Texas Medical Center Training Program in Antimicrobial Resistance (TPAMR)

Funded by the National Institute of Allergy and Infectious Diseases (NIAID), T32 AI141349

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Program Co-Directors: **Kevin Garey**, Pharm D, Professor and Chair, Department of Pharmacy Practice and Translational Research, University of Houston; and **Lynn Zechiedrich**, PhD, Professor, Molecular Virology and Microbiology, Baylor College of Medicine

https://www.gulfcoastconsortia.org/home/training/tpamr/

Meet the Trainees

Paul Kilgore, PhD
Department of Microbiology and Immunology, University of Texas Medical Branch
Appointment: August 1, 2023 – July 31, 2024
Primary Mentor: Dr. Ashok Chopra, Microbiology and Immunology, University of Texas Medical Branch
Co-Mentor: Dr. Sara Dann, Internal Medicine, University of Texas Medical Branch
Co-Mentor: Dr. Sunhee Lee, Microbiology and Immunology, University of Texas Medical Branch
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.

Jacob McPherson, PharmD
Department of Pharmacy Practice and Translation Research, University of Houston
Appointment: July 1, 2023 – June 30, 2024
Primary Mentor: Dr. Kevin Garey, Pharmacy Practice and Translation Research, University of Houston
Co-Mentor: Dr. Julian Hurdle, Center for Inflammatory Diseases, IBT, Texas A&M University

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.

William Shropshire, PhD
Department of Infectious Diseases & Infection Control, University of Texas MD Anderson Cancer Center
Appointment: July 1, 2022 – June 30, 2024
Primary Mentor: Dr. Samuel A. Shelburne, Department of Infectious Diseases & Infection Control, University of Texas MD Anderson Cancer Center
Co-Mentor: Dr. Awdhesh Kalia, Health Professions, Division Academic Affairs, University of Texas MD Anderson Cancer Center
Co-Mentor: Dr. Yousif Shamoo, BioSciences, Rice University

Elucidating Molecular Mechanisms Underlying Successful Adaptation to Carbapenem Antimicrobials in High Risk Carbapenem Resistant Escherichia coli Lineages

Escherichia coli remains a leading cause of invasive, nosocomial infections. The most challenging *E. coli* infections are those that develop antimicrobial resistance to the class of antibiotics known as carbapenems, which are considered 'treatments of last resort'. There is much active research into *E. coli* strains which have already developed carbapenem resistance. Nevertheless, there currently is limited understanding of how particular *E. coli* lineages are able to initially adapt to antibiotic exposures and become tolerant to the drug. We hypothesize that there are select populations of *E. coli* which can develop a 'pre-resistant' phase through potentiating genomic and transcriptomic changes that increase the likelihood of developing an increasingly antimicrobial resistant phenotype. Using extraintestinal, uropathogenic *E. coli* sequence type 131 (ST131) as a model strain, we plan to characterize these changes through experimental evolution platforms. To confirm clinical significance, we will compare these experimental results with a clinical arm of our study, to determine which common pre-resistant factors persist across these high-risk sequence types that are able to develop carbapenem resistance. The goal of this research is to provide a platform for novel interventions to prevent *E. coli* and other important bacterial pathogens from developing carbapenem resistance.