OPEN-NOTES QUIZ #2

1. Name: _____*Greg Crowther*_____

2. The paper by Fidock et al. (2000) investigated resistance to the antimalarial drug chloroquine.

    a. How does chloroquine normally kill *Plasmodium* cells? (2-3 sentences)

    In the digestive vacuole of the parasite, hemoglobin is broken down into its amino acids and the prosthetic group heme, which is toxic to parasites if it builds up. Chloroquine binds to the heme, preventing crystallization of the heme and leading to a toxic buildup.

    b. From a research and/or clinical standpoint, list at least one way in which chloroquine's specific target is a "good" (desirable) drug target, and at least one way in which it is NOT such a good target. You do not need to refer to the ISOA/ARF Drug Development Tutorial, but certain sections of it may be helpful. (2-3 sentences)

    Good:
    - *The target (heme crystallization) is extremely well-validated at this point. It is clear that interference with this target kills parasites.*
    - *Human cells have no process that is closely analogous to heme crystallization, so it should be relatively easy to find compounds that target this process without hurting human cells. Indeed, chloroquine has proven safe in humans.*
    - *Several simultaneous mutations seem necessary for resistance, so evolution of resistance was relatively slow (which is good).*

    Not so good:
    - *The target is not a specific enzyme or even a specific protein, so target-based screens for compounds that bind or inhibit cannot be done in the usual way. Likewise, genetic approaches (including antisense strategies) cannot be used for target validation.*
    - *At this point, resistance to chloroquine is widespread, so targeting heme crystallization is not nearly as effective as it used to be.*
    - *[from Jen and Tracy] Heme crystallization is only important in one stage of the parasite life cycle, whereas an ideal drug target might be critical for survival in multiple/all stages of the life cycle.*

3. In the first paragraph of their Introduction, Fidock et al. state, "Understanding the molecular basis of CQR should assist design of new antimalarials that can replace or be used in adjunct with CQ." In developing new malaria drugs, why might it be helpful to know the mechanism by which parasites acquire resistance to chloroquine? Please give and explain at least one reason. (2-3 sentences)

    Possible reasons include:
    - *Perhaps a new drug directed at the parasite's mechanisms of resistance could be developed and co-administered with chloroquine.*
    - *Understanding chloroquine resistance may hint at more general insights into how resistance develops in general, and thus which targets might be more and less susceptible to the development of rapid resistance.*