6/26/18 Tri/TOB meeting minutes

Attendees: John Domagala (JD), Dawn Reyna (DR), Elke Lipka (EL), Matt Doherty (MD), Chris Waters (CW)

1. The SBIR grant received a score in the 40s. It likely suffered from the lack of mechanism and triclosan’s negative perception. We will resubmit the CF/NCFB this September in lieu of a new grant focused on diabetic foot ulcers. For the resubmission, we may include oxyclozanide or other triclosan analogues as an alternative to triclosan and focus on FabV to determine the mechanism.
2. The triclosan/tobramycin combination appears to have broad-spectrum activity, based on *in vitro* MICs. The current model for the mechanism hypothesizes that triclosan acts as a proton ionophore and disrupts the cells ability to maintain a membrane potential in biofilm, which inhibits resistance nodulation division (RND) type efflux pumps. The inhibition of the efflux pumps allows tobramycin to accumulate within the cells, which then inhibits protein synthesis and causes cell death. This may be specific to biofilms rather than planktonic cells.
3. Experiments with evolutionary mutants has shown that a mutation to elongation factor G results in resistance to the triclosan/tobramycin combination, but increases sensitivity to triclosan. This is surprising given the critical role elongation factors have in protein synthesis, but *Pseudomonas* has two elongation factors, *fusA1* and *fusA2*.
4. The amount of data now available for the mechanism will affect our specific aims in the resubmission. We might want to find biomarkers for Fab activity so we can directly measure the effect of triclosan and further define the mechanism. We may also want to investigate triclosan analogues or other compounds that disrupt the proton motive force.
5. We can most likely increase our chances of funding if we can show efficacy in mice. It may be worth using a Kickstarter campaign to generate the funds for a study at a CRO. John said he would inquire with Transpharm to determine if this is possible.
6. For the grant resubmission, we plan to emphasize the bacterial ribosomal mutation, as this shows the activity is specific to bacteria. We also want to emphasize that triclosan is not seen in the blood after dosing in the lungs, limiting potential systemic effects. We may want to define the mechanism further by focusing on the ribosome. We also need to account for lung surfactant, as this could inhibit the mechanism *in vivo*, by including Survanta in experiments. We will also add data demonstrating broad-spectrum activity. We will also send the resubmission to heart, lung, and blood (NHLBI) in addition to NIAID as an alternate. It may also be worth looking into submitting a proposal to the CF Foundation in the future.
7. With regards to diabetic foot ulcers, there are concerns over formulations, as the drug may be unable to penetrate the biofilm in a topical application depending on the formulation. John said he would look into potential formulations.
8. In terms of our commercial plan, we discussed submitting a proposal to Mtrack or looking into MSU funding options for a pilot study with a CRO, if these funding routes allow for work at CROs. We also discussed working with MiLead and finding a strategic partner, but we likely need efficacy data, based on Elke’s discussion with Debiopharm at the Bio conference.
9. We will most likely need an SBIR before forming a business, but forming a company could allow for small bits of funding for pilot experiments, like efficacy in mice at a CRO. We will revisit this after we get the summary statement from our April SBIR submission.