Homework due at the start of class on July 10

Read "ISOA/ARF Drug Development Tutorial" by Jens Eckstein (http://www.alzforum.org/drg/tut/ISOATutorial.pdf) and do the assignment below, consulting any additional sources as needed.

General background

This tutorial, though not from a journal and not illustrated, is the clearest easily accessible overview of the drug development pipeline that I could find. It will serve as background for the rest of the quarter's readings, each of which represents some stage of the drug discovery/development pipeline (from target discovery and screening to clinical trials).

As you read the tutorial, note the importance of chemistry in most steps of the pipeline, the importance and limitations of animal experiments, and the difficulty and expense of the process as a whole. Consider what role (if any) academic research can and should play in this process.

Some additional comments on the tutorial follow.

Target Discovery – Overview. Note the basic distinction between physiology-based and target-based discovery. In infectious disease research, physiology-based discovery is more commonly called phenotypic or cell-based discovery.

Target Discovery – Disease Mechanism. What is wrong with the list of five disease mechanisms on page 3? (Hint: where does malaria fit in?)

Target Discovery – Target Type and "Drugability." While I prefer to spell druggability with two g's, I like the definition provided here, encompassing both access to the target and efficacy.

Target Validation – Overview. In infectious disease research we often talk about genetic validation versus chemical (i.e., pharmacological) validation. Genetic validation generally provides genetic evidence (including RNAi data) that a target is essential for survival or virulence of the pathogen, e.g., the pathogen dies if you knock out the target's gene. Chemical validation can be as simple and limited as showing that compounds can bind to and affect the function of a target, or as sophisticated as proving that the compound kills the pathogen through its effect on a specific target.

Screening and Hits to Leads – in Silico/CADD and SBDD. Note the term "docking," which refers to computer modeling of how a ligand might bind to a target site. While the word docking suggests a physical coming together, in drug discovery it seems to refer only to computer predictions.

Lead Optimization – Overview. Note the term Structure-Activity Relationships (SAR), another staple of drug discovery.

Worksheet to hand in

1. name, date, and assigned article

Greg Crowther, 7-13-13, "ISOA/ARF Drug Development Tutorial"

2. At the bottom of page 2, the tutorial cites the Jurgen Drews Science article that you read earlier. Go back to that article and find the part where Drews argues that the number of unexploited drug targets exceeds the number of existing targets by 10-fold. Do you find him convincing? Briefly explain. (3-4 sentences)

To me, Drews' reasoning in the left and middle columns of p. 1962 seems dodgy. First of all, his estimate that 5-10 of genes are involved in a multifactorial disease is based on studies of two diseases but then assumed to be applicable to 100-150 other diseases. More importantly, he assumes that most of these 5-10 genes per disease are "suitable targets for drug intervention," which seems questionable. In fact, toward the end of p. 1962, he notes, "The fact that 'targets' can be hypothetically associated with diseases … does not mean that they represent suitable intervention levels for new drugs." The difficulty of a target making it through the validation process (described in the sentences after that quote) suggests to me that far fewer than 5-10 targets per disease are tractable.

3. Page 5 mentions antisense RNA and RNAi. They sound pretty similar. What's the difference, according to Wikipedia or another good source? (2-3 sentences)

Antisense RNA is single-stranded RNA that binds to complementary mRNA and physically prevents translation into protein. RNAi has a similar outcome but starts with long double-stranded RNA, which gets cleaved into shorter double-stranded segments, which in turn get separated into single-stranded RNA, including "guide strands" that get incorporated into the RNA-Induced Silencing Complex (RISC) and cause degradation of mRNA that is complementary to the guide strands.

Or, as Clementine said, "Antisense RNA is a molecule, whereas RNAi is a process."

4. In the context of drugs, what does the word formulation (top of page 12) mean? (1-2 sentences)

A drug's formulation is the way in which it is "packaged" (combined with other substances) for delivery into the body. This includes the overall shape and appearance of the drug (as a pill, capsule, syrup, etc.) as well as the presence of specific ingredients that may improve absorption, palatability, etc.

5. Briefly explain how the three phases of human clinical trials differ from each other. (~3 sentences)

Phase 1 is most concerned with safety and dosage, usually in healthy volunteers, whereas Phase 2 is focused more on efficacy in patients (while continuing to study safety as well) and Phase 3 is

a more comprehensive study of both safety and efficacy. The number of subjects generally increases from Phase 1 to Phase 3.

