**The Central Dogma of Biology and Hemoglobin**

The goal of this problem is to develop more facility with thinking about the connection between nucleic acids and proteins as embodied in the Central Dogma of Biology. In addition, one of your first exercises in bioinformatics will be to examine sequences of hemoglobin from different organisms, so this is also an opportunity to think about hemoglobin in preparation for that exercise.

Nearly all of the oxygen carried by blood in animals is bound and transported by the protein hemoglobin contained in erythrocytes (red blood cells). Each tetrameric hemoglobin molecule is composed of pairs of two different subunits, alpha (\(\alpha\)) and beta (\(\beta\)).

A portion of one strand of the gene coding for the \(\beta\)-subunit of hemoglobin is shown below:

5' -AGTAACGCGACTTCTCCTCAGGAGTCAGGTGCACCATCTGTTCAGG-3'

A. Write down the sequence of the complementary strand in the 5’ to 3’ orientation. Label both the 5’ and 3’ ends.

B. Write down the Open Reading Frame (ORF) coding for the N-terminal portion of the \(\beta\)-subunit in the 5’ to 3’ orientation. Give a brief description of the reasoning you used to identify the ORF (Limit 2 sentences).

C. Write down the messenger RNA sequence that corresponds to this part of the gene.

D. Translate the sequence that you determined in Part B. Label the N-terminus and C-terminus of the translated sequence. A Codon Table is provided below.
D. Sickle cell anemia is a genetic disease derived from mutation(s) to the gene coding for the hemoglobin β-subunit. Mutations to this gene result in the production of an aggregation-prone hemoglobin variant. Upon deoxygenation, the mutated sickle cell hemoglobin protein becomes insoluble and forms polymers that aggregate into tubular fibers, whereas wild-type hemoglobin remains soluble in its deoxygenated state. Formation of aggregated hemoglobin fibers produces erythrocytes with a thin, elongated, crescent shape that resemble the blade of a sickle (See figure below).

People who are homozygous for the sickle cell allele have sickle cell anemia, and they suffer repeated crises brought on by physical exertion. Additionally, the erythrocytes of affected individuals are easily ruptured, resulting in a lack of blood (anemia). Capillaries of affected
Individuals become blocked by long, abnormally shaped cells, which results in organ failure; a major factor in the early death of affected individuals. Without treatment people with sickle cell anemia usually die in early childhood.

Individuals heterozygous for the sickle cell allele experience a milder condition called sickle cell trait. Only about 1% of the total erythrocytes sickle upon deoxygenation in these individuals. Individuals exhibiting this condition can live normal lives as long as they avoid vigorous exercise. Interestingly, they exhibit a greater resistance to lethal forms of malaria than individuals with two wild-type hemoglobin alleles.

Written below is the amino acid sequence that corresponds to the N-terminal 13 residues of the mutated sickle cell hemoglobin β-Subunit.

Met-Val-His-Leu-Thr-Pro-Val-Glu-Lys-Ser-Ala-Val-Thr-

i. What are the difference(s) in amino acid sequence between the wild-type and sickle cell hemoglobin β-subunits? Limit your answer to one sentence.

ii. Using the codon table above, suggest the simplest possible mutation(s) to the β-hemoglobin gene that would account for the difference(s) in amino acid sequence between wild-type and sickle cell β-hemoglobin. Limit your answer to two sentences or less.

iii. Based on the known difference(s) between the wild-type and sickle cell β-hemoglobin protein sequences, propose an explanation for how the sickle cell mutation causes hemoglobin aggregation. Focus your discussion on the physiochemical properties of the amino acids. Assume that any mutation(s) in the hemoglobin β-subunit occur on the exterior of the protein. Limit your answer to three sentences or less.