Hepcidin: The Key Regulator of Iron in the Blood
St. Dominic Middle School SMART Team
Elsie Jessup, Dominick Kowall, Alyssa Larcheid, Samuel Larcheid, Claire Lois, Sara Malowski, Emma Pittman, Joseph Platz, Melissa Poccetti, Tyler Sheefcter, Nicole Simson, Emma Wenger
Teacher: Ms. LaFlamme
Medical College of Wisconsin, The Blood Center of Wisconsin

I. Introduction to Hepcidin and Iron Homeostasis
Iron is found everywhere on Earth and is essential to life. The human body contains 3-4 grams of iron and over fifty percent is found in red blood cells (RBCs). Without iron, the oxygen carrying protein hemoglobin that fills RBCs cannot be made and the bone marrow cannot carry out erythropoiesis (RBC production). All iron in the body is absorbed from the diet in the duodenum. The peptide hormone, hepcidin, controls the release of the dietary iron from duodenal enterocytes (RBC production). All iron in the body is absorbed from the diet in the duodenum.

Figure 1: Hepcidin binding to ferroportin
Hepcidin is binding to the iron export channel ferroportin (FPN) on the enterocyte, hepatocyte, and macrophage. Binding causes both to be drawn into the cell by endocytosis where they are degraded. Hepcidin synthesis in the liver is affected primarily by the iron needs of erythropoiesis, plasma transferrin, and certain inflammatory cytokines, intracellular iron storage, and plasma iron (Figure 2). The human body has evolved a very complex system to conserve and recycle iron. However, the body does not regulate iron excretion, which in some circumstances, such as hereditary hemochromatosis, can result in iron overload, a condition in which excess iron is deposited in cells causing severe organ damage.

Figure 2: Hepcidin and Iron Homeostasis
1. Hepcidin synthesis in the liver is regulated primarily by the iron needs of erythropoiesis, plasma transferrin (Fe-Tf), and certain inflammatory cytokines.
2. Iron enters the plasma blood via ferroportin (FPN) on duodenal enterocytes and spleen macrophages, which are the major sites of iron storage.
3. Transferrin, a plasma iron carrier protein, picks up iron as it is entering the blood plasma through transferrin receptors 1 and 2 (TRF1 and TRF2). When hepcidin binds to ferroportin, both are drawn into the cell by endocytosis and degraded in a lysosome. Circumstances such as hereditary hemochromatosis, can increase iron absorption and storage. Overproduction of hepcidin may result in iron deficiency anemia.

Figure 3: Duodenal enterocytes
Enterocytes that line the duodenum absorb iron from the diet. Iron enters enterocytes through membrane transporters. Heme iron enters through the heme transporter (blue). Nonheme iron enters using the Disulfide Metal Transporter. Iron can be converted to iron bound spherical protein ferritin (yellow) for later use. Iron moves out of the cell into the blood through iron export channel ferroportin. The plasma iron transport protein, transferrin, picks iron from ferroportin. Hepcidin controls iron entering the blood through ferroportin.

Figure 4: Spleen Macrophage
Macrophages in the spleen recycle old red blood cells after their life span of about 120 days. The red blood cells are ingulaged by macrophages and degraded in lysosomes. The iron is recycled and leaves the cell through ferroportin. Transferrin (yellow red) transports the recycled iron in the plasma. Transferrin is the only source of iron for erythropoiesis in the bone marrow.

Figure 5: The St. Dominic SMART Team designed the physical model of hepcidin shown here using 3D-printing technology. The model displays the hepcidin (orange spheres) on the surface of the cell and enterocytes (above) are degraded. When hepcidin is present, both are drawn into the cell by endocytosis and degraded in a lysosome.

Abstract
Hepcidin, a peptide hormone, is the key regulator of plasma iron levels in humans, and is known to play an important role in various human diseases, such as iron overload. When hepcidin is not expressed in the liver, ferroportin, a trans-membrane iron export channel found primarily on enterocytes, hepatocytes and macrophages where iron is sequestered, binds to ferroportin and are drawn into the cell by endocytosis and degraded in a lysosome. When hepcidin levels increase, ferroportin levels on cells decrease and iron cannot be released from cells into the blood. Hepcidin production by the liver is affected by erythropoiesis in the bone marrow, blood oxygenation, certain inflammatory cytokines, intracellular iron storage, and plasma iron. The St. Dominic SMART Team (Students Modeling A Research Team) had the following objectives in mind: to find hepcidin found on duodenal enterocytes, hepatocytes, and spleen macrophages and ferroportins not bound to hepcidin, and to investigate areas of the cell where hepcidin traffick.

