Exploiting Plasmid-Mediated Resistance: Discovery of Small-Molecule Inhibitors for the Artificial Activation of the Kid-Kis Toxin-Antitoxin System in Plasmid R1

Liao, Pinyu (School: Inglemoor High School)

Antibiotic resistance is one of the leading challenges to public health today, and a primary contributor to the rapid rise of resistance is plasmids, which facilitate the spread of multi-drug resistance genes within bacterial populations through horizontal gene transfer. Therefore, plasmids are critical targets to prevent the rapid spread of antibiotic resistance. In particular, low-copy number plasmids often contain toxin-antitoxin systems that act lethally when activated, so due to the role of toxin-antitoxin systems in facilitating internal cell death, the disruption of the protein-protein interaction between the toxin and the antitoxin may be a promising novel target for antibiotic development. Key interacting regions of the Kid-Kis toxin-antitoxin interaction were identified as binding sites for the de-novo design of small-molecule inhibitors using the webserver LEA3D. To predict the activity of novel inhibitors, a QSAR classification model was constructed with OCHEM using published experimental data on a related system. The most promising inhibitors with drug-like properties were molecules targeting the Glu66 to Arg72 region of the Kis antitoxin, as four out of five inhibitors were classified as active compounds. Calculations for Gibbs free energy (p=0.00000252) and pKd (p=0.000459) showed statistically significant binding affinity compared to control molecules with no known affinity for the target, representing a significant binding specificity towards the target interaction region. In the fight against antibiotic resistance, the design of small-molecule inhibitors targeting toxin-antitoxin systems may be an important discovery for the selective targeting of plasmid-mediated resistance through the application of internal mechanisms toward antibiotic development.

Awards Won:

Second Award of \$2,000 University of Arizona: Renewal Tuition Scholarship