6. There are no illustrations in this tutorial. Create a simple explanatory diagram (hand-sketched or created with computer software) that illustrates the drug development pipeline as a whole or some aspect that you find important and/or confusing.

The diagrams were varied, of course. I really loved some of them! A few examples are shown below.

Jen Arthur's submission includes simple yet effective hand drawings, as if doing the phrase "drug development" in a round of Pictionary.

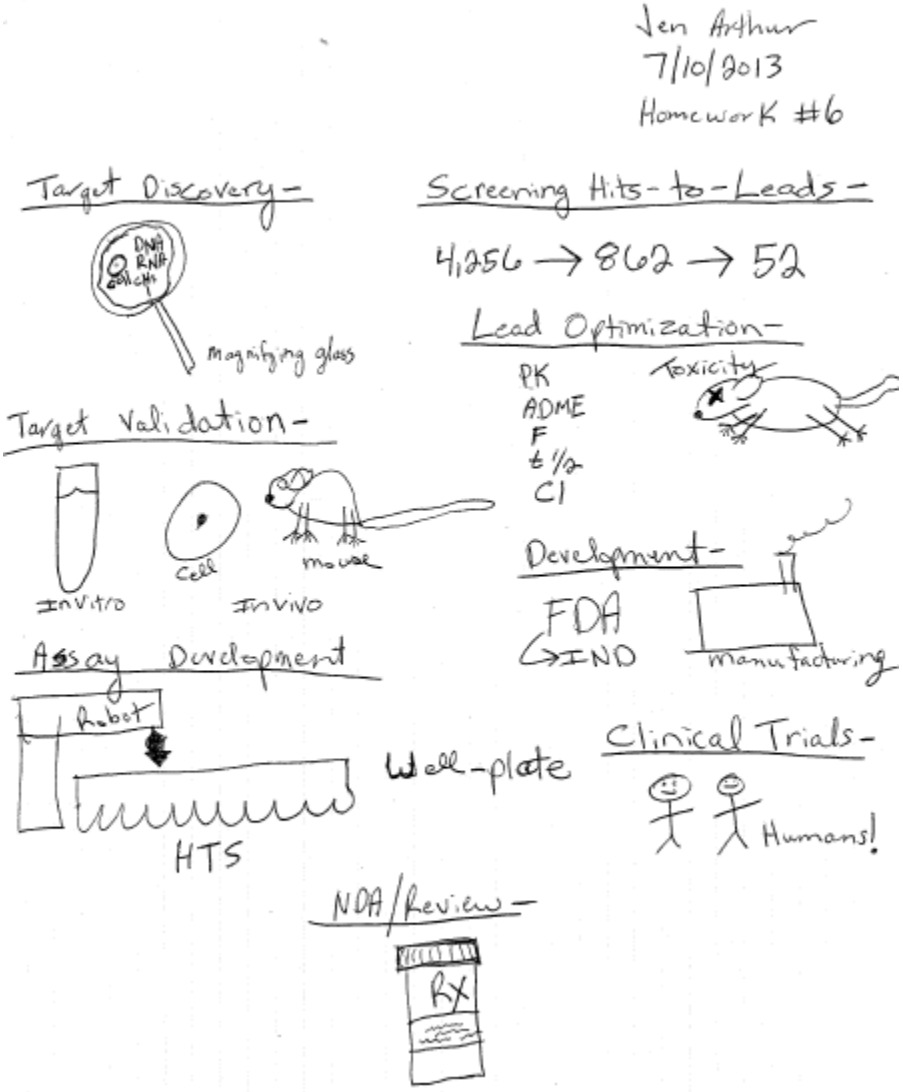
Chris Franz's use of dollars signs makes it very clear where in the drug development process most of the expenses occur.

Ashlyn Giddings' diagram has nicely concise text summaries of each major step.

