Thesis Title: Effect of 3-Hydroxypyridin-4-ones (CP20 and CP94) on the Disposition of ^{59}Fe-Transferrin in Normal and Iron Overloaded Rats

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ABSTRACT

3-Hydroxypyridin-4-ones (CP's) are orally active iron chelators shown to be more potent than desferrioxamine in mobilizing iron in cell cultures and iron overloaded animals. The effect of these iron chelators on the iron mobilizing activity have been focused on the intracelluar iron storage pool but little attention is pressed on their effect on the disposition of iron from the blood, central compartment (transferrin bound iron).

This study is designed to study the effect of CP20 (1,2-dimethyl-3-hydroxypyridin-4-one) and CP94 (1,2-diethyl-3-hydroxypyridin-4-one) on the disposition of radioactive labeled transferrin iron in both normal and iron overloaded rats. A single dose of chelators and ^{59}Fe-transferrin were introduced directly into intravenous of conscious rats via jugular vein catherter. The results showed that at high plasma radioiron concentration (when CP's were given 10 min after the ^{59}Fe-transferrin), both chelators induced urinary iron excretion and CP94 was more potent than CP20 in decreasing radioiron distribution into various organs. Most of the radioiron were excreted in the first 24 hour (10-20% from based line

excretion) in the urine, less in the feces (<5%) and the insignificant amounts of radioactivities (<2%) were excreted in the next 48 hour. In contrast, plasma radioiron was less than 1% of the earlier model as most of the radioiron were already distributed into target organs. Only trace amount of radioactive iron was detected in the urine and feces during 72 hours of followed up.

This study provided evidence that both CP20 and CP94 could effectively chelate/remove iron from the plasma with CP94 more effective than CP20. The source of chelation attribute to the transferrin bound iron. The effective removal of excessive iron from the plasma could reverse the tissue to plasma concentration gradient in hemochromatosis and result in the eventual removal of excessive iron deposited in the inner tissue or cellular pools.