Biology 485 / July 29, 2013
In-class discussion questions for "Discovery and Biochemical Characterization of *Plasmodium* Thioredoxin Reductase Inhibitors from an Antimalarial Set" (Theobald et al. 2012)
Prepared by Tyler Bradshaw, Chad Sumulong, and Daniel Saiku

1. Draw a schematic of the overall process of the assay. Briefly describe each step. What is the purpose of the two "regeneration" reactions? Why was Trx incubated with NEM?

2. What was the researchers' conclusion about the structural differences between mammalian and Plasmodium TrxR? How does their conclusion differ from their initial hypothesis about the mode of inhibition of the TrxR enzyme?

3. Look at Figure 3.A and B and indicate where the Km concentration for Txr and NADPH is on the graph. Why did the authors design their assay to maintain the reactants at Km concentrations?

4. Just by looking at Table 1, how were researchers able to conclude that the drug selectively inhibited the malarial parasite? Why is it odd to have a higher whole cell IC50 value than the target based IC50 value?

5. Although the crystallographic structure of the TrxR enxyme was undetermined at the time Theobald et al. (2012) published their paper, it is now known. Consult "Crystal Structure of the Plasmodium falciparum Thioredoxin Reductase-Thioredoxin Complex" in order to explain how the TxrR enzyme works [PMID: 23845423]. Indicate the two dimers of the TrxR enzyme and the order of redox reactions.

6. What did the researchers not do in this study that could have improved the paper?