Putative High-pIC50 SpDHBP Synthase Inhibitors against Multi-Drug Resistant S. pneumoniae

Lai, Catherine

Streptococcus pneumoniae (MDRSp) has become multi-drug resistant. WHO lists it as the leading cause of child mortality globally. In developing countries, MDRSp causes 25-30% of child deaths. Many pharmaceutical companies take the financially more attractive approach of using existing antibiotics to develop new ones, but this risks meeting the same MDRSp resistance has built up. My project took a different approach, by inhibiting SpDHBP synthase, a key enzyme in MDRSp synthesis of riboflavin. Riboflavin biosynthesis is also absent in humans, reducing the chance of cytotoxicity. Furthermore, SpDBHP synthase is homological with many pathogens, so my results could apply broadly. I screened for inhibitors with the desirable attributes of specificity, viability, safety, and efficacy. A machine-learning algorithm was used to train a support vector machine on a benchmark set of small-molecule inhibitor starting points, identifying druggable regions. A 63-DDR/21-QDR Infiniband supercomputer was then used to build a 3-D pharmacophore to screen 22,723,923 compounds for specific hits. Molecular dynamics simulation and docking confirmed their viability, with quantified binding affinities. Receptor-ligand interactions and poses were constructed to reveal the biology behind the bindings. Clinical safety was predicted with ADME-Tox pharmacokinetics and CYP-mediated sites of epoxidation. Finally, structural similarity algorithms were used to predict pIC50 values to measure efficacy. As a result, I identified two putative inhibitors, with attractive binding affinities. Their predicted pIC50 potencies are as good as, if not superior to, those of current antibiotics. Going forward, the next step is to subject the inhibitors to biological assays.

Awards Won:

Second Award of $2,000