The Globins: Oxygen's Catch and Release

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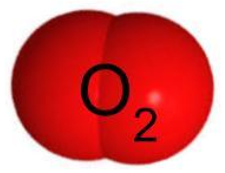
Our Task:

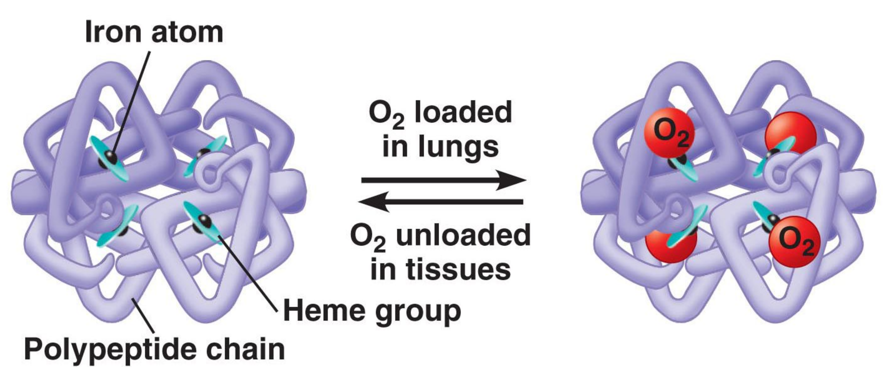
To investigate globins and explain the blood-based disorder, thalassemia

Structure & Function of Oxygen

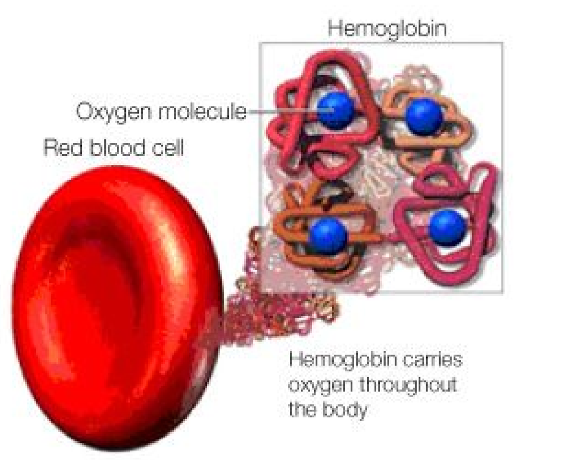


Handle with Care!

Humans require oxygen for metabolic functions such as cellular respiration, cell reproduction, production of heat and energy, and oxidation (disposal) of poisons.



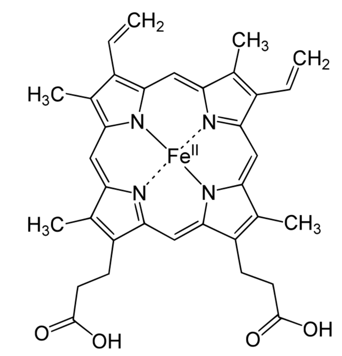
Packing Oxygen Safely Away



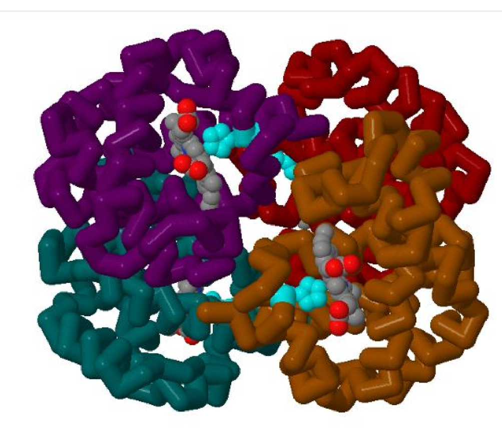
Oxygen is the most abundant element in the human body that is highly reactive which allows it to be classified as an oxidizing agent to form numerous compounds. It is required for a variety of bodily processes; however, excess oxygen causes molecular damage, molecular precipitation, and cellular death.

Globin & Hemoglobin Overview

Globins are proteins containing a globin fold with eight alpha helical segments. Myoglobin and hemoglobin are the most prominent types. Others include androglobin, cytoglobin, globin E, globin X, globin Y, and neuroglobin.



