**NAME:**

**Assignment 1: Exploring kinase structure and function**

**YOU ARE EXPECTED TO WORK ON THIS ASSIGNMENT ON YOUR OWN. CHECKING YOUR WORK WITH OTHERS, WORKING ON THE ASSIGNMENT TOGETHER, SHARING ANSWERS, ETC. ARE NOT ALLOWED AND IS CONSIDERED CHEATING.**

**You should not spend more than 4 hours on this assignment.**

Assignment details:

150 points

6 page upper limit, 3 page lower limit (including pictures – make your pictures big enough to be enjoyed).

Final paper due **10/16 by the end of the day (11:59 pm)** via email to csohl@mail.sdsu.edu

Arial, 11 pt font, single spaced, 0.5” margins.

Include citations

*Save the file name with your last name, and make sure you type your name on the document itself*

Kinase assignment:

You will randomly draw a kinase during the first week of class for assignment 1. These kinases are listed by their cBioPortal code, which may or may not be their most commonly known name: Alk, Btk, FGFR1, FGFR2, Flt3, JAK2, JAK3, KDR, Kit, Met, Ret, Src, or Syk. If you feel very strongly about selecting a tyrosine kinase not on the list, let me know. Read at least two primary articles on your chosen enzyme, as well as any reviews as needed.

Key notes:

A) When you select your point mutation in cBioPortal, ensure the mutation is located in the kinase domain.

B) When you chose your PDB code to work with, ensure you select a crystal structure of the kinase domain portion of the kinase that has the wild type version of your residue clearly visible.

**Check both A and B BEFORE investing time in this assignment**.

Assignment:

1. What is the full name of your enzyme? Is it a receptor or non-receptor kinase? In what pathway is this enzyme involved? Show a screenshot of your kinase pathway (cite your source). What is the purpose of this pathway under normal (i.e. non-cancerous) conditions? *(15 points, 1 paragraph)*
2. Include a screenshot of cBioPortal showing the overview tab of the protein, as well as the mutations tab. Now select one point mutation from cBioPortal of interest and list which you chose. You can pick any one you wish within the kinase domain, but often the most common are the most interesting. *(10 points, 1-2 sentences)*
3. Has this kinase been implicated in cancer? What cancer types in particular? Is the kinase typically associated with activation or deactivation in cancer? Does this most commonly happen by amplification, deletion, or mutation? Do you propose this enzyme is a tumor suppressor or oncogene? *(20 points, 1 paragraph)*
4. According to the literature, what are the consequences to the tumor cell when this enzyme is altered? What are the immediate downstream effects as well as the overall effects? *(20 points, 1 paragraph)*
5. Select one PDB file of the enzyme, ensuring the protein is wild type at the residue in which you are interested, and clearly visible. Use Pymol to view the structure. Provide an image highlighting the location of the mutation and the affected amino acid. In what domain (hinge, activation loop, p loop, etc.) is the mutation located? Highlight the alpha-C helix, P-loop, activation loop, domains with color (explain your color scheme), arranging with the N-lobe on top and C-lobe on the bottom. If your mutation is not directly in one of these domains, what is the closest domain? If you have a hard time assigning residues to these domains, look back at some of the earliest structure papers for your kinase, or look at reviews – these should contain this information. Otherwise, identify these features yourself based on structural homology with other kinases. *(30 points, 1 paragraph)*
6. How far is the mutation from the active site (use measurement tools)? You can measure to where ATP binds, or catalytic residues, just make sure you’re measuring to the distance to the binding pocket. Do you think it would interact with ATP? Why or why not? *(15 points, 1 paragraph)*
7. How far is the mutation from the activation loop (use measurement tools)? You can use a range of distances, from the portion of the activation loop that is closest to the farthest, or just one measuring from the middle of the activation loop. Whatever you decide, just describe what you’re measuring. Do you think your mutation plays a role in activation? Why or why not? *(15 points, 1 paragraph)*
8. Make the mutation in the PDB file using Pymol. Explore different rotamers and decide on the most likely. Defend your choice. Show a screenshot of this rotomer, displaying your results clearly and highlighting the mutation. What do you foresee the consequences of this mutation are? Why? Answer this biochemically (i.e., how does it affect catalytic activity), and biologically (what are the phenotypic consequences in the cell). *(25 points, 1 paragraph)*

Cite the papers used in preparing this, and of course cite all the papers to which you explicitly refer. Attach your bibliography, and do not add it to your total page count.