

Texas Medical Center Training Program in Antimicrobial Resistance (TPAMR)

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Program Directors: **Anthony Flores**, MD, PhD, Associate Professor, Pediatrics, Infectious Disease, The University of Texas Health Science Center at Houston; and **Cesar Arias**, MD, PhD, Professor, Internal Medicine, Infectious Disease, Houston Methodist Research Institute

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



Stephanie Egge, MD

Division of Infectious Diseases, Houston Methodist Research Institute

Appointment: 7/1/2022-6/30/2023

Primary Mentor: Dr. William R. Miller, Division of Infectious Diseases, Houston Methodist Research Institute

Co-Mentor: Dr. Dimitrios Kontoyiannis, Department of Infectious Diseases, Infection Control, and Employee Health, University of Texas MD Anderson Cancer Center

Co-Mentor: Dr. Barbara Trautner, Department of Surgery, Baylor College of Medicine

Emergence of TonB-dependent receptor mediated cefiderocol resistance among multidrug-resistant (MDR) Pseudomonas aeruginosa clinical isolates

Carbapenem-resistant (CR) *Pseudomonas aeruginosa* is a challenging nosocomial pathogen with limited therapeutic options. The novel iron siderophore antibiotic cefiderocol circumvents most resistance mechanisms in CR-*P. aeruginosa* by using special proteins called TonB Dependent Receptors (TBDR) to enter the bacterial cell. Our work has shown that mutations in the pathways that control expression of these TBDR genes appear in up to 20% of CR-*P. aeruginosa* isolates, and may lead to the emergence of resistance on exposure to cefiderocol. The aim of my project is to characterize the frequency with which these mutations occur in clinical isolates of PA, and characterize their effect on cefiderocol susceptibility and the emergence of resistance. This information can be used to design stewardship and treatment strategies to guide optimal use of cefiderocol.



Taryn Eubank, PharmD

Pharmacy Practice and Translational Research, College of Pharmacy, University of Houston; Infectious Disease, Houston Methodist Research Institute

Appointment: July 1, 2021 – June 30, 2023

Primary Mentor: Dr. Kevin Garey, Department of Pharmacy Practice and Translational Research, College of Pharmacy, University of Houston

Co-Mentor: Dr. Barbara Trautner, Department of Medicine, Baylor College of Medicine

Co-Mentor: Dr. Blake Hanson, Department of Epidemiology, School of Public Health, The University of Texas Health Science Center at Houston

Co-Mentor: Dr. Julian Hurdle, Center for Infectious and Inflammatory Diseases, IBT, Texas A&M University

Emerging Antimicrobial Resistance in *Clostridioides difficile*

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States with 223,900 estimated cases and 12,000+ deaths. *C. difficile* is inherently resistant to most antibiotic classes although the most commonly used antibiotic to treat CDI, vancomycin, is generally considered pan-susceptible. Recently, a SNP change in the *vanG* gene cluster was shown to decrease vancomycin susceptibility. This study aims to explore the molecular epidemiology of isolates with decreased vancomycin susceptibility with a focus on the *vanG* gene cluster, assess clinical outcomes associated with these reduced susceptibility strains, and develop a model to understand the pharmacokinetic-pharmacodynamic relationship of this emerging resistance mechanism.



Kara Hood, PhD

Department of Internal Medicine, Infectious Disease, Houston Methodist Research Institute

Appointment: October 1, 2021 – September 30, 2022

Primary Mentor: Dr. Cesar A. Arias, Internal Medicine, Infectious Disease, Houston Methodist

Research Institute

Co-Mentor: Dr. Anna Konovalova, Microbiology and Molecular Genetics, UT Health Science Center at Houston

Co-Mentor: Dr. Yousif Shamoo, BioSciences, Rice University

Molecular Characterization of Transmembrane Proteins of the Lia System Involved in Daptomycin Resistance in Enterococci

Enterococci are gram-positive commensals that can cause life-threatening bacteremia in immunocompromised patients. Susceptible infections are treated with vancomycin, but the rise of vancomycin-resistant enterococci (VRE) is a serious threat to public health. VRE can be treated with daptomycin but the development of daptomycin resistance is often rapid and dramatic; therefore, resistance mechanisms must be understood to circumvent their development. Mutations that confer daptomycin resistance in *Enterococcus faecalis* are often found in the three-component signaling system LiaFSR. LiaFSR regulates the organization of the lipid membrane to divert daptomycin away from the cell septum and prevent disruption of cell division. This project aims to directly measure LiaF's activation of LiaS, the putative interaction LiaF with its proposed inhibitor LiaX, and how other downstream proteins mediate the cell's membrane remodeling response once the pathway has been triggered.



William Shropshire, PhD

Department of Infectious Diseases & Infection Control, University of Texas MD Anderson Cancer Center

Appointment: 7/1/2022-6/30/2023

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.

The TPAMR program is administered by the:



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The GCC is a collaboration of:
*Baylor College of Medicine, Rice University, University of Houston,
University of Texas Health Science Center at Houston
University of Texas Medical Branch at Galveston
University of Texas MD Anderson Cancer Center
Institute of Biosciences and Technology of Texas A&M University
Houston Methodist Research Institute*