Drug Design project tips **Chemistry/Biochemistry 162/262**

The first step is to select a general area of drug application. Perhaps you know of a disease someone has for which the treatment is less than optimal. For example, side effects may be quite bad. Another approach is to identify an area that is broadly acknowledged as being in need of further improvement. One example is the treatment of infectious diseases (e.g., TB) that because of resistance development within the microbial strains, is in dire need of improvement. Cancer and virally transmitted diseases are some of the bigger unsolved areas. However, many less "visible" areas are interesting too. Aging. Allergic rhinitis. Sleeping sickness. Hair loss The list goes on. You could browse journals such as the *Journal of Medicinal Chemistry*, *Biochemistry*, *Science*, *Nature*, or *Molecular Pharmacology* to get an idea what people are working on. And of course, use the Web. Pick something that you will find fun and learn from.

Next, you need to read a lot about what's known. How do the present drugs work? What are their structures? This research will dig up whether a molecular target for the disease is known. It is easier to design drugs if the target is known and it is certainly easier to formulate a proposal if the target is known. If the target is known, the next thing to ask is if the structure of the target (enzyme, receptor) is known, which will determine the strategy of drug design you employ. If the structure is known, taking a "structure-based" approach is a reasonable, but not required strategy. I anticipate that we will have a suite of drug discovery programs from Schroedinger available in few weeks, these allow you to perform modeling and docking analyses. If the structure of the target is not known, your focus will be more on assays, screening, QSAR and medicinal chemistry to modify existing drugs. In general, more non-structure based projects are available, because not too many target structures are available.

Do not worry at this point that you do not know all the methods yet. You will learn relevant material through the course and will prepare each week parts of your proposal based on what you already have learned. Some strategies to develop drugs that we will cover focus on QSAR, mechanism-based inhibitors, transition state analogs, and combinatorial libraries. We will also discuss prodrug design, and rational alteration of drug metabolism to achieve better effectiveness. You will see how these fit into your design proposal when the time comes.

What is expected? A written report (under five to six pages excluding references), with a title, references, graphics if helpful in explaining 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,
- the present state of the art, in which you outline current approaches
- the validation, in which you discuss the target validation or approaches to one could take to find the target
- your approach, in which you explain what you plan to do in order to design a better drug. This section needs to be fairly detailed. Make sure to explain your rationale (why this will work) and method (e.g. the chemistry needed to make your compounds). Lay out experiments that need to be done in order to test the efficacy of the drug in vitro and in vivo.
- your self-criticism, in which you discuss potential up- and down-sides of your plan. Concern yourself with drug metabolism and the other drug design/development issues covered in the class. Do you see any potential side effects?

- your strategic plan. Remember, in real life you need money to realize your dream idea. The venture capitalists want to see a business plan as much as they want to hear your science. Identify resources that you need to carry out the work and come up with some justified estimate what it will cost to get you're your drug to the market under the best-case scenario.

Talk to me at all stages of your project: use me as a resource!

How we grade the projects.

Final proposal. Last year, the points for the final proposal were distributed into the following categories

1) Description of the disease: the cause, the course, and the cures. Statistics on disease prevalence and mortality.
   8 points
2) Target validation.
   8 points
3) Your rationale and detailed characterization of the target. Molecular visualization.
   6 points
4) Assay(s) to test the efficacy of your proposed drug.
   6 points
5) Your design details (synthesis of the drug or implementation of any technology involved)
   6 points
6) Your self-criticisms, discussion of metabolism and toxicity of your drug.
   6 points
7) Your strategic plan. Intellectual property issues and the budget.
   6 points
8) Overall organization and neatness
   4 points

Last year, the high score was 48/50 and the low score was 18/50.

Poster presentation. Last year, the points for the poster presentation were distributed equally between four categories

1) Background research and target validation
2) Novelty of the idea
3) Proposed work plan
4) Quality of the presentation

The high score for poster was 20/20 and the low score was 4/20