

Drug Development Milestone III

Due date: Monday, March 9, 2009

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 inhibitors for alcohol dehydrogenase. 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 high-through-put assay. It is sufficient to describe an assay that allows measuring the activity of your lead compound and a range of 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.