OPEN-NOTES QUIZ #3

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Please answer ONE of the following two questions.

1. K.K. Ojo et al. (2010) showed that calcium-dependent protein kinase 1 (CDPK1) from *Toxoplasma gondii* has good potential as a drug target. *T. gondii* is fairly closely related to *Plasmodium*. If you wanted to determine whether the *P. falciparum* CDPK1 or CDPK4 is a good drug target, what experiment(s) would you do and what would the data look like if the enzyme is indeed a good target?

   Basically, you could do the same experiments with P. falciparum cells and the P. falciparum enzymes that were done with T. gondii cells and the T. gondii enzyme. That is, you could test bumped kinase inhibitors (BKIs) against the P. falciparum CDPK1 and CDPK4 and mammalian kinases to see whether there is selective inhibition of the P. falciparum enzymes; you could test BKIs against P. falciparum cells to see whether they inhibit cell growth or host cell invasion; and you could mutate the gatekeeper residues of CDPK1 and CDPK4 to see whether the mutations render the enzymes and cells insensitive to the BKIs.

2. M.L. Baniecki et al. (2007) found many compounds that were potent killers of all tested strains of *P. falciparum*, and a few compounds that were <u>not</u> equally effective against all strains. Should these not-equally-effective compounds be pursued for drug development? Give 1-2 reasons why they might still be worth pursuing, <u>and</u> 1-2 reasons why they might not be.

   Some possible reasons to pursue:
   - *Compounds might still be useful in combination therapy, where a cocktail of compounds collectively is able to kill all strains.*
   - *Since these are just the initial hits from the screen, they could potentially be improved through medicinal chemistry such that they eventually are potent killers of all strains.*

   Some possible reasons NOT to pursue:
   - *There were lots of hits. They can't all be pursued simultaneously, so they have to be prioritized somehow. With so many hits that DO kill all strains well, why bother with the ones that don't?*
   - *Pre-existing resistance among currently tested strains may be a sign that the compound acts through a mechanism used by existing drugs (less appealing than a compound that acts through a novel mechanism).*