AMR
ANTIMICROBIAL
RESISTANCE
Interdisciplinary
Research Group

Research Projects in the SMART AMR IRG
(August 16, 2019)

1. **Biofilm-penetrating nanoparticles for drug delivery**
   Our research projects aim to overcome various challenges associated with antimicrobial resistance, and include the development of nanoparticle formulations engineered for *(a)* the co-delivery of synergistic antimicrobial polymer and drug combinations, *(b)* the controlled release and localization of polymyxins to improve bioavailability and reduce nephrotoxicity, and *(c)* the disruption and/or penetration of physical barriers that impede drug efficacy such as biofilm matrices and mucous.

   MIT Principal Investigator(s):
   Paula HAMMOND (Chemical Engineering)

   Singapore Co-Investigator(s):
   Mary CHAN (NTU, School of Chemical and Biomedical Engineering)

2. **Developing antibiotics and adjuvants that target RNA modification enzymes**
   All forms of RNA in all organisms are chemically modified on the nucleobase and sugar moieties, with these RNA modifications emerging as critical players in bacterial pathogenicity. Many bacterial pathogens respond to the stresses of infection and antibiotic treatment with a genetically-programmed entry into a slowly- or non-replicative state accompanied by the formation of a biofilm. Bacteria in this state are typically resistant or tolerant to a broad range of antibiotics. This project focuses on developing inhibitors of RNA-modifying enzymes to reverse this phenotypic drug resistance using an antibiotic development platform employing both structure-based design and screening-based discovery.

   MIT Principal Investigator(s):
   Peter DEDON (Biological Engineering)

   Singapore Co-Investigator(s):
   Julien LESCAR (NTU, School of Biological Sciences)
   Chuan Fa LIU (NTU, School of Biological Sciences)

3. Developing role of the epitranscriptome in bacterial biofilms and phenotypic antibiotic resistance

All forms of RNA in all organisms are chemically modified on the nucleobase and sugar moieties, with these RNA modifications emerging as critical players in bacterial pathogenicity. Many bacterial pathogens respond to the stresses of infection and antibiotic treatment with a genetically-programmed entry into a slowly- or non-replicative state accompanied by the formation of a biofilm in which they are resistant to a broad range of antibiotics. This project aims to understand how *E. fecalis* and *P. aeruginosa* reprogram of dozens of modified nucleosides in tRNAs and rRNAs leading to biofilm formation, persistence, and phenotypic drug resistance.

MIT Principal Investigator(s):
Peter DEDON (Biological Engineering)

Singapore Co-Investigator(s):
Kimberly KLINE (NTU, School of Biological Sciences)

4. Role of the epitranscriptome in antimicrobial resistance in malaria parasites

We recently discovered a system of translational control of gene expression in all living organisms, involving dozens of RNA modifications – the epitranscriptome – coupled with an alternative genetic code of synonymous codon usage. Our research project aims to define the role of the tRNA epitranscriptome in the emerging resistance of malaria parasites to artemisinin in SE Asia. Using wild-type and Kelch mutant *P. falciparum* strains, preliminary studies show that strains with Kelch-mediated resistance prefer a metabolically and translationally "less active" state when encountering artemisinin stress and respond by down-regulating tRNA modifications that would normally increase during the RBC phase of parasite development. This project will characterize these pathways to identify potential targets for resistance-reversing drugs.

MIT Principal Investigator(s):
Peter DEDON (Biological Engineering)

Singapore Co-Investigator(s):
Peter PREISER (NTU, School of Biological Sciences)

5. **Targeting gametocyte development as a strategy to prevent spread of drug resistant malaria parasite**

   Multidrug resistant malaria is rapidly developing in SE Asia, posing a very serious threat to the progress made in the last decade to control this parasitic disease. The transmission of drug resistant malaria parasites from human to human via the mosquito vector depends on the complete and effective development of the sexual gametocyte stage in the host. We have recently obtained evidence that the host cytokine, Tumor Necrosis Factor α (TNFα), promotes gametogenesis by enhancing the expression of the parasite protein, PfAP2-G, which is the master regulator of gametogenesis. A key outcome of this project would be to identify and validate a set of host as well as parasite proteins that are essential for gametocyte induction that can be potential targets for therapeutic intervention to prevent the spread of drug resistance.

   MIT Principal Investigator(s):
   Jianzhu CHEN (Biology)

   Singapore Co-Investigator(s):
   Peter PREISER (NTU, School of Biological Sciences)

6. **Overcoming microbial drug resistance: Adjuvant therapeutics that enhance host immunity**

   With the current rise of resistance to antimicrobial agents, new methods of treatment of bacterial infections are needed. Peripheral macrophages can be polarized into M1 and M2 states. M1 macrophages produce large amounts of proinflammatory cytokines, and are implicated in the killing of pathogens and tumour cells. M2 macrophages moderate the inflammatory response, and can promote angiogenesis and tissue remodeling in cancer. This project aims to discover novel uses for drugs as M1 polarizing compounds, thus allowing novel combination therapies similar to cancer treatment.

   MIT Principal Investigator(s):
   Jianzhu CHEN (Biology)

   Singapore Co-Investigator(s):
   Kimberly KLINE (NTU, School of Biological Sciences)