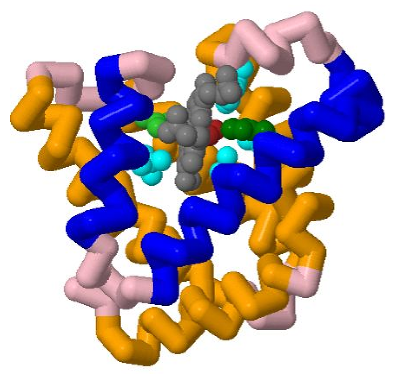
Hemoglobins are located throughout the cytoplasm of red blood cells. One red blood cell contains up to 250 million hemoglobins. Therefore, each cell is capable of transporting 1 billion oxygen molecules. Hemoglobin is responsible for transporting oxygen from the lungs to tissues through allosteric control regulation.



Hemoglobin from PDB 2HHB

Functional hemoglobin is made up of alpha (**purple** and **red**) and beta chains (**teal** and **brown**) which are monomers similar to myoglobin. The heme groups are shown in cpk colors held in place by proximal histidines.

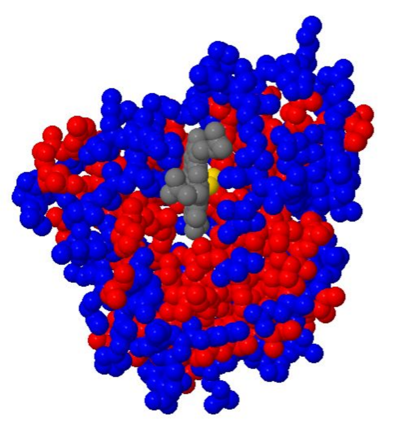
The binding process of hemoglobin and oxygen involves allosteric control which means that the environment affects the binding efficiency of the protein. Levels of CO_2, BPG, and pH affect hemoglobin's ability to bind with oxygen. Consequently, binding causes a change in formation of the protein.

