# Homework due at the start of class on June 26

Read "Drug discovery: a historical perspective" (J. Drews, *Science* **287**: 1960-4, 2000; PubMed ID 10720314) and do the assignment below, consulting any additional sources as needed. You may be able to access the full text of the Drews article by going to http://pubmed.gov, doing a search for the PubMed ID, and following a link from the article's abstract page to the publisher's website. Alternatively, you can access the article online from the E-Journals section of the UW Libraries website (http://www.lib.washington.edu/types/ejournals/), as follows:

- If you are working off-campus, log in by clicking on the box at the upper right of the web page.
- Under "Find e-journals by title," select S.
- Among the listings of journals beginning with the letter S, find *Science*. Follow the link to the publisher's website, then find the article in the journal's archives by using the citation information (title, author, volume, page numbers, and year) listed above.

General background

Unlike most articles that we will cover during the quarter, this one is a review article – a secondary source, as opposed to "primary literature." Reviews have the advantage of summarizing lots of previous studies without getting bogged down in experimental details; however, a full understanding of the material often requires consultation of the sources cited by the review.

We will read this article as a bit of a warm-up for the quarter, not scrutinizing it exhaustively but using it as the first step of our journey into the malaria drug discovery literature.

A note about the word "target," a.k.a. "drug target"…. In the context of drug development, "target" usually refers to the drug's site of action (e.g., a specific protein where it binds). However, "target" might also refer to a more general pathway or process modulated by the drug (e.g., glycolysis or translation), or even the organism targeted by the drug (e.g., *Plasmodium falciparum*). Furthermore, a target can be the target of an existing drug, or the target of a research compound that may or may not eventually be developed into an actual drug. The bottom line is that the meaning of the word "target" is VERY context-dependent!

Worksheet to hand in

1. name, date, and assigned article

**Greg Crowther, 6-29-13, "Drug discovery: a historical perspective" by J. Drews**

2. Recombinant proteins and monoclonal antibodies are mentioned in the Abstract and on pp. 1961-2. What are these things? (1-2 sentences each)

**In general, a recombinant protein is one expressed from recombinant DNA (as opposed to naturally occurring DNA). Recombinant proteins are often created by scientists to be expressed and purified in large quantities for research, industrial, or medical purposes. A monoclonal antibody is an antibody that recognizes one particular epitope of an antigen, naturally made by a clonal (genetically identical) population of B cells.**

3. The author traces the roots of drug discovery back to the early 1800s. In general, what are the minimum requirements of what a civilization needs to know in order to pursue drug discovery? (1-3 sentences or equivalent "bullet points")

**Answers will vary. My list:**

- **Ability to distinguish between sickness and health**
- **Understanding of scientific method (to do any testing of substances)**
- **Model of disease (to avoid haphazard human testing)**
- **Ability to isolate substances**
- **Sufficient interest / a market**

4. Even non-chemists can understand the names of compounds to some extent. In Fig. 2, consider sulfanilamide as a starting point for sulfa drugs. How do the names sulfadiazine and sulfathiazole correspond to their chemical structures? (1-2 sentences each)

**A diazine is a benzene ring with 2 N's in place of C's, so sulfadiazine includes this (on the left side, as pictured). An azole is a 5-membered ring with an N and at least 1 other non-C member of the ring – S in the case of a thiazole – so sulfathiazole includes that (on the left side, as pictured).**

5. In Fig. 3, which of these classes represent protein targets? Which represent non-protein targets? Which are ambiguous? (2-3 sentences or bullet points)

**Receptors, enzymes, ion channels, and nuclear receptors should all be proteins, in general. "Hormones & factors" could, in principle, include both proteins and non-proteins (e.g., steroid hormones are not proteins). "Unknown" is likewise ambiguous. DNA is not protein (duh).**

6. In Fig. 4, what do the images in each of the three panels indicate about the compounds being tested? (1-2 sentences per panel)

- **LEFT: phosphonucleolin staining indicates cells in mitosis, so a darkly stained well indicate that a compound arrests mitosis**
- **CENTER: compounds were tested for their ability to interfere with the polymerization of tubulin**
- **RIGHT: fluorescence microscopy was used to determine whether compounds altered the normal distribution of actin, microtubules, and chromatin during mitosis and during interphase**

7. The center column of p. 1963 mentions protein-protein interactions as possible drug targets. To get an updated view of this possibility, locate and skim the article "Expanding the number of 'druggable' targets: non-enzymes and protein-protein interactions" by Makley & Gestwicki (PubMed ID 23253128). Why are protein-protein interactions challenging to target with drugs, and how might we overcome this challenge? (2-4 sentences)

**The binding pockets involved in protein-protein interactions are often shallow and broad and thus difficult to identify and target with small molecules (as opposed to the relatively distinctive and obvious binding sites of enzymes). Nevertheless, several methods can be used to find proteins' binding pockets and ligands that can bind to these pockets. These include affinity-based techniques (chemical shifts in NMR spectra; surface plasmon resonance), stability-based techniques (differential scanning fluorimetry; isotope exchange with mass spectrometry), and "in silico" (computer modeling) techniques.**