Figure 8:  Hepcidin Agonists and Antagonists Research
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II. Iron Absorption and Recycling
Nonheme iron enters the body in food, whereas heme iron enters in red blood cells. Heme iron is absorbed in the duodenum. Nonheme iron enters using the Divalent Metal Transporter. Iron can be stored in the blood through ferroportin. The plasma iron transport protein, transferrin, picks up iron as it is entering the blood plasma through transferrin receptors 1 and 2 (TRF1 and TRF2). When hepcidin binds to ferroportin, both are drawn into the cell by endocytosis and degraded in a lysosome. When hepcidin is present, both are drawn into the cell by endocytosis and degraded in a lysosome. Circumstances such as hereditary hemochromatosis, can increase iron absorption and storage. Overproduction of hepcidin may result in iron deficiency anemia.

Figure 9:  Hepcidin Agonists Increase the Effects of Hepcidin
Hepcidin Agonists Increase the Effects of Hepcidin

III. Hepcidin Structure & Function
Hepcidin, a 25 amino acid peptide that regulates plasma iron levels by binding to its receptor, ferroportin (an iron export channel). Hepcidin has a 5-hairpin structure, which is stabilized by four disulfide bonds. The first five amino acids are the most important for binding to ferroportin. In the E. Nemeth et. al. experiments [5], removing N-terminal amino acids progressively, one by one, decreased hepcidin’s ability to trigger endocytosis both in vitro and in vivo. All bioactivity was lost when the first five amino acids (Asp1, Thr2, His3, Phe4, and Pro5) were removed.

Figure 10:  Hepcidin Antagonists Reduce the Effects of Hepcidin
Hepcidin Antagonists Reduce the Effects of Hepcidin

IV. Iron Overload and Hereditary Hemochromatosis
Hereditary hemochromatosis is a group of genetic diseases characterized by too much iron absorption and storage. Over time, iron overload develops as iron accumulates in major organs, like the liver, heart, pancreas, and spleen, disrupting their normal function. The liver biopsy in Figure 7 shows severe iron overload. The iron deposits in the hepatocytes are stained blue.

Figure 11:  Hepcidin Agonists Increase the Effects of Hepcidin
Hepcidin Agonists Increase the Effects of Hepcidin

V. Current Treatments for Iron Overload
There are no cures for iron overload but there are treatments to prevent and treat damage. Excess iron can be removed by phlebotomy. Deferoxamine is a preferred treatment because regularly schedules blood donation can keep iron levels normal. Chelation is used when blood donation is not possible. The drug deferasirox binds iron so that it can be excreted in the urine. However, it must be given as a subcutaneous infusion taking 8-12 hours. A wearable pump is usually worn. A newer drug, deferiprone, can be taken orally.

Figure 12: Deferoxamine is used to chelate iron. When it is binding iron, iron urine takes on an orange color.

VI. Hepcidin Agonists and Antagonists Research

VII. Summary
Hepcidin is the key regulator of plasma iron levels in humans and plays a central role in hereditary hemochromatosis (HH). Since the body does not regulate iron excretion, iron overload can develop over time in HH patients as excess iron accumulates in major organs, such as the liver, heart, pancreas and spleen, disrupting their normal function. Phlebotomy and iron chelating drugs are currently being used to keep plasma iron levels at normal levels. Research is underway to develop hepcidin agonists and antagonists to treat hereditary hemochromatosis and other iron overload conditions.

Figure 13:  Hepcidin Agonists Increase the Effects of Hepcidin
Hepcidin Agonists Increase the Effects of Hepcidin

VIII. References
4. Hemochromatosis Type 4a and 4b
5. Hemochromatosis Type 3
6. Hemochromatosis Type 2
7. Hemochromatosis Type 2b
8. Hemochromatosis
9. Deferoxamine is used to chelate iron. When it is binding iron, iron urine takes on an orange color.
11. Fe-deficiency anemia: new molecular mechanisms.