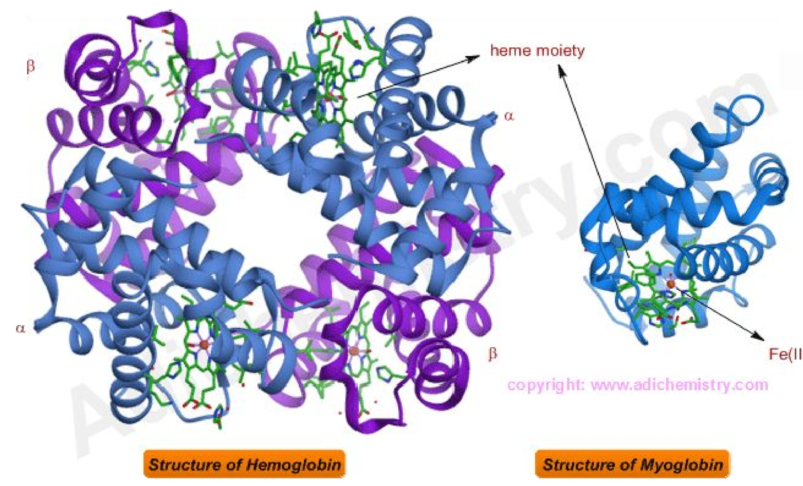


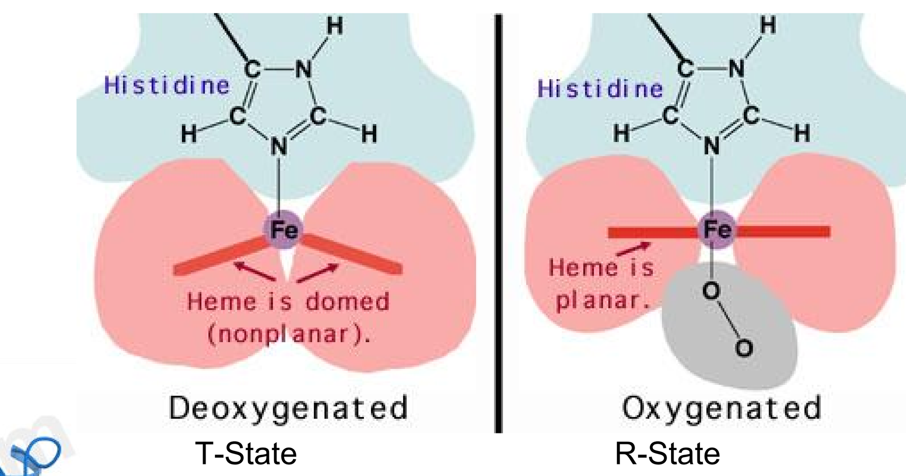
Myoglobin from PDB 1MBO

Myoglobin is found in muscle tissue for the purpose of storing oxygen. The groove of the myoglobin molecule on the left shows the heme group featured in **gray**. The proximal histidine is highlighted on the left in **lime green** and the distal histidine is shown on the right in **dark green**. The proximal and distal histidines trap the heme group with the **oxygen** in place Each of these histidines aid in the binding process.

The model on the right illustrates the **polar** and **nonpolar** sections of the myoglobin seen in **blue** and **red**. The heme group is highlighted in **gray** with the oxygen (**gold**) bound in place

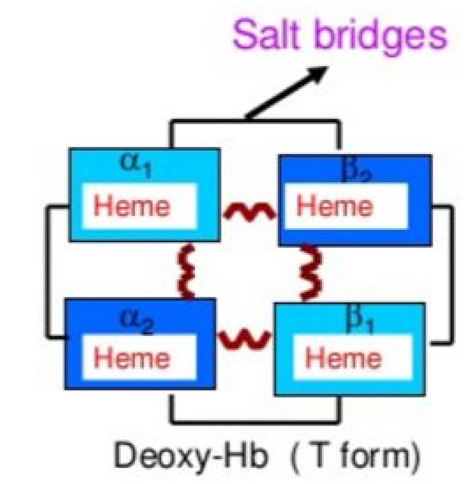


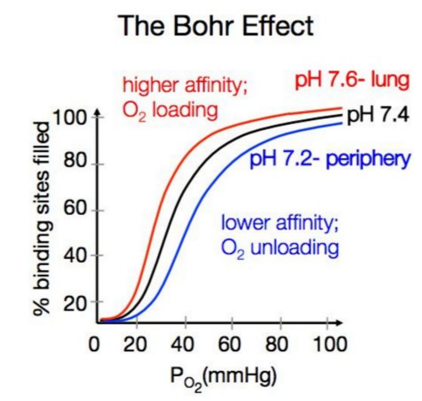




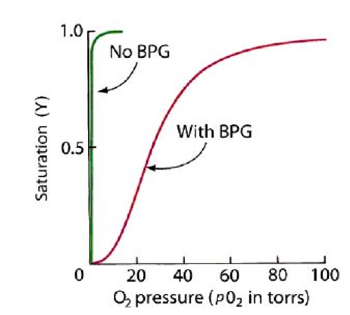
Hemoglobin has two states: the T-state and the R-state. The T-state means that the hemoglobin is tense and has a lower oxygen affinity; therefore, the hemoglobin is generally deoxygenated in this state. The R-state means that the hemoglobin is relaxed with a high affinity for oxygen, so it is generally oxygenated in this position.

The Bohr Effect takes place when a low pH and a high concentration of Co_2 cause the formation of salt bridges. Consequently, this causes the hemoglobin to undergo a conformational change to the T-state, thus preventing the binding of oxygen to the heme group which affects the functionality of hemoglobin.



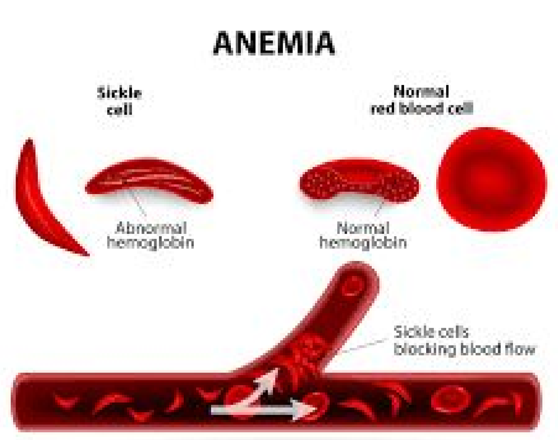


Another element in the role of hemoglobin is the binding process of 2,3 BPG to hemoglobin. BPG is created as an alternative pathway to glycolysis, and it binds to hemoglobin in its T-state which lowers hemoglobin's oxygen affinity.

