Antimicrobial Resistance Training Program in the Texas Medical Center (AMR-TPT)

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https://www.gulfcoastconsortia.org/home/training/amr-tpt/

Meet the Trainees

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Appointment: July 1, 2024 – June 30, 2025

Primary Mentor: William R. Miller, MD, Department of Infectious Diseases, Houston Methodist Research Institute

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Elucidating the relationship between bacterial iron utilization and cefiderocol resistance

*Pseudomonas aeruginosa* is a Gram-negative, nosocomial pathogen that causes life-threatening acute infections in intensive care units and debilitating chronic infections in those with cystic fibrosis. Unfortunately, this pathogen is becoming increasingly difficult to treat due to the emergence of multidrug-resistant strains. This emergence can be partially attributed to intrinsic mechanisms of resistance such as loss of outer membrane porins, several multidrug efflux pump systems, and a chromosomal cephalosporinase (PDC). Recently, the FDA approved a new cephalosporin antibiotic, cefiderocol, for the treatment of bacterial pneumonia including *P. aeruginosa*. This drug utilizes a chlorocatechol moiety frequently found in bacterial siderophores. Cefiderocol chelates ferric iron after which it is imported via *P. aeruginosa* xenosiderophore receptors such as PirA and PiuA. These receptors give *P. aeruginosa* an advantage over competing pathogens by allowing the bacterium to cheat off other species’ siderophores and are therefore highly expressed under iron-restrictive host conditions. However, multiple studies have reported clinical failure in using cefiderocol for pseudomonal infections and observed nonsusceptibility in strains that have never encountered the drug before. Using whole genome sequencing, we have identified major pathways associated with the emergence of cefiderocol resistance among *P. aeruginosa* clinical isolates. These include the TonB-dependent siderophore receptors (e.g.: *piuA*, *pirA*) and their transcriptional regulators (e.g.: *pirR*), regulators of PDC overexpression (e.g.: *ampR*), and regulators of multidrug efflux pumps (e.g.: *cpxS*). The specific phenotype of these pathways and their relative contribution to resistance is incompletely understood. Through this project we aim to study the genetic and environmental factors that contribute to *P. aeruginosa* cefiderocol resistance.
Repurposing Non-Antibiotic Based Therapeutics to Combat Multi Antibiotic Resistant Bacteria

Global deaths due to antibiotic resistance has been estimated at 700,000 per year. Without effective antibiotics, the risk of surgical procedures-associated deaths increases dramatically. The discovery of new antibiotics in the 21st century is minimal at best. Thus, the goal of this project is to identify FDA-approved non-antibiotic drugs that can be effective against antibiotic resistant bacterial infections. We have identified amoxapine, an antidepressant, that was able to effectively treat bacterial infections. We originally showed this efficacy using models of pneumonic plague but have subsequently shown efficacy of amoxapine in animal models of Clostridioides difficile associated diarrhea as well as Klebsiella pneumoniae associated respiratory infections and sepsis. However, we have not identified the specific mechanism(s) by which amoxapine is working although we have ruled out the possibility of amoxapine directly killing bacteria. Preliminary studies suggest that amoxapine is working by modulating the innate immune system through several possible mechanisms including production of antimicrobial peptides, induction of autophagy or the inflammasome, or by modulating host microbiota. This project focuses on identifying how amoxapine treatment can induce autophagy and activation of the inflammasome, both parts of the innate immune system. By identifying how amoxapine is working to combat antibiotic resistant infections, we can bring this treatment closer to the clinic and help identify new drugs that might act by similar mechanisms to further combat antibiotic resistant bacteria by acting on the host which is much less likely to result in an increase in antibiotic resistance than by developing new antibiotics.

Basis of Commensal Bacillota Resistance to a Novel PolC-type DNA Polymerase III Inhibitor, Ibezapolstat, and the “Narrower” Spectrum of Activity Towards Clostridioides difficile

The human gut microbiome plays an important role in the prevention and control of the leading human gut pathobiont, Clostridioides difficile. Ibezapolstat is a novel Gram-positive selective spectrum (GPSS) antibiotic for the treatment of C. difficile infection (CDI) through targeting the PolC-type DNA Polymerase III (PolC), the catalytic subunit of bacterial DNA replication leading-strand synthesis. We find PolC an attractive target for microbiome-sparing, CDI-antibacterial development for polC evolutionary restriction to Bacillota, and absence from Actinomycetota, Bacteroidota, or Pseudomonadota, the other dominant human gut bacterial phyla. However, in clinical trials of ibezapolstat for CDI, we observed an increased abundance of beneficial Bacillota sub-taxa known to further prevent CDI that were curiously ibezapolstat non-susceptible. Hence, this project aims to elucidate the determinants of Bacillota intra-phylum differences in ibezapolstat non-susceptibility for its “narrower” spectrum of activity towards Clostridioides difficile.
Rapid molecular diagnostic of microbiome dysbiosis to predict individual risk of Clostridioides difficile infection.

Clostridioides difficile poses a significant infectious disease threat as an antibiotic-resistant pathogen, particularly in healthcare settings where it causes severe gastrointestinal illness and burdens healthcare systems. However, because this bacterium commonly colonizes the intestine asymptomatically, diagnosing pathogen-associated disease remains challenging due to the lack of a definitive test. To address this deficiency in the field we are working with bioMerieux to develop a conceptually different approach to diagnostic testing capable of identifying C. difficile infection based on distinct microbiome signatures identified in susceptible patients. This rapid multiplex PCR test could revolutionize patient care by enabling quicker treatment decisions and reducing pathogen spread in hospitals. My project goal is to develop and validate this point-of-care assay with samples from patients clinically diagnosed with C. difficile infection. Once validated, I'll proceed to evaluate its effectiveness in prospective studies. Additionally, I will craft user-friendly software to simplify result interpretation for healthcare professionals. Our efforts mark a prototypical shift in diagnostics to the battle against C. difficile infections.

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Appointment: February 1, 2024 – January 31, 2025
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