BIOGRAPHICAL SKETCH

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NAME: Miller, William

eRA COMMONS USER NAME (credential, e.g., agency login): wrmiller1

POSITION TITLE: Assistant Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Texas A&M University, Biochemistry, College Station, Texas	B.Sc.	05/2005	Biochemistry
McGovern Medical School at UTHealth Houston, Houston, Texas	M.D.	05/2010	Medicine
McGovern Medical School at UTHealth Houston, Houston, Texas	Resident	06/2014	Internal Medicine/ Pediatrics
University of Texas McGovern Medical School and MD Anderson Cancer Center, Houston, Texas	Fellow	06/2017	Infectious Diseases

A. Personal Statement

My work has focused on understanding the mechanisms of antibiotic resistance (AMR) in healthcare-associated pathogens, with the aim of translating this knowledge to impact patient care at the bedside. Many aspects of my research are driven by the challenges faced in the clinical practice of infectious diseases, specifically identifying and treating bacteria with new or emerging mechanisms of resistance. During my fellowship training at the UTHealth McGovern Medical School and MD Anderson Cancer Center, I gained experience in both the clinical and microbiological aspects of AMR. I completed a third fellowship year on the advanced research track focusing on basic science and successfully competed for an NIH/NIAID K08 Career Development Award. This award allowed me to expand my skill set to include a genomic approach to identifying the determinants of resistance and resulted in publications describing several novel mechanisms of resistance in healthcare-associated pathogens, including Enterococci and carbapenem-resistant *Pseudomonas aeruginosa*. This work led to my current interest in the impact of iron transport and heteroresistance on cefiderocol susceptibility in *P. aeruginosa*, and the defense of the enterococcal cell envelope from antibiotics and antimicrobial peptides. In October of 2021, I joined the Division of Infectious Diseases at Houston Methodist Hospital, with robust institutional support for building a leading research program focused on AMR. My current position with the Center for Infectious Diseases at the Houston Methodist Research Institute provides an excellent environment to further our understanding of emerging mechanisms of resistance to antibiotics. My goal is to continue my growth as a physician-scientist and pioneer new studies at the intersection of our mechanistic understanding of AMR and clinical practice.

Relevant publications:

1. **Miller WR**, Arias CA. ESKAPE pathogens: antimicrobial resistance, epidemiology, clinical impact and therapeutics. Nat Rev Microbiol. 2024 Oct;22(10):598-616. PMID: 38831030.
2. Egge SL, Rizvi SA, Simar SR, Alcalde M, Martinez JRW, Hanson BM, Dinh AQ, Baptista RP, Tran TT, Shelburne SA, Munita JM, Arias CA, Hakki M, **Miller WR**. Cefiderocol heteroresistance associated with mutations in TonB-dependent receptor genes in *Pseudomonas aeruginosa* of clinical origin. Antimicrob Agents Chemother. 2024 Aug 7;68(8):e0012724. PMCID: PMC11304687.
3. **Miller WR**, Nguyen A, Singh KV, Rizvi S, Khan A, Erickson SG, Egge SL, Cruz M, Dinh AQ, Diaz L, Thornton PC, Zhang R, Xu L, Garsin DA, Shamoo Y, Arias CA. Membrane Lipids Augment Cell

Envelope Stress Signaling via the MadRS System to Defend Against Antimicrobial Peptides and Antibiotics in *Enterococcus faecalis*. J Infect Dis. 2024 Apr 5. PMCID: PMC11841629..

4. Streling AP, Al Obaidi MM, Lainhart WD, Zangeneh T, Khan A, Dinh AQ, Hanson B, Arias CA, **Miller WR**. Evolution of Cefiderocol Non-Susceptibility in *Pseudomonas aeruginosa* in a Patient Without Previous Exposure to the Antibiotic. Clin Infect Dis. 2021 Dec 6;73(11):e4472-e4474. PMCID: PMC8825772.

Ongoing and recently completed projects that I would like to highlight include:

R21 AI190338
Miller (PI)
03/01/2025-2/28/2027
Mechanisms of Resistance and Clinical Outcomes of non-Carbapenemase Producing Carbapenem-Resistant *Klebsiella pneumoniae* Infections

R21 AI175821
Miller (PI)
01/20/2023-12/31/2024
Emergence of TonB-dependent receptor mediated cefiderocol resistance among multidrug-resistant (MDR) *Pseudomonas aeruginosa* clinical isolates

K08 AI135093
Miller (PI)
05/03/2018-04/30/2023
Role of YxdJK and DAK in the Enterococcal Envelope Stress Response