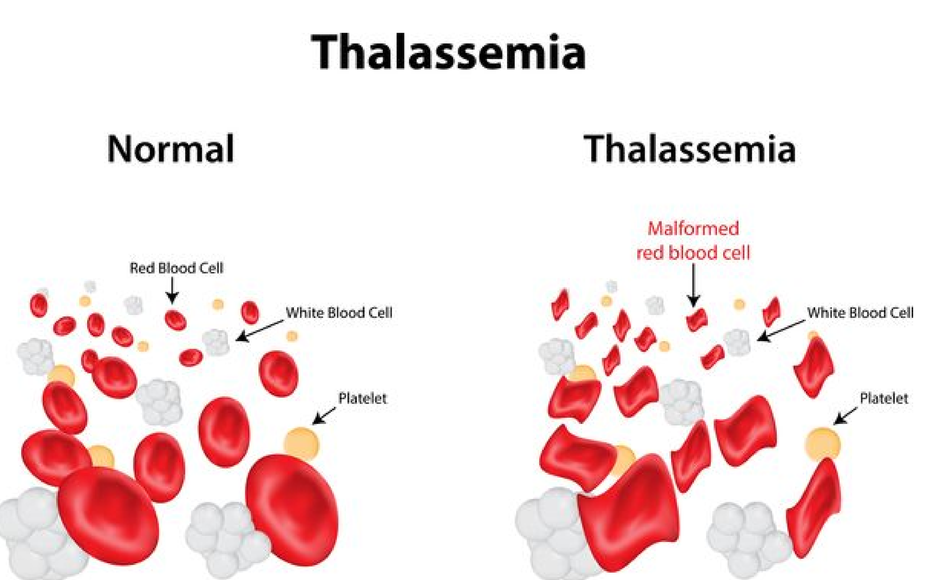


Hemoglobinopathies

1. Aggregating Hemoglobins
 - Sickle Cell Anemia

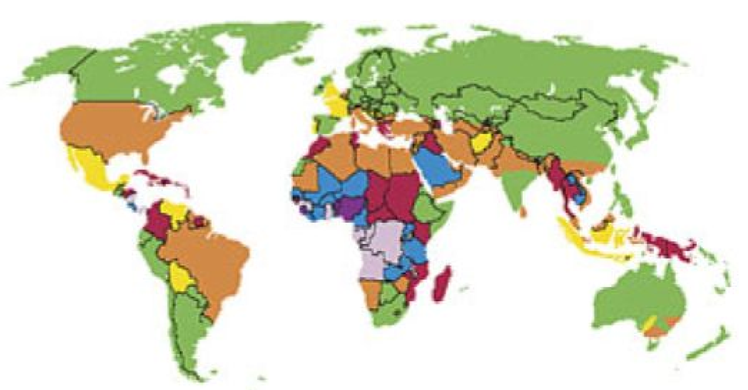


2. Heme Group Dysfunction
3. Unstable Hemoglobins
4. Abnormal Hemoglobins Without Clinical Significance
5. Imbalanced Synthesis of Globins
 - Thalassemia



Thalassemia

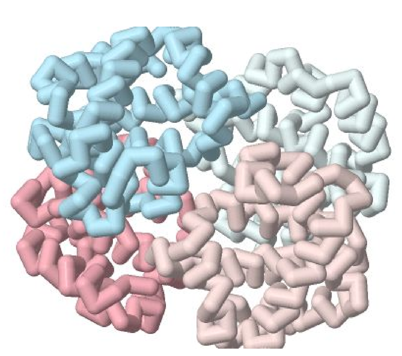
- Each year, between 300,000 and 500,000 individuals are born with a severe form of this hemoglobin disorder, 50,000-100,000 of whom die from beta-thalassemia major.
- Genetic blood disorder involves inheritance of defective gene, causing the production of an abnormal form of hemoglobin
- Two major types of thalassemia: alpha and beta
  - Each type involves either the alpha or beta chain of the hemoglobin that is affected
  - Beta thalassemia is usually more severe
  - Both diminish production of globin polypeptide chains
- About 5% of people have a globin variant, but only 1.7% have alpha or beta thalassemia
- Impaired erythropoiesis



A larger population of individuals are inflicted with thalassemia in Mediterranean, Southeast Asian, and African countries