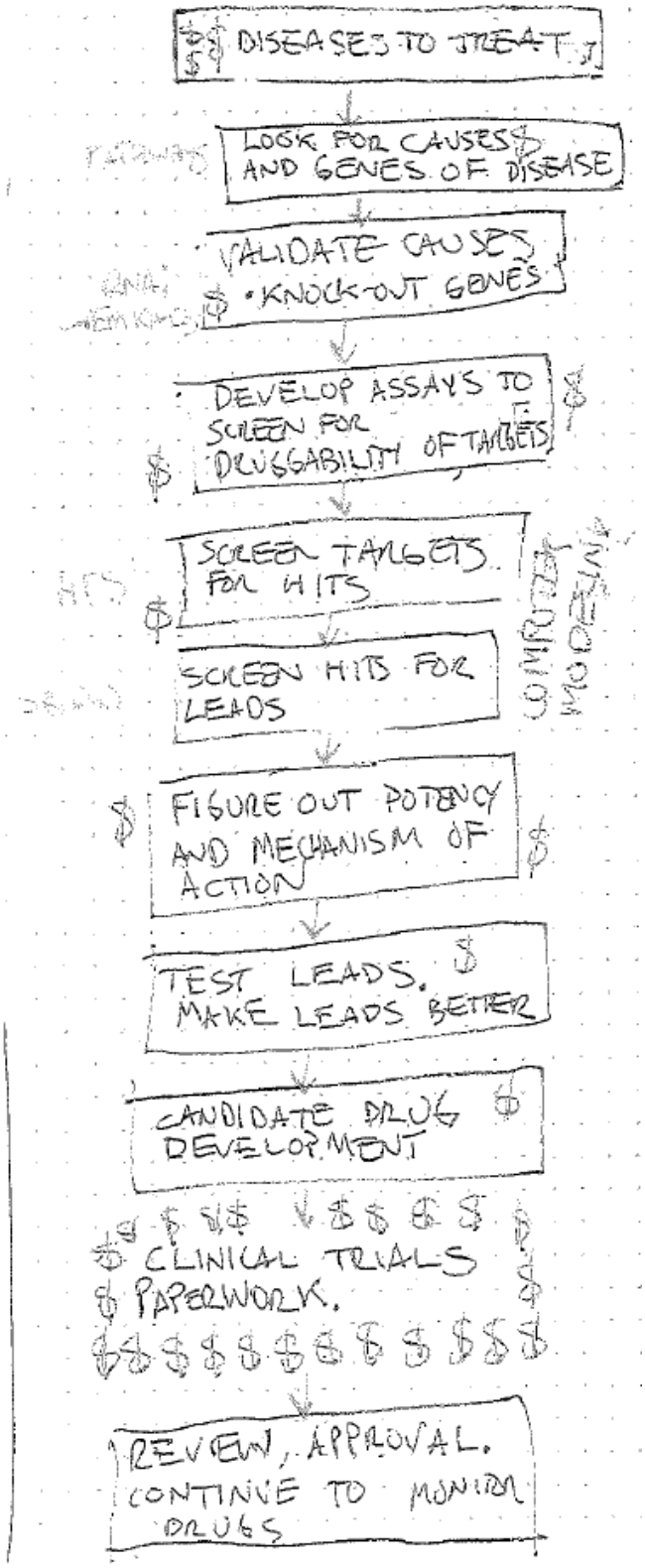
Julia Olson's figure makes the point that the steps of the process can overlap considerably in time. This does NOT come through in a typical diagram, where steps are generally presented as a linear progression from beginning to end, with no overlap or circling back.

For me, Kaiser Valshon's diagram captures the fact that the drug development process is both orderly and messy. Though this reproduction may not be legible, his submitted version is reasonably clear. Yet in my opinion the handwritten text and arrows provide a visceral feel of the process's many twists and turns that may not be conveyed as well by a set of computer-generated PowerPoint boxes.

