Sickle Cell Disease Case Study

The Taylor family includes two parents, Bill and Denise, and their three biological children, 22-year old Sydney, 19-year-old Thomas, and 14-year-old Rhonda. All three children were diagnosed with sickle cell disease (SCD), also known as sickle cell anemia, before their first birthday. Last year, Sydney died of a stroke related to her sickle cell disease. Recovering from their loss and reflecting on their own lives, Thomas and Rhonda have decided to enroll in clinical trials that could treat their genetic condition.

In Part I, you will work through the questions to understand sickle cell disease on a molecular and systemic level. Then, in Part II, you will answer questions to develop an understanding of the mechanisms of the two clinical trials.

**Part I—Understanding Sickle Cell Disease**

Red blood cells are among the smallest cells in the human body. They have no nucleus and almost no organelles. The cytoplasm of red blood cells consists mainly of a solution of water and hemoglobin (Hb), a protein that binds oxygen, carbon dioxide and some other small molecules. Like all proteins, hemoglobin is transcribed from genes. There are three Hb genes and therefore three Hb proteins: α-Hb and β-Hb, and γ-Hb. During the fetal period, γ-Hb and α-Hb are expressed. Then, around the time of birth, the expression of γ-Hb is almost entirely suppressed and expression of β-Hb begins. In an average adult red blood cell, 96% of the Hb molecules are β-Hb, 3% of Hb molecules are only α-Hb and 1% of Hb molecules are fetal Hb. Some adults express higher levels of fetal Hb.

1. Which of the following is *most likely accurate* about protein shape in general?

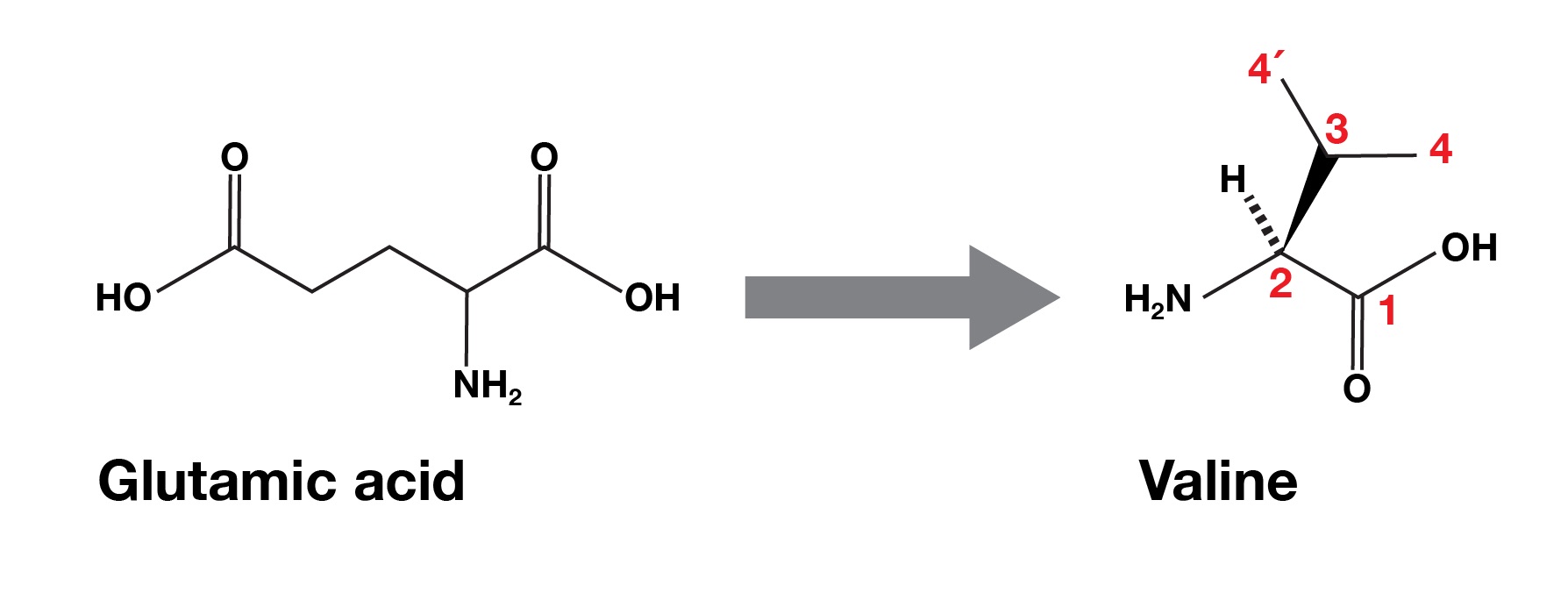
A) Protein shape is inconsequential, as long as the amino acid sequence remains the same

B) Physiological conditions (such as pH, temperature, etc.) can induce protein shape changes

C) Ligand binding can induce shape changes in proteins

D) Both B and C

Before attempting Question 2, please watch the video linked to the QR code and read the paragraph below.