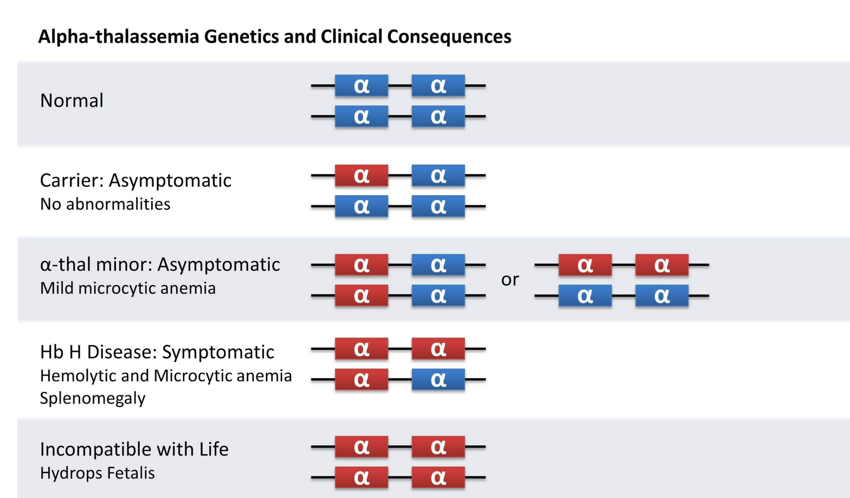
Lowest percentages of individuals afflicted with thalassemia in a country's population are indicated progressively in green, yellow and orange. Larger levels are indicated progressively in red and blue, and areas with the highest frequency are shown in purple.

The **alpha** chains of the hemoglobin molecule are shown in **pink** and the **beta** chains are highlighted in **blue**. The chains that are affected determines which type of thalassemia is present.



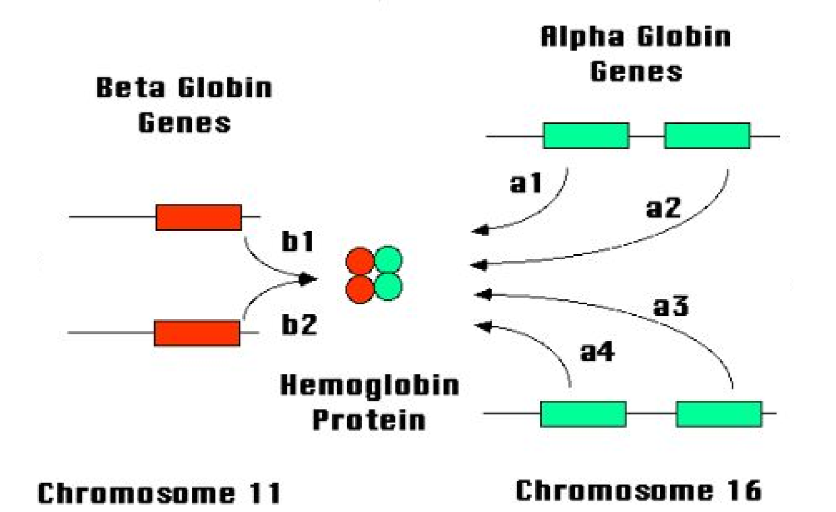
Alpha Thalassemia

- Reduced production of hemoglobin
- Four genes: two HBA1 and two HBA2
- Severity is dependent on mutated genes inherited, and/or the number of deleted genes
  - Hb Bart Syndrome: deletion or mutation of all four genes
  - HbH: deletion or mutation of three genes
  - Mutations in one or two genes results in mild or absent symptoms
- Excess beta chains cause HbH formation (Heinz bodies) and hemolysis (destruction of red blood cells)



Beta Thalassemia

- Mutation of the HBB gene in the eleventh chromosome
- Causes a decrease or lack of synthesis of the beta chains in hemoglobin
- Two main types of beta thalassemia
  - Beta thalassemia minor
  - Beta thalassemia major (Cooley's anemia)
- Symptoms of beta thalassemia include fatigue due to lack of oxygen, Iron overload due to frequent blood transfusions, enlarged liver and spleen, stunted growth and deformations