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2025 -	Advisor, Subcommittee on Antimicrobial Susceptibility Testing, Clinical and Laboratory Standards Institute (CLSI)
2024 -	Co-chair, Cefepime/Zidebactam Breakpoints Ad-Hoc Working Group, CLSI
2023 - 2023	Co-Chair, Sulbactam/Durlobactam Breakpoints Ad-Hoc Working Group, CLSI
2021 -	Assistant Professor of Medicine, Academic Institute, Internal Medicine, Infectious Diseases, Houston Methodist Hospital, Houston, TX
2021 -	Member, Stenotrophomonas Antimicrobial Susceptibility Breakpoints Ad-Hoc Working Group, CLSI
2021 -	Editorial Board Member, Antimicrobial Agents and Chemotherapy
2019 -	Member, Cefazolin High Inoculum Ad-Hoc Working Group, CLSI
2017 - 2021	Assistant Professor, Division of Infectious Diseases, UTHealth Houston, TX
2015 - 2016	Chief Fellow, Infectious Disease Fellowship Program, UTHealth Houston, TX
2013 - 2014	Chief Resident, Combined Internal Medicine-Pediatrics Residency Program, UTHealth Houston, TX

Honors

2023	Fellow, Infectious Diseases Society of America (IDSA)
2017 - 2020	Dean's Teaching Excellence Award, McGovern Medical School at UTHealth Houston
2017	Young Investigator Award in Infectious Diseases, IDSA Education and Research Foundation (ERF)
2015	Robert C. Moellering Award for Excellence in Antimicrobial Resistance Trainee Travel Grant, IDSA-ERF
2013	Fellows Program on Careers in Academic Medicine, National Institutes of Health, National Medical Association

2009	Alpha Omega Alpha Medical Honor Society, Delta Chapter of Texas, McGovern Medical School at UTHealth Houston
2005	Department of Biochemistry and Biophysics Award for Undergraduate Research, Texas A&M University
2005	Phi Beta Kappa National Honor Society, Kappa of Texas Chapter, Texas A&M University
1998	Eagle Scout, Boy Scouts of America

C. Contributions to Science

1. **Enterococcal cell envelope stress response to antimicrobial peptides (AMP) and AMP-like antibiotics.** Daptomycin (DAP) is a lipopeptide antibiotic with features similar to AMPs of the human immune system. DAP has become a front-line antibiotic for the treatment of invasive infections due to vancomycin-resistant enterococci; however, serious concerns regarding resistance arising upon therapy remain. My work identified two novel pathways leading to changes in susceptibility to DAP and innate immune peptides in Enterococci. We characterized the regulon of the MadRS network (membrane antimicrobial peptide defense, previously YxdJK), providing evidence that this system decreases DAP susceptibility via upregulation of the *dltABCD* genes. Importantly, we identified a new operon associated with bacterial survival in the presence of the innate immune AMPs LL-37 and human β-defensin 3. Our work also characterized *dak*, a gene encoding a fatty acid kinase associated with the metabolism of exogenous fatty acids. Loss of function *dak* mutants led to changes in membrane fluidity, with an alteration of the membrane lipid species and phospholipid acyl-tail saturation. We demonstrated that these changes are associated with increased formation of biofilm and result in an impaired growth phenotype characterized by abnormal cell division septal synthesis.

    a. Nguyen AH, Tran TT, Panesso D, Hood KS, Polamraju V, Zhang R, Khan A, **Miller WR**, Mileykovskaya E, Shamoo Y, Xu L, Vitrac H, Arias CA. Molecular basis of cell membrane adaptation in daptomycin-resistant *Enterococcus faecalis*. JCI Insight. 2024 Nov 22;9(22). PMCID: PMC11601895.

    b. **Miller WR**, Nguyen A, Singh KV, Rizvi S, Khan A, Erickson SG, Egge SL, Cruz M, Dinh AQ, Diaz L, Thornton PC, Zhang R, Xu L, Garsin DA, Shamoo Y, Arias CA. Membrane Lipids Augment Cell Envelope Stress Signaling via the MadRS System to Defend Against Antimicrobial Peptides and Antibiotics in *Enterococcus faecalis*. J Infect Dis. 2024 Apr 5. PMCID: PMC11841629..

    c. Prater AG, Mehta HH, Beabout K, Supandy A, **Miller WR**, Tran TT, Arias CA, Shamoo Y. Daptomycin Resistance in *Enterococcus faecium* Can Be Delayed by Disruption of the LiaFSR Stress Response Pathway. Antimicrob Agents Chemother. 2021 Mar 18;65(4). PMCID: PMC8097453.

    d. **Miller WR**, Tran TT, Diaz L, Rios R, Khan A, Reyes J, Prater AG, Panesso D, Shamoo Y, Arias CA. LiaR-independent pathways to daptomycin resistance in *Enterococcus faecalis* reveal a multilayer defense against cell envelope antibiotics. Mol Microbiol. 2019 Mar;111(3):811-824. PMCID: PMC6417935.

