/BMP6 system, and generate cell surface-targetable sHJV moiety fusion proteins, and then use them to restore HJV/BMP6 signaling. Different sHJV-targeting moiety fusion proteins are being engineered and tested for expression in vitro. Successfully engineered candidates will eventually be tested in Hjv knockout mice (a model of JH) for their ability to restore iron homeostasis.