

CHEM 342 - Introduction to Biochemistry

Hemoglobinopathy Assignment - Due Last Friday of the Semester

Attention: This is a major research and writing assignment worth one fifth (20%) of your final grade in the course. Do not treat it lightly. The intent is for you to *do your very best work*. The paper you turn in should demonstrate that you truly understand and can apply what you have learned in this course. It should reveal your ability to reflect on a scientific topic and *communicate it visually and in writing* to others in a meaningful context. It is an opportunity to display your ability to formulate and explore personal learning issues, to find and assimilate relevant information from the scientific literature, and then synthesize everything into a meaningful paper that is not just a term paper. If done well, you might want to include your paper in an online portfolio to demonstrate that you have achieved the standards expected of you at the University of Delaware. Every year, the best paper from the class is submitted for the Edward Rosenberry Undergraduate Writing Award.

Hemoglobinopathies: Hemoglobinopathies are genetic diseases in which the normal structure and function of hemoglobin is altered. Sickle cell anemia is the first and perhaps the best known hemoglobinopathy. In the case of sickle cell anemia, a single base substitution mutation in the β -globin gene results in a single amino acid replacement in the sixth position of the β -globin subunits of hemoglobin. That small chemical change enables deoxygenated hemoglobin to self-associate, forming long polymers that distort the shape of red blood cells, causing them to clog capillaries and block oxygen transport to peripheral tissues. None of the other hemoglobinopathies is like sickle cell anemia. Each is distinct in its own way. While many of these are single-nucleotide-substitution mutations, deletions, and insertions that have little or no clinical effects, the consequences of others vary from benign to severe, as in the case of thalassemias.

Background for the Assignment: [Linus Pauling](#) introduced the concept of molecular disease by demonstrating that the gene for sickle cell anemia was directly related to a chemical alteration of hemoglobin in the red blood cells of affected individuals. A few years later, [Vernon Ingram](#) identified a single amino acid replacement at position 6 of the beta chains of sickle cell hemoglobin (HbS) and showed that the sequence of the remaining 145 amino acids of the beta chains and all 141 amino acids in the alpha chains of hemoglobin were unchanged compared to normal hemoglobin (HbA). Subsequently, others determined the exact nucleotide substitution mutation in the beta globin gene possessed by sickle cell patients. These discoveries prompted a stampede of sorts to discover other hemoglobin variants and the corresponding mutations in DNA. Many medical biochemists have made a career studying these usually rare hemoglobinopathies. There are now over 1000 different mutations known to affect the amino acid sequence or production of hemoglobin.

Assignment: Using a [list of hemoglobinopathies](#) ([alpha-chain](#), [beta-chain](#), [thalassemias](#)), spend some time and pick an *interesting* example to investigate as the basis for a 5-10 page, double-spaced, well-organized supplement for a textbook. “Interesting” in this context means a mutation that illustrates some biochemical concept or general phenomenon in biochemistry that will be the

framework for your supplement. Select a variant that no one else in class has chosen. Your report should have the following elements:

- A biochemical concept or methodology illustrated by your particular hemoglobinopathy. In other words, you must give your hemoglobinopathy general biochemical importance.
- A description of the genetic mutation and its consequences for hemoglobin structure, function, stability, and clinical symptoms.
- [Computer-generated image](#) of the three-dimensional structure of your variant hemoglobin showing the location or region of the molecule affected where appropriate. Be sure that the illustration is *informative* with respect to the principle you are highlighting. All figures need explanatory captions. Other illustrations can be included to augment the text. Tapan Patel, has created a web-site that will lead you step by step through the process of [making a useful computer image of your hemoglobin variant](#). Another useful webpage is a tutorial for [Deep View](#).
- Citations to all references and illustrations (if not original) using the standard citation format of the [Journal of Biological Chemistry](#). Part of the purpose of this assignment is for you to demonstrate your ability to find, use, and properly document information from the library. Inclusion of *at least* and preferably more than 10 relevant citations to primary research articles some of which show the exploration of learning issues beyond the particular hemoglobinopathy for a minimum for a grade of "C."
- Your "voice". This is not just a report of factual information your references have provided. It is a synthesis of information that puts your stamp on the text.

Preparation for this Assignment: Each group should have met with Catherine Wojewodzki, a science librarian in 117C Morris Library (831-8085, or Cathyw at udel.edu) during (or before) the third week after Spring Break. She is familiar with this project and can provide assistance in tracking down the information you need. In the past, students have had problems because they did not take full advantage of the resources available. You will need to develop these library research skills as part of your undergraduate education. (They go well beyond "Googling" the Internet.)

Cathy Wojewodzki normally likes to work with 6-8 students at a time. Find some convenient times for your group to meet and then have one member of your group contact Cathy to schedule a meeting. Please schedule your meeting by mid-April. Each session will take 30 - 45 minutes.

Cathy will work with you on your actual hemoglobin variants. If you make your selection and get it approved before you attend this session, you will not have to repeat the work. Groups will meet in Room 116B in Morris Library Reference Room area and use the laptop computers in there. You are welcome to bring your own, if you prefer.

Evaluation: This assignment will be evaluated for its composition, content, clarity of presentation, and depth of your analysis. An "A paper" must go beyond simple reporting of information. For example, a molecular graphics representation of your hemoglobin variant showing the location of any mutational modification, but make sure it shows something worth seeing. Remember, this should be *your synthesis* of the information, [not a paraphrasing words by others](#). Late papers will not be accepted without a grade penalty.

Other Options: Students who would rather explore aspects of hemoglobin function, evolution, or properties of unusual hemoglobins from other species may do so in consultation with Dr. White. There are related topics available such as Glucose-6-P deficiency (favism).

Suggestions:

1. Nobel Prize winner, [Max Perutz](#) (1914-2002), spent 20 years working on the X-ray crystallography of hemoglobin before he finally determined its three-dimensional structure in 1957. There after he spent much of the rest of his life studying the structure of interesting hemoglobin variants. One strategy you might try is to search and examine the publications of Max Perutz on [PubMed](#) or the [Web of Science](#). Remember, you can often get full text copies through the University of Delaware's [electronic journal](#) subscriptions. You may also find some of the [sites linked to the course home page](#) of use.
2. Log on to one of the protein data bases and explore their reference lists and tabulations of hemoglobin variants. Some data bases include:
[NCBI](#) (National Center for Biomedical Information),
[PDB](#) (Protein Data Bank) or
[Swiss-Prot](#) (Swiss protein data base).
Simply start your search at any of these by typing in "human hemoglobin" and follow the links of interest.
3. Feel free to discuss your ideas and any difficulties you have with me (Dr. White) preferably well before the due date.

Making your request: All requests must be cleared by sending an e-mail message to Dr. White who will check to be sure no one else in the class has selected the same topic. Your request should be brief but include the name of the hemoglobin variant, the nature of the mutation, at least two *primary* literature citations to relevant references that you have actually looked at. Selections should be made on or before the second Friday after Spring Break. [HbC and HbS are not available](#).