Drug Design Project: Information and Tips

Part of your grade in Drug Design courses will come from a development of a "Drug Design Project". Students who will take the second quarter of Drug Design in Winter 2010 will be able to take their project to a completion and will present their projects during the annual Drug Design Poster Event. Students taking Chem 162A during the Fall 2009 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 Chem162A are:

1) Select and characterize a disease that you plan to cure with a drug that you could design

2) Identify and provide validation for a molecular target relevant to the disease you selected. Note that you are allowed to embark into "chemical genomics" pathway in case there are no obvious targets. The latter approach still requires a thorough understanding of the disease and if you go with "chemical genomics" route, you should provide a comprehensive description of the biology and biochemistry of the disease

3) Propose an approach to identify lead compounds for development of a drug for the disease you selected. If you have a validated target, this typically means development of a specific biochemical, cell-based, or *in silico* assay. If you follow "chemical genomic" route, this would mean development of high-throughput cell-based screening methods.

A more detailed guidance on how to meet these milestones is given on next pages. 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 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 what is known about the biology of the disease and discuss current approaches

- the validation, in which you discuss the target validation or approaches to one could take to find the target

- your approach, to identify lead compounds that can be further modified 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 principle of your assay).

- your self-criticism, in which you discuss potential up- and down-sides of your plan. Focus on material relevant to these four milestones and do not concern yourself with topics such as drug metabolism or side effects, which will be covered in the winter quarter class?

Drug Development Milestone I

Select and characterize a disease that you plan to cure with a drug that you could design
Due date: Wed, Oct 28, 2009

As a first part of your project, you are expected to identify a disease that you want to work on. Submit two-to-three page summary where you discuss the nature of the disease, give statistics concerning its prevalence and mortality, and discuss current approaches that are used to tackle this disease. Your discussion of the nature of the disease should cover both the clinical manifestations (e.g. diphtheria, if untreated, leads to inflammation and eventual failure of the heart muscle) and important biochemical mechanisms (e.g. diphtheria toxin inactivates molecules that are critical for protein synthesis by attaching a ribosyl moiety to them)

How to go about deciding about the disease? 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. However, you need to remember that you need to come up with a reasonable proposal. Diseases that have not been sufficiently characterized, or diseases that are known to arise from a variety of molecular mechanisms might be too difficult for your project. As you read the literature, you will quickly develop a feeling if the disease is sufficiently well understood.

Students in the course may work alone or form a team of two when working on their project. If you feel confident in your ability to tackle such a problem alone go on with the disease of your choice. If you feel that you could benefit form a formal partnership with another student, team up. However, students who team up cannot pick their own project but shall work on one of the "feature projects" listed below. Students who work alone are allowed to work independently on the "feature projects". No more than one team can work on a particular feature project.

Feature projects:

- Altzheimer's disease
- Avian influenza
- Breast cancer
- Diabetes mellitus type 2
- Hepatitis C
- High pain sensitivity / chronic pain
- Metastasis of tumor cells (i.e. focus on preventing the attachment of circulating tumor cells in other tissues)
- Multiple sclerosis
- Tuberculosis

Drug Development Milestone II

Validate one target for a disease that you plan to cure with a drug that you could design

As a second part of your project, you are expected to validate one target pertaining to the disease that you want to work on. As part of your second assignment, present and critically discuss the evidence that validates your target(s). Make sure to read and reference the original research that provided validating data, and discuss limitations of such studies. For most targets, a thorough validation can be concisely written up into about one-page essay but you are allowed to be longer if necessary.

Remember some of the key messages from the validation exercise you did earlier:
1) You need to work through a lot of literature. I anticipate that a good answer will involve a few review papers and **several original research** reports. You actually need to read and partially understand these, not just quote them because they were mentioned in the review papers. When reading complex research papers, you may want to follow the order
    a) Abstract (tells you if this is a relevant paper)
    b) Introduction (if well written, gives good background and pointers to earlier works)
    c) Discussion and conclusions (hopefully explains what was found)
    d) Results (do you really agree with their interpretation of what was observed)
    e) Methods (get the general idea what approach was used, do not worry about details)

    You may find that an old publication provides key data that validates the target but you still need to check more recent works for additional evidence. You will not be excused if you build your drug design project around on a target that is known to be invalid.

