

Drug Development Milestone II

Due date: Sunday, Feb 22, 2009

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 (FKBP12 example).
- 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 a much 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).