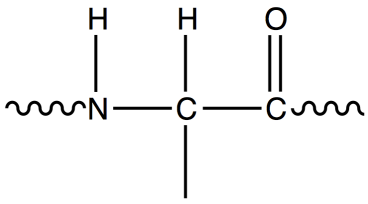
NAME:_____ **Exam 1**

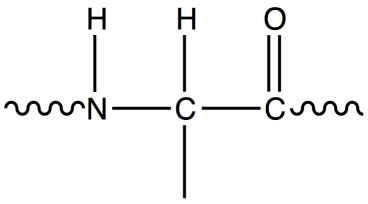
1. Paetzel *et al.* determined the structure of wildtype (WT) and mutant C3 domains of Cardiac Myosin Binding Protein C (cMyBP-C). The WT domain contains an arginine at position 502, while the mutant contains tryptophan at position 502.

   a. Fill in the chemical structure of the WT and mutant versions of cMyBP-C at position 502.

WT R502



Mutant W502



   b. Indicate the chemical properties of arginine and tryptophan.

Property	**R**	**W**
Hydrophobic		
Hydrophilic		
Basic		
Acidic		
Hydrogen Bond Donor		
Hydrogen Bond Acceptor		
Aromatic		

   c. What other amino acids substitutions at position 502 may have similar overall characteristics as the tryptophan substitution studied by Paetzel *et al.*

2. Paetzel *et al.* studied cMyBP-C in a solution containing sodium phosphate buffer and sodium chloride. Given jars of solid:

   - Sodium phosphate monobasic dihydrate ($NaH_2PO_4 \bullet 2H_2O$; acidic form; MW 156.01 g/mole; pKa 7.00)
   - Sodium phosphate dibasic heptahydrate ($Na_2HPO_4 \bullet 7H_2O$; basic form; MW 268.07 g/mole; pKa 7.00)
   - Sodium chloride (NaCl; MW 58.44 g/mole)

   Describe how to prepare 1 L of solution at pH 6.5 containing:

   - 0.500 mole/L total phosphate
   - 1.000 mole/L total chloride

3. The following sub-sequences as part of the larger cMyBP-C gene were used in the structural studies of Paetzel *et al.*

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   [WT] 5′-G ACC TTC AAA TAC CGG TTC AAG AAG GAC GG-3′
[R502W] 5′-G ACC TTC AAA TAC TGG TTC AAG AAG GAC GG-3′
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The table below contains the standard genetic code:

First letter	Second letter: U	Second letter: C	Second letter: A	Second letter: G	Third letter
U	UUU, UUC: Phe UUA, UUG: Leu	UCU, UCC, UCA, UCG: Ser	UAU, UAC: Tyr UAA: Stop UAG: Stop	UGU, UGC: Cys UGA: Trp UGG: Trp	U C A G
C	CUU, CUC, CUA, CUG: Leu	CCU, CCC, CCA, CCG: Pro	CAU, CAC: His CAA, CAG: Gln	CGU, CGC, CGA, CGG: Arg	U C A G
A	AUU, AUC: Ile AUA, AUG: Met	ACU, ACC, ACA, ACG: Thr	AAU, AAC: Asn AAA, AAG: Lys	AGU, AGC: Ser AGA: Stop AGG: Stop	U C A G
G	GUU, GUC, GUA, GUG: Val	GCU, GCC, GCA, GCG: Ala	GAU, GAC: Asp GAA, GAG: Glu	GGU, GGC, GGA, GGG: Gly	U C A G

When the WT and R502W genes (including the sub-sequences shown above) underwent the processes of DNA replication, transcription, and translation; very few differences between each of these processes existed when comparing WT to the R502W mutant. **List the differences in the processes of DNA replication, transcription, and translation when comparing cells producing the WT protein to cells producing the R502W mutant protein.**

4. Open the structures of the WT (2MQ0) and R502W (2MQ3) mutant proteins in PyMol. Under actions, generate a formal charge estimate for each protein.

    a. **What is the formal charge of the WT protein?**

    b. **What is the formal charge of the R502W mutant protein?**

    c. **Explain this observation.**

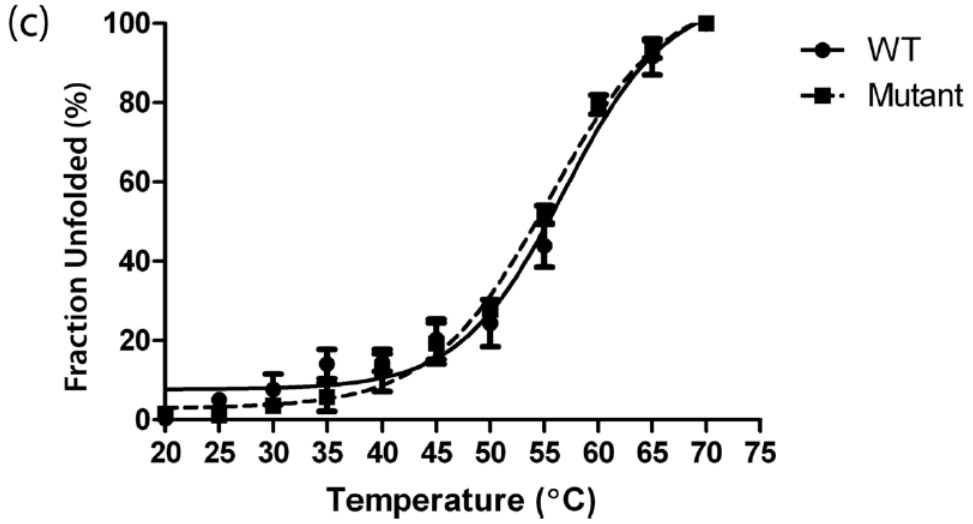
5. Several mutations in cMyBP-C are observed to lead to the hypertrophic cardiomyopathic pathology. Which of the following mutations would alter the protein surface chemistry on the same side of the protein as the R502W mutation and thus possibly have the same pathogenic mechanism?

    R458H **G490R** **R495G** **K504(deletion)**

    G507R **G23W** **E542Q**

6. The melting temperature (Tm) for a protein is the temperature at which the concentration of folded protein is equal to the concentration of unfolded protein.

   a. **What is the Tm of the WT protein?**
   b. **What is the Tm of the mutant protein?**



   c. **Given the Paetzel *et al.* structures, why is it not so surprising that the R502 to W502 mutation does not have a significant effect on the secondary and tertiary stability of the folded protein?**

   d. **Given the Paetzel *et al.* structures, is alteration of secondary, tertiary, or quaternary protein structure proposed to result in the hypertrophic cardiomyopathic pathology (HCM) associated with the arginine to tryptophan primary structure mutation? Explain.**