Sickle cell disease is a genetic disorder in which the gene for β-hemoglobin is mutated (βS). The specific mutation that causes sickle cell disease results in replacement of one amino acid (glutamic acid) with a different one (valine). Glutamic acid is a polar amino acid with a negative charge on one end; valine is a non-polar, non-charged amino acid (it does not have oppositely charged ends). When βS is deoxygenated (not bound to oxygen) the valine is exposed and forms a small hydrophobic pocket on the protein surface.

2. What might happen if more than one molecule of this mutated protein were found in the cytoplasm of the same cell?

A) The mutated proteins would repel each other and be found far apart

B) The mutated proteins would be found in the lysosome.

C) The mutated proteins would be drawn together and tend to clump

D) The mutated proteins be repelled from the plasma membrane and be found more internally than non-mutated proteins.

3. Using your answer from question #2, why do you think that these molecules would demonstrate this behavior?

A) Due to interactions among the charges of neighboring amino acids

B) Due to the hydrophobicity of the valine amino acid

C) Due to the repulsive properties of the protein to the phospholipids of the plasma membrane

D) Due to the newly sticky plasma membrane

4. Sickle Cell Disease is named for the characteristic shape that red blood cells of affected individuals can take. Why does the whole cell change shape?

A) The mutated form of Hb polymerizes forming long fibers of proteins that can distort the cell membrane.

B) Oxygen stress causes the mitochondria to clump on the cell membrane, pulling the cell into an elongated shape.

C) There are few copies of Hb in sickle cell disease, therefore the cell shrivels down to the sickle shape.

D) Due to the mutation, many of the organelles die, so the cell loses volume

5. Individuals with sickle cell disease often find that their symptoms worsen in times when oxygen is less available (such as at high altitudes) or in greater demand (such as during exercise). What is it about oxygen stress that could exacerbate this disease?

A) More red blood cells are in circulation during oxygen stress, causing more cell clumping to occur.

B) The plasma membrane is less stable in low oxygen conditions, allowing the cell to change shape more easily.

C) There are more proteins competing for oxygen in the red blood cells of a sickle cell patient, and as the proteins compete, they clump.

D) The hydrophobic valine is exposed when hemoglobin is not bound to oxygen, therefore the clumping of proteins is more likely when oxygen concentration is low.

6. A stroke is defined as “a sudden, disabling attack or loss of consciousness caused by an interruption in the flow of blood to the brain.” Which of the following best explains how Sydney’s stroke could have been caused by her sickle cell disease?

A) The change in hemoglobin causes more red blood cells to be produced and so many cells can clog the small blood vessels in the brain

B) The change in shape of the red blood cells causes the cells to get stuck in the small blood vessels of the brain, preventing distribution of oxygen

C) The mutation also affects blood vessel walls, making them weaker and prone to rupture

7. Sickle cell disease is a complex disease with a simple cause. The disease stems from one single change that then has downstream consequences. Where is the original change that leads to the rest of the alterations?

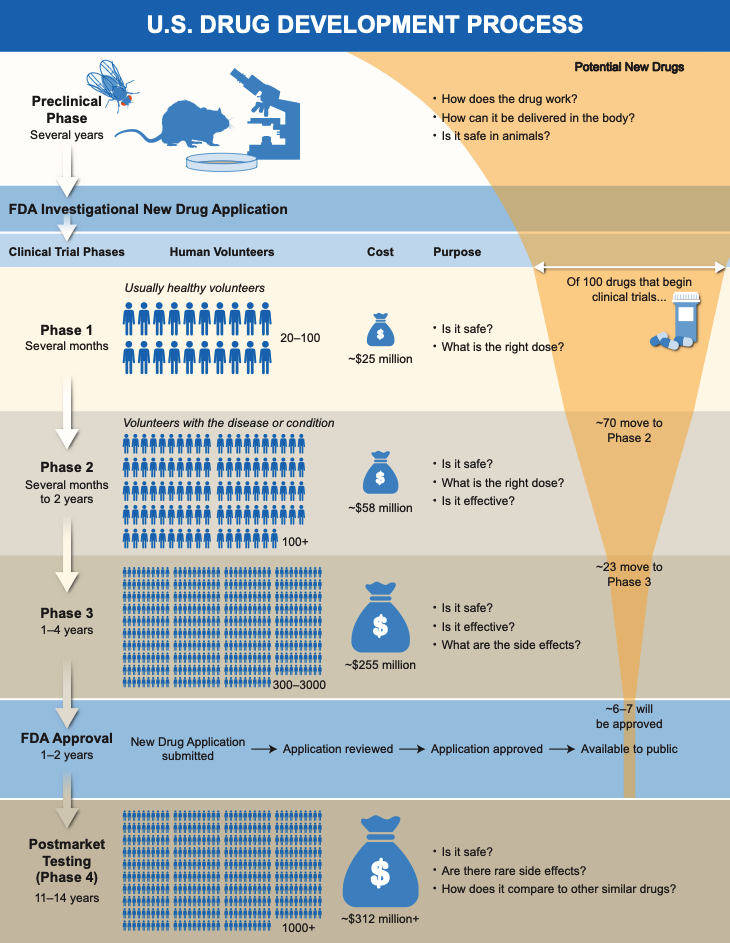
A) A point mutation in the genome

B) A tendency for red blood cells to change shape

C) A change in protein shape

D) Pain and damage to tissues due to decreased oxygen delivery

**Part II—Understanding the clinical trials**

Rhonda and Thomas have been recruited to join clinical trials to try to cure their sickle cell disease. While joining a clinical trial offers a lot of hope, it is pretty scary for the patient and sometimes only a small percent of patients actually directly benefit from the treatment. Here is an overview of how clinical trials work. 