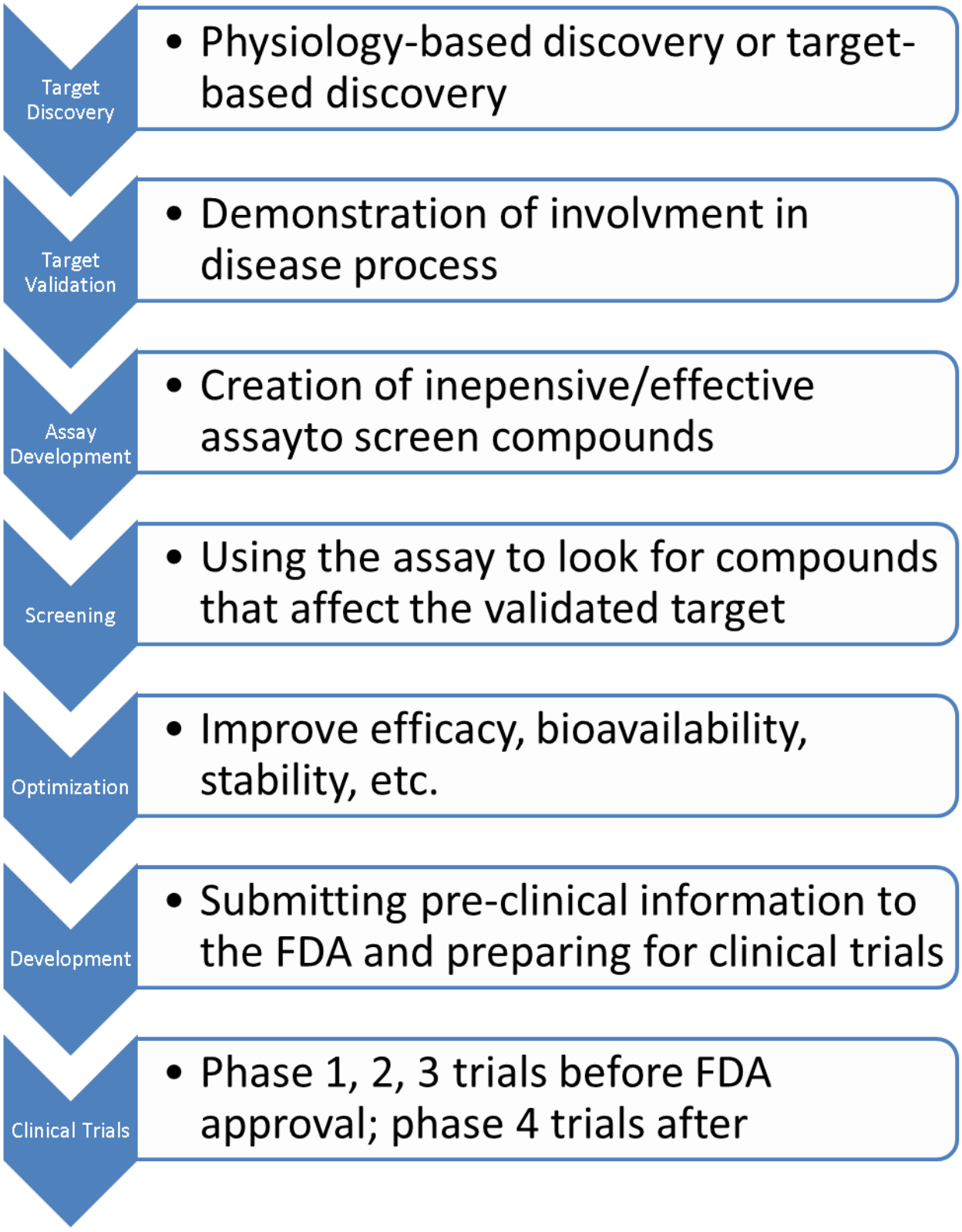
[by Jen Arthur]



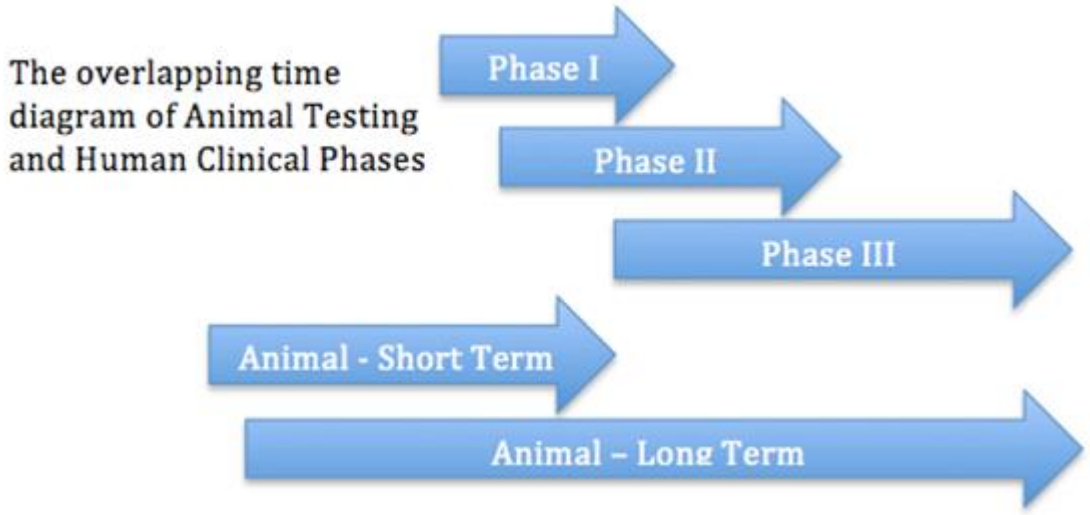
[by Chris Franz]



[by Ashlyn Giddings]



[by Julia Olson]



[by Kaiser Valshon]