OPEN-NOTES QUIZ #1

1. Name: _____*Greg Crowther*_____

2. In your first homework assignment, you consulted the article "Expanding the number of 'druggable' targets: non-enzymes and protein-protein interactions" by Makley & Gestwicki. According to this article, non-enzyme targets are more difficult to study than enzyme targets; therefore one might think that the majority of existing drugs act upon enzymes. Cite other evidence from your readings that contradicts this idea, and give a possible reason why enzymes may not be the most "popular" class of drug target.

   Figure 3 from the J. Drews article (2000) shows that enzymes actually represent a minority (28%) of drug targets. There are several possible reasons. Until recent years, most drug development was done via phenotypic screening (e.g., sprinkle compounds onto cells and see what happens without necessarily knowing what specific proteins are being targeted); the target didn't need to be easy to study because it often wasn't studied. Also, although enzymes have traditionally been thought to be more "druggable" than other proteins, that isn't necessarily the case. Also, Makley & Gestwicki focused on small-molecule ligands, but Drews includes recombinant proteins and monoclonal antibodies as drugs, and these aren't small molecules, so the discovery landscape is different for them.

3. Recall that the clinical symptoms of malaria occur during the erythrocyte (red blood cell) stages. The maverick scientist Kary Mullet has an idea for a vaccine that would not impair *Plasmodium* parasites' invasion of liver cells and multiplication within them, but would prevent invasion of erythrocytes. You have been told to evaluate this idea. What additional information (either already known, though perhaps not by you, or unknown) would be most important for you to have? Briefly explain your reasoning.

   A first step might be to clarify whether people can get symptoms of malaria, suffer any health problems, or form any gametocytes as a result of liver-stage infection. As far as I know, the answers are no, no, and no, and there is some evidence that sporozoites arresting late in the liver stage would constitute a better vaccine than more feeble sporozoites that do not advance as far (e.g., PubMed ID 21787828). One would also want to know what specific antigen(s) was/were under consideration – a highly expressed surface protein (if so, is it well conserved or susceptible to mutation?) or some sort of disabled parasite? If live parasites are to be used, can they be generated in numbers adequate for vaccine production, and is there any chance of them mutating in a way that would re-enable erythrocyte invasion?