Rhonda and Thomas went into two separate trials due to their difference in age. Both of these clinical trials involve an area of therapeutics called *gene therapy*. In gene therapy, a virus is often used to deliver a working copy of a gene into the cells that need it (called *target cells*). We will discuss the therapy mechanism behind each of the trials.

8. Why is a virus often used to deliver the gene to the target cells?

A) Cells have cell surface receptors that bind DNA, but these receptors are specific and may not recognize this gene.

B) Being large and negatively charged, DNA will not readily cross the plasma membrane.

C) Viruses are guaranteed to always make it inside every cell of the body

9. The goal of each of the clinical trials is to get a functional gene into red blood cells to alter how hemoglobin is being made. What cell type should the virus target?

A) Hematopoietic stem cells

B) Red blood cells

C) White blood cells

D) Hepatocytes

Explain why this is the cellular target for sickle cell disease therapy:

10. As the gene therapy drug goes to clinical trial, a group of scientists needs to decide on the protocol for delivering the therapeutic. This therapeutic will be injected, which of the injection sites below would be the most direct route for reaching the target cells?

A) Veins

B) Bone marrow

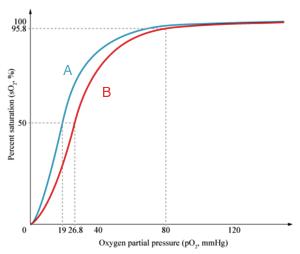
C) Liver and spleen

D) Lymph nodes

In Rhonda’s trial for children, the gene that turns off fetal hemoglobin production and turns on adult hemoglobin production (gene BCL11A) is targeted. If this therapy is successful, Rhonda will make a higher proportion of fetal hemoglobin, even in adulthood. Because her fetal hemoglobin gene does not have the sickle cell mutation in it this therapy will decrease the proportion of βS in each of Rhonda’s RBCs. One difference between fetal hemoglobin and adult hemoglobin is that fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin.

Thomas is enrolled in a clinical trial in which a functional copy of the adult hemoglobin gene is delivered.

Can you think of any drawbacks or potential complications to gene therapy? Record these below for later discussion:

11. Here is a graphic of the oxygen-dissociation curve showing two types of hemoglobin. One of the dissociation curves represents the functional adult hemoglobin expressed by Thomas after his therapy, the other line represents Rhonda’s new fetal hemoglobin after the successful delivery of the therapeutic. Which line is Rhonda’s?

A) A

B) B

If you were an adult sickle cell patient, which trial would you want to enroll in? Are there pros/cons to each? Would your answer change if you were a young woman who might want to become pregnant some day?

12. Using your answer from question 10, imagine that, after the transplant, Rhonda is exercising. She is building up both lactic acid and CO2 in her bloodstream. Draw onto the graph where you think Rhonda’s oxygen-dissociation curve will be in these new conditions. Then choose among the following answers.

A) Rhonda’s exercise curve will be represented by line B or to the right of line B

B) Rhonda’s exercise curve will be to the left of line A

C) Rhonda’s exercise curve will be represented by line A

13. After Rhonda’s first delivery of the therapy, she begins to produce more fetal hemoglobin. Each of her cells now holds approximately 40% fetal hemoglobin and 60% adult hemoglobin. Predict the most likely outcome:

A) Rhonda does not experience much noticeable improvement in her symptoms because there is still adult hemoglobin in each cell and therefore the proportion of cells that will form the sickle shape is still the same.

B) Rhonda is cured, she has no cells that ever sickle, even under adverse conditions.

C) Rhonda has a reduction in symptoms. Because there are fewer hydrophobic proteins, there is far less clumping possible within each cell. Therefore, the likelihood of a cell taking on the sickle shape is reduced.

14. Thomas’s parents are pleased with the reduction of his symptoms, but they beg his doctors for another dose of the therapy. The doctors explain that because the gene is delivered by a viral vector, Thomas will only receive the therapy one time. What is their reason?

A) Viruses are very expensive to engineer and they will not provide a second dose even if it would further reduce Thomas’s symptoms

B) After the first delivery of the gene, every cell that could ever benefit from the therapy has already been treated because red blood cells have a long lifespan.

C) Red blood cells have long lifespans, so the new red blood cells that have fetal Hb will live a long time and proliferate in the blood. Thomas and his parents just need to wait for these red blood cells to proliferate and take over the blood supply and her symptoms will disappear entirely.

D) After the immune system sees a virus for the first time, it can mount a much more effective immune response the second time and in subsequent exposures. Thomas’s immune response will eliminate the virus before it can deliver the gene therapy.

