

NON -TECHNICAL ABSTRACT:

The spread of multidrug resistant (MDR) bacteria is causing havoc in hospitals and communities globally because most antibiotics are no longer effective. The problem highlights an urgent unmet need for discovery of novel antibiotics. With over 14 years of antibiotic drug discovery experience both in industry and academia, the applicant has a long-term goal of finding novel antibiotics by studying bacterial essential and disease-causing processes. Previous funding from CSUPERB has enabled us to make great progress in discovery of antibacterial inhibitors targeting essential proteins. In this application, we propose to develop a complementary strategy of disabling disease-causing capabilities of MDR bacteria. We and our collaborators in Dr. Chen's lab at National Research Council of Canada (NRC) have identified a hospital outbreak isolate (LAC-4) of MDR *Acinetobacter baumannii* with extreme virulence in mice but have been hampered in further investigations by the lack of usable antibiotic selectable markers. We propose to develop a novel selection system based on a known essential gene *fabI* whose over-expression renders a cell resistant to triclosan, a potent biocide (but not an antibiotic) against most MDR *A. baumannii* strains. We will validate this selection system by using it to inactivate 5 genes suspected to be involved in LAC-4 virulence; mutants of LAC-4 engineered to lack a particular virulence factor will be tested for virulence in mice by Dr. Chen's group at NRC. If a virulence factor is found to contribute to LAC-4's unusual virulence, we will design and test, both in bacterial cells and in a mouse model, antisense peptide nucleic acids as potential therapeutics to disable the virulence factor. Antisense agents are effective tools of gene silencing and peptide nucleic acids maintain the sequence specificity of a nucleic acid but are more stable than the nucleic acids they mimic. Since the PI and Dr. Chen have been collaborating for a few years both in research and in student training, the proposed research will not only strengthen an already productive collaborative research and student training relationship, but also contribute significantly to the fight against MDR bacteria. Furthermore, the technologies and the patents to be filed for them should become the basis for commercialization of discovered therapeutics, contributing to the advancement of the California biotechnology industry and public health.