Treatment Methods

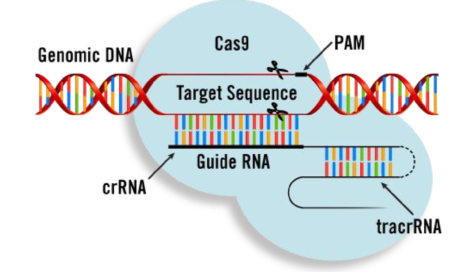
Standard treatments for thalassemia, depending on the severity of the condition and the symptoms, include:

- Blood transfusions usually every 3-4 months and daily iron chelation therapy which removes excess amounts of iron from the body

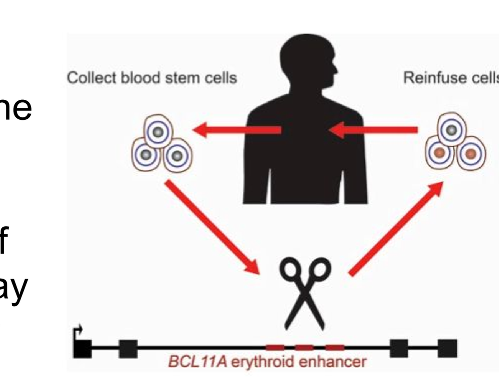
Comparison of chelation therapy through technological advancements

- Stem cell (bone marrow) transplants are another form of treatment that allows for the production of healthy new red blood cells by first irradiating the patient to remove unhealthy cells and then transplanting bone marrow that contains healthy stem cells. The patient risks issues with radiation and compatibility problems with the donated stem cells. After treatment, the patient no longer requires regular blood transfusions.

- Gene therapy is also being explored through the use of CRISPR/Cas9 which is a tool based on a bacterial protein that allows specific sections of DNA to be targeted. The promoter of the beta gene is removed and the gene for gamma globin is activated to increase production of fetal hemoglobin which has a higher affinity for oxygen.



BCL11A is a gene responsible for affecting HbF levels. The BCL11A enhancer can be removed to re-express the gene that creates fetal hemoglobin. However, BCL11A is a gene involved in the development of other cells, and its removal may affect other aspects of cellular growth and reproduction.



Mr. Robert Mannino at Georgia Tech-Emory University spoke about living with thalassemia, blood transfusions and chelation therapy, and his app for detecting the need for a transfusion

Dr. Daniel Bauer at the Boston Children's Hospital and professor at Harvard Medical School spoke with SMART Team about thalassemia and his work regarding gene therapy including CRISPR-Cas9 and BCL11A.

https://oxygensupercharger.com/oxygen-functions/, https://ghr.nlm.nih.gov/condition/beta-thalassemia, http://kidshealth.org/en/parents/beta-thalassemia.html#, http://health.howstuffworks.com/human-body/systems/circulatory/heart.htm, https://medlineplus.gov/ency/article/000587.htm, http://www.medicinenet.com/script/main/art.asp?articlekey=7431,http://treatment-thalassemia.blogspot.com/2013/08/treatment-for-thalassemia-by-bone.html, https://www.nhlbi.nih.gov/health/health-topics/topics/thalassemia/treatment, http://www.adichemistry.com/inorganic/bioinorganic/hemoglobin/hemoglobin-myoglobin.png, https://www.flickr.com/photos/cdcsocialmedia/29753231931/in/album-72157631636182411/, http://hsci.harvard.edu/people/daniel-e-bauer-md-phd, http://www.proteopedia.org/wiki/index.php/2dn2, http://www.rcsb.org/pdb/explore.do?structureId=1ash, https://en.wikibooks.org/wiki/Structural_Biochemistry/Hemoglobin, https://faculty.etsu.edu/currie/hemoglobin.htm, https://ghr.nlm.nih.gov/condition/alpha-thalassemia, http://en.wikipedia.org/wiki/Bohr_effect, https://en.wikipedia.org/wiki/Hemoglobinopathy, https://oxygensupercharger.com/oxygen-functions/, https://sites.google.com/site/christianleechem/_/rsrc/1329326736342/chapter-4-an-introduction-to-chemical-reactions/diagram/FG03_003.GIF, https://classconnection.s3.amazonaws.com/815/flashcards/1428815/png/hemo1335037423234.png, https://ghr.nlm.nih.gov/gene/HBB#location, http://cbc.arizona.edu/classes/bioc462/462a/NOTES/hemoglobin/BPGbinding.gif