Drug Design Project **Information and Tips** **CHEM 162B (2012)**

Part of your grade in Drug Design courses will come from a development of a "Drug Design Project". Students who have taken Chem162A will be able to continue their project development; students who have not taken Chem 162A can pick one of the projects developed in past and take it further. Students will present their projects during the annual Drug Design Poster Event. Students taking Chem 162 during the Winter 2011 will be able accomplish three important milestones toward completing the Project. Part of your grade will be based on your success in completing these milestones.

The milestones that you are expected to complete during the Spring 2012 are:

1) Characterize a validated protein/nucleic acid target for the disease that you are working on. If the target is an enzyme, describe in detail the reaction it catalyzes. If the target is not an enzyme, describe in detail its physiological role and mode of operation

2) Obtain or create a virtual library of possible drug candidates that are expected to bind to this target and carry out virtual screening to identify best binders

3) Describe adsorption, distribution, metabolism, excretion, and possible toxicity aspects of your drug candidate(s). If appropriate, propose modifications to improve your drug.

You are expected to turn in your work on each milestone by the due dates specified; you'll automatically receive 3 points per each milestone if you submit a significantly developed work by the due date. You will earn extra 5 points if you submit all milestones by the due date. You will receive feedback on your ideas that will help you to refine your proposal and you will submit the refined proposal on how to meet these four milestones at the end of the quarter. Each milestone in your refined proposal is worth 12 points. In summary, you could earn 50 points if you submit reasonably well developed plans by due dates and will resubmit perfect proposal by the end of the quarter.

What is expected in your final write-up? A written report (under nine pages excluding references), with a title, references, lots of graphics that clearly explains your ideas, and structures of compounds. Sections should include

- a background, in which you describe why there is a need for what you are proposing. Briefly discuss current therapies, and include the background about the lead compound, if appropriate. This can be a summary of a previous proposal on the topic you are working on

- a technical description of the work you performed in this course (the three milestones). Write this up similarly to a methods section in scientific publications.

- an overview of main results obtained (structures, properties of molecules, predicted binding scores) and their critical analysis. Most of your figures (transition state geometries, electrostatic potential maps, docked poses, schemes for possible metabolic reactions) should be included in this section

- your self-criticism, in which you discuss potential promises and likely limitations of the drug you have designed. Focus on material relevant to these three milestones and do not concern yourself with topics such as cost, manufacturing, and intellectual property issues.

Drug Development Milestone I

Due date: Apr 25, 2012

Characterize a validated protein target / enzymatic reaction for the disease that you are working on

As a first part of your project, you are expected to characterize a validated target for the disease you are working on. Visualize the protein that you are targeting and create images of the binding pocket / active site. If ligand-bond structures of the target are available, examine the protein ligand complexes, and discuss main interactions between the bound ligand and the target protein; develop a pharmacophore model based on the target structure. If ligand-bound structures of the target are not available, perform computational analysis to identify major surface cavities in the protein and examine their suitability as binding pockets for drugs. If you happen to work on a disease in which the target protein structure is unknown; find from a protein data bank a homologous protein and perform homology modeling using a suitable web service to obtain 3D model for your target.

If the target protein is an enzyme, describe the reaction it catalyzes and identify the transition state either based on the published data (kinetic isotope effect, past computational studies) or your chemical insight. If the reaction is relatively simple (e.g. one step S_N2 displacement), determine the transition state structure using computational approaches that you learned in this class. Locating transition states in more complex reactions (e.g. if a combination of nucleophilic and acid-base catalysis is involved) is more challenging. In such cases you can use your chemical intuition to propose a possible transition state structure but you are not required to perform actual calculations. Consult with your instructor on technical aspects of locating the transition state of the reaction catalyzed by your target enzyme.

If the target protein is not an enzyme, focus on its mechanism of action. What proteins does it interact with; which are the domain or surface regions involved in these interactions. You can create color-coded 3D representations that highlight different functional parts of the protein. If it is a membrane protein, perform hydropathy analysis and identify transmembrane domains. Find from the literature, which parts of the protein are extracellular, and which parts intracellular. If the target is not an enzyme, you should have the 3D structure of the binding pocket, if not of the complete protein. If there is no structure, use homology modeling to obtain a model; if this fails you cannot proceed and need to pick another disease/target.

Drug Development Milestone II

Due date: May 16, 2015

Perform virtual screening and characterize your lead compound and possible drugs that you have developed via virtual screening

As a second part of your project, you are expected obtain/generate a virtual library of molecules expected to bind to your target and perform a virtual screening of these molecules. In most cases, this means that you will perform computational docking of your molecules to the binding pocket of the target.

Perform a literature search to see what virtual screening approaches have been used before for this, or closely related target(s), and what the results were. Based on this information, devise your virtual screening strategy.

If your lead is based on the mechanism of catalysis (e.g. TS analogue or suicide inhibitor), you need to carry out docking of this lead and a few modifications that you decide based on the visual examination of the active site.

If your lead is largely literature-based (competitive substrate analog, allosteric inhibitor etc), perform virtual screening of a small thematic or focused library. You can use a medium-sized virtual library from Ligand.Info or ZINC databases; or generate a small library yourself by building molecules from scratch. If there are known ligands (e.g. your lead compound) with experimentally available binding constant, include these to the library as well. Your thematic or focused library shall contain at least ten unique and novel chemical structures in addition to known binders.

If you do not have a good lead, you need to perform random screening of a large (at least 25 molecules) diverse virtual library in an attempt to identify a lead compound via computer modeling. Include at least five approved drugs into your random screening.

You may choose to perform conformational analysis of your ligands with Tinker before performing rigid docking. Perform virtual screening with a docking program of your choice (UCSF DOCK is available in the computer lab). If you did not generate conformers in the previous step, perform flexible ligand docking. If possible, evaluate the performance of the docking method based on the calculated scores and experimental binding affinities of known binders. Identify five most promising novel molecules.

If you suspect that your molecules could bind to unwanted targets (e.g. humans and pathogens share the same enzyme) and the structure of the unwanted target is available, use docking program to test if your best drug candidates bind tightly to the unwanted target.

Drug Development Milestone III

Due date: May 30, 2012

Describe adsorption, distribution, metabolism, excretion, and possible toxicity aspects of your drug candidate(s). If appropriate, propose modifications to improve your drug.

Briefly characterize physico-chemical properties of molecules you have designed. Provide molecular weight and logP values of your best compounds and known inhibitors. Does your compound confirm to Lipinski's rule of fives? You may use web servers such as

http://www.molinspiration.com/services/logp.html or,
http://intro.bio.umb.edu/111-112/OLLM/111F98/newclogp.html ,

Perform a literature search to identify possible ways how your drug is metabolized, give the structures of anticipated metabolites, and discuss the implications of metabolism of your drug (are the metabolites reactive/toxic?). Can you predict if there is a significant first-pass effect (elimination in liver) with your compound?

Is your drug supposed to be short acting? If yes, discuss how your drug could be further modified to increase its metabolism or elimination. Is your drug supposed to be long-acting? If yes, how could you increase its half-life?

Is your drug expected to react its intended target (e.g. can it cross the blood-brain barrier or enter the target cells?) Is it so toxic that is shall be activated only in the target cells? How could you modify it in order to facilitate the tissue-specific delivery or bioactivation at the desired site?