OPEN-NOTES QUIZ #4

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Please answer ONE of the following two questions.

1. You have now read three papers about DHODH as a malaria drug target. DHODH is an enzyme in the pyrimidine biosynthesis pathway. To what extent do the DHODH data validate other members of the pyrimidine biosynthesis pathway as good potential drug targets? Explain.

   Validation of DHODH validates other members of the pathway to the extent that the pathway appears essential for survival and growth of the parasite; therefore interruption of the pathway at any step (not just DHODH) should kill the parasite. However, there are many limitations to this validation-by-proxy thinking:
   - *The fact that DHODH is "druggable" (inhibitable with small drug-like molecules) does not necessarily mean that other enzymes in the pathway are also druggable.*
   - *Much of the DHODH inhibitor development depended on detailed knowledge of DHODH's 3D molecular structure. Such structural information may not be available for other members of the pathway.*
   - *Likewise, other members of the pathway will not necessarily be easy to produce in purified form (recall the difficulties of expressing Plasmodium proteins in E. coli) or to study in a catalytic assay.*
   - *When a metabolic pathway is interrupted, the cells may die because a metabolite in the pathway is toxic when it builds up to very high levels. Interruption of the pathway at a different step may lead to the buildup of a different metabolite, which may or may not be as toxic.*

2. Imagine that you run a malaria research lab. You have been approached both by the authors of the July 29 article ("Discovery and biochemical characterization of Plasmodium thioredoxin reductase inhibitors from an antimalarial set" / PubMed ID 22612231) and the authors of the July 31 article ("In vitro and in vivo antimalarial activity of peptidomimetic protein farnesyltransferase inhibitors with improved membrane permeability" / PubMed ID 15556768). Both sets of authors want you to help them make further progress toward new malaria drugs. You only have the resources to collaborate with one group. Which group will you choose? Why?

   Either choice is defensible.

   Pluses of the thioredoxin reductase project include:
   - *The authors are at a giant pharmaceutical company (GlaxoSmithKline), with corresponding resources at their disposal.*
   - *The nicely designed assay can be applied to screening of additional compound libraries.*
   - *Species selectivity (inhibition of P. falciparum enzyme without inhibiting human enzyme) looks feasible, whereas the farnesyltransferase inhibitors appear to work on both the human and Plasmodium enzymes.*

Pluses of the protein farnesyltransferase project include:

- *Mechanism of action is pretty well established (i.e., the compounds do kill parasites by acting at protein farnesyltransferase).*
- *Inhibitors have already been shown to suppress malaria in mice (pretty far along the development pipeline relative to the thioredoxin reductase paper).*
- *Progress might also lead to new drugs for cancer and against T. brucei and T. cruzi (see introduction of paper).*