2) Having a clinically efficient drug that binds to the target does not necessarily validate the target.

3) Not every paper that deals with curing a disease is about target validation. Evaluate each paper critically; do not just believe the hype authors are giving.

4) Keep in mind that for the success in your project your target has to be druggable. So, while one might argue that chromosome 21 is a valid target for Down's syndrome; it is not druggable based on our current technologies. Do not pick targets that require you to invent a time-machine, nano-robot, or Maxwell daemon for treating the disease.

Some students may wish to work on a project where the target is unknown. For example, you may have heard or read about a surprisingly valuable side-effect of a currently existing drug and want to design a combinatorial library around this structure to find compounds that show a stronger "side-effect". In this case, please describe what approaches you would take to identify the target of your drug. As this is (bio)chemistry class, your approach must be based on biochemistry and molecular biology methods.

If your target is not previously validated, you should pursue validation approaches that are available to you (SNP and microarray analysis).   You need provide significant level of detail here; answers like "I will validate the target through SNP analysis" are not worth much. Analyzing some publicly available microarray (e.g. from http://www.ebi.ac.uk/microarray-as/ae/) or SNP data is an appropriate way to show that you know how to validate a target even if your conclusions may be statistically weak. Note that the databases typically carry fragment names (such as 205225_at) and you need to use Stanford Source to reveal the corresponding protein name (estrogen receptor 1).

Drug Development Milestone III

As a third part of your project, you are expected to come up with a plan how to identify potential drug candidates for the disease you are working on. If you have a validated target, this typically means development of a specific biochemical assay. If you follow "chemical genomic" route, this would mean development of high-throughput cell-based screening methods.

Please discuss what the rationale behind using such an assay is, describe the assay in detail, and identify any potential limitations. Your assay can be molecular-biology based (e.g. quantification of particular mRNA using molecular beacons), biochemical (e.g. measuring ligand binding to the receptor), cell-based (e.g. monitoring the formation of a fluorescent reaction product in live cells), histological (analysis of tissue appearance), clinical (determination of viral load), or end-point assay (improvement in host health). In any case, create at least one image that illustrates the principle behind the assay. You should create the image yourself; the image you create may be based on existing images that depict this assay.

The lecture material should give you a good starting point and may be sufficient in simple scenarios, such as in vitro identification of agonists for nicotinic acetylcholine receptor. You most likely need to work with scientific literature in order to best to decide which particular approach is most appropriate. Original research papers also allow you to learn more about details of specific assays. It is a good practice, but not an absolute requirement to hunt down the original research in which the assay was developed or applied to your target. For some more pioneering projects such papers may not simply exist; it is sufficient that you provide evidence that a particular assay or animal model is appropriate to your target and disease.

If your approach is more "me-too", where you are hoping to improve on already existing known bioactive molecule, you do not need to design a high-throughput assay. It is sufficient to describe an assay that allows measuring the activity of your lead compound and its analogs. If your approach is "me-too", then it is critical that you identify the limitations of the lead, identify the pharmacophore and auxotrophic groups, and propose structure-activity studies. You may propose rational, ligand-based design approaches to optimize your target or perform a QSAR analysis of a set of known biologically active molecules in order to find more potent ones.

Keep in mind that we are not talking about human clinical trials here yet but at most well-characterized animal models of the disease.

Be specific about where your collection of molecules to be screened comes from. If you are proposing to identify a truly novel compound, it is sufficient to state that you are using some existing library, and characterize this briefly. If you are proposing a "me-too" approach based on a known lead compound, provide a synthetic route that allows preparing a combinatorial library of such analogs.

You may propose virtual screening as an additional assay if the structure of your validated target is known and available. The advantage of this approach is that you will be able to carry out the virtual screening in the CHEM162B course. However, because we have not covered this approach this quarter, it cannot be your main assay.