2. **Mechanisms of cefiderocol resistance in *Pseudomonas aeruginosa*.** *P. aeruginosa* is an important opportunistic pathogen and a leading cause of healthcare-associated infections. My lab has characterized several novel mechanisms of resistance to the new siderophore cephalosporin cefiderocol in clinical isolates of *P. aeruginosa* with direct therapeutic implications. We described the first clinical case of the emergence of resistance to cefiderocol in a clinical *P. aeruginosa* isolate in the absence of exposure to the drug. This phenotype was associated with mutations in genes encoding TonB-dependent iron import channels and the intrinsic pseudomonal cephalosporinase. We linked heteroresistance, or the presence of antibiotic-resistant subpopulations in an otherwise susceptible background, to changes in TonB-dependent receptors in clinical isolates from before the introduction of cefiderocol. Further, in collaboration with Dr. Vincent Tam, we described the emergence of cefiderocol resistance from a heteroresistant isolate in the clinical setting and explored alternative iron-depleted media types for use in studying cefiderocol susceptibility. My lab is actively investigating the specific genetic changes that underlie the cefiderocol heteroresistance phenotype and strategies to prevent the emergence of resistance to cefiderocol on therapy.

    a. Egge SL, Rizvi SA, Simar SR, Alcalde M, Martinez JRW, Hanson BM, Dinh AQ, Baptista RP, Tran TT, Shelburne SA, Munita JM, Arias CA, Hakki M, **Miller WR**. Cefiderocol heteroresistance associated with

mutations in TonB-dependent receptor genes in *Pseudomonas aeruginosa* of clinical origin. Antimicrob Agents Chemother. 2024 Aug 7;68(8):e0012724. PMCID: PMC11304687.

b. Eales BM, Smith JE, Pouya N, Teran NS, **Miller WR**, Tam VH. Alternative iron-depleted media for cefiderocol susceptibility testing. Int J Antimicrob Agents. 2024 Jul;64(1):107193. PMCID: PMC11789364.

c. Teran N, Egge SL, Phe K, Baptista RP, Tam VH, **Miller WR**. The emergence of cefiderocol resistance in *Pseudomonas aeruginosa* from a heteroresistant isolate during prolonged therapy. Antimicrob Agents Chemother. 2024 Jan 10;68(1):e0100923. PMCID: PMC10777823.

d. Streling AP, Al Obaidi MM, Lainhart WD, Zangeneh T, Khan A, Dinh AQ, Hanson B, Arias CA, **Miller WR**. Evolution of Cefiderocol Non-Susceptibility in *Pseudomonas aeruginosa* in a Patient Without Previous Exposure to the Antibiotic. Clin Infect Dis. 2021 Dec 6;73(11):e4472-e4474. PMCID: PMC8825772.

3. **Epidemiology and treatment of multidrug-resistant Gram-negative infections.** Infections due to multidrug-resistant Gram-negative organisms are an increasingly common clinical challenge. My lab has actively participated in several ongoing collaborative studies aimed at investigating the genomic epidemiology and use of novel antibiotics in the treatment of infections due to multidrug-resistant organisms. We described a novel arrangement of Guiana Extended Spectrum β-lactamases in Sequence Type 309 *P. aeruginosa* that led to resistance to carbapenems, ceftolozane/tazobactam, and ceftazidime/avibactam, but retained susceptibility to the combination of ceftazidime/avibactam plus aztreonam. Using genomic surveillance of a longitudinal collection of carbapenem-resistant *P. aeruginosa*, we characterized the changes in the population over time, including the increasing acquisition of exogenous β-lactamases. In association with Dr. Micah Bhatti at MD Anderson Cancer Center, we have also investigated several methods to assess for synergy in combination antibiotic therapy for *P. aeruginosa* and carbapenem-resistant Enterobacterales in the clinical microbiology laboratory.

   a. Khan A, Tran TT, Rios R, Hanson B, Shropshire WC, Sun Z, Diaz L, Dinh AQ, Wanger A, Ostrosky-Zeichner L, Palzkill T, Arias CA, **Miller WR**. Extensively Drug-Resistant *Pseudomonas aeruginosa* ST309 Harboring Tandem Guiana Extended Spectrum β-Lactamase Enzymes: A Newly Emerging Threat in the United States. Open Forum Infect Dis. 2019 Jul;6(7):ofz273. PMCID: PMC6602888.

