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Biol 485: Discovery and biochemical characterization of plasmodium thioredoxin reductase inhibitors from an antimalarial set

(questions written by Tyler Bradshaw, Daniel Saiku, and Chad Sumulong;
answers provided by Chad Sumulong)

1. What is Thioredoxin reductase (TrxR) and what is its relationship with thioredoxin (Trx)? Why is TrxR a good drug target?
Thioredoxin (trx) is a substrate of Thioredoxin reductase, an enzyme that helps relieve oxidative stress. Researchers thought that TrxR was a good drug target because of its differences between it and the human enzyme, which is mentioned in question 2.

2. What species-specific differences do the authors cite as their rational for the possibility of designing drugs to selectively target the P. falciparum TrxR?
Between the two species enzymes, the mammalian TrxR contained a selenocysteine compound in its active site, which gave researchers the opportunity to create a drug target that could selectively inhibit the bacterial enzyme.

3. What were the roles of Insulin and glucose-6-phosphate dehydrogenase in this study?
Insulin and gluvose-6-phosphate dehydrogenase were used in the enzyme assays to help keep the Km of the substrates at optimal levels. This was done to allow researchers to see a noticeable difference in enzyme activity due to drug inhibition.

4. What is a Km? What do different values of Km tell us about substrate affinity?
The Km is translated to be the substrate concentration level at half of the enzyme's kinetic maximum activity (Vmax). A substrate with a lower Km has high affinity while a substrate with high Km has lower affinity.

5. Referring to Table 1, which compound is the most potent inhibitor of P. falciparum TrxR? Explain.
According to Table 1, compound 3 is the most potent inhibitor because of its higher pIC50 value. This means that at a lower concentration, it is able to inhibit the enzyme by 50%, while the other drugs need higher concentrations to inhibit the enzyme 50%.

6. After reading last week's paper, Baldwin et al. (2005) [PMID: 15795226], the class realized many of the frustrations of target-based assays. How do the authors of this paper rationalize their choice of target-based assay? (Hint: Discussion section)
The researchers rationalize that although the compounds have been show to inhibit enzymatic activity in whole cell assays, using target-based assays can help bridge the gap and provide a definitive link between the whole cell assays and the compounds. This leads to a better understanding of how to create drugs, make them selective, etc.