   b. Khan A, Erickson SG, Pettaway C, Arias CA, **Miller WR**, Bhatti MM. Evaluation of Susceptibility Testing Methods for Aztreonam and Ceftazidime-Avibactam Combination Therapy on Extensively Drug-Resistant Gram-Negative Organisms. Antimicrob Agents Chemother. 2021 Oct 18;65(11):e0084621. PMCID: PMC8522751.

   c. Sakurai A, Dinh AQ, Hanson BM, Shropshire WC, Rizvi SA, Rydell K, Tran TT, Wanger A, Arias CA, **Miller WR**. Evolving landscape of carbapenem-resistant *Pseudomonas aeruginosa* at a single centre in the USA. JAC Antimicrob Resist. 2023 Jun;5(3):dlad070. PMCID: PMC10243771.

   d. Shields RK, Abbo LM, Ackley R, Aitken SL, Albrecht B, Babiker A, Burgoon R, Cifuentes R, Claeys KC, Curry BN, DeSear KE, Gallagher JC, Golnabi EY, Gross AE, Hand J, Heil EL, Hornback KM, Kaye KS, Khuu TV, Klatt ME, Kline EG, Kubat RC, Kufel WD, Lee JH, Lepak AJ, Lim A, Ludwig JM, Macdougall C, Majumdar A, Mathers AJ, McCreary EK, **Miller WR**, Monogue ML, Moore WJ, Olson S, Oxer J, Pearson JC, Pham C, Pinargote P, Polk C, Satlin MJ, Satola SW, Shah S, Tamma PD, Tran TT, van Duin D, VanNatta M, Vega A, Venugopalan V, Veve MP, Wangchinda W, Witt LS, Wu JY, Pogue JM. Effectiveness of ceftazidime-avibactam versus ceftolozane-tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections in the USA (CACTUS): a multicentre, retrospective, observational study. Lancet Infect Dis. 2024 Dec 16;. doi: 10.1016/S1473-3099(24)00648-0. [Epub ahead of print] PMID: 39701120.

4. **The cefazolin inoculum effect in Methicillin-susceptible *Staphylococcus aureus* (MSSA).** The cefazolin inoculum effect is defined by an increase in the minimum inhibitory concentration (MIC) of cefazolin (typically to ≥16 μg/mL) when susceptibility testing is performed at high inoculum (≥10^7 CFU/mL) as opposed to standard inoculum (10^5 CFU/mL). This has implications for the treatment of complicated MSSA infections with a high burden of organisms or a lack of source control. Our work, in conjunction with Dr. Cesar Arias and Dr. Barbara Murray, suggests that the presence of the effect is associated with poor clinical outcomes in patients treated with cefazolin or cephalothin, and the use of a β-lactamase inhibitor is

sufficient to protect cefazolin from hydrolysis in a rat model of endocarditis. Current work is aimed at adapting diagnostic testing methods for use in the clinical lab and examining the impact of the effect in patients treated with cefazolin versus anti-staphylococcal penicillins.

a. Dingle TC, Gamage D, Gomez-Villegas S, Hanson BM, Reyes J, Abbott A, Burnham CD, Dien Bard J, Fritz S, **Miller WR**, Westblade LF, Zimmer B, Arias CA, Butler-Wu S. Prevalence and Characterization of the Cefazolin Inoculum Effect in North American Methicillin-Susceptible *Staphylococcus aureus* Isolates. J Clin Microbiol. 2022 Jul 20;60(7):e0249521. PMCID: PMC9297818.
b. **Miller WR**, Singh KV, Arias CA, Murray BE. Adjunctive Clavulanic Acid Abolishes the Cefazolin Inoculum Effect in an Experimental Rat Model of Methicillin-Sensitive *Staphylococcus aureus* Endocarditis. Antimicrob Agents Chemother. 2018 Nov;62(11) PMCID: PMC6201062.
c. **Miller WR**, Seas C, Carvajal LP, Diaz L, Echeverri AM, Ferro C, Rios R, Porras P, Luna C, Gotuzzo E, Munita JM, Nannini E, Carcamo C, Reyes J, Arias CA. The Cefazolin Inoculum Effect Is Associated With Increased Mortality in Methicillin-Susceptible *Staphylococcus aureus* Bacteremia. Open Forum Infect Dis. 2018 Jun 1;5(6):ofy123. PMCID: PMC6007512.
d. Rincon S, Carvajal LP, Gomez-Villegas SI, Echeverri AM, Rios R, Dinh A, Pedroza C, Ordoñez KM, Nannini E, Sun Z, Fowler VG, Murray BE, **Miller WR**, Palzkill T, Diaz L, Arias CA, Reyes J. A Test for the Rapid Detection of the Cefazolin Inoculum Effect in Methicillin-Susceptible *Staphylococcus aureus*. J Clin Microbiol. 2021 Mar 19;59(4). PMCID: PMC8092731.

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