

The University of Tennessee Health Science Center
St. Jude Children's Research Hospital
Le Bonheur Children's Hospital



ANNUAL REPORT 2018-2019

The Center for Pediatric Experimental Therapeutics





The Center for Pediatric Experimental Therapeutics
881 Madison Ave.
Memphis, TN 38163
901-448-1493 Administrative Office
901-448-7217 Director, P. David Rogers

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This is a publication of:
The University of Tennessee
The Center for Pediatric Experimental Therapeutics.

Randy Boyd
President

Steve Schwab
Chancellor, UTHSC

P. David Rogers
Director

<https://www.uthsc.edu/pharmacy/dcpts/cpet.php>

Center for Pediatric Experimental Therapeutics

Mission Statement

The mission of the Center for Pediatric Experimental Therapeutics (CPET) is the integration of basic, applied, and clinical sciences towards the development of new treatments for childhood diseases.

Benchmarks for success include:

(1) the number and quality of publications, (2) the quantity and quality of competitive funding to support Center activities, (3) the training opportunities for students, residents and postdoctoral fellows, and (4) the educational offerings by Center investigators to the scientific community. Specific goals:

Education

1. To improve the quality of education by coordinating existing resources and by attracting outstanding nationally and internationally recognized faculty in pediatric experimental therapeutics.
2. To disseminate information resulting from Center research to health professionals and citizens in Tennessee, the Mid South region, and Nation through publications, presentations, participation in professional organizations, and continuing education.
3. To establish the Center as an internationally recognized resource for educational and research training in the area of pediatric experimental therapeutics attracting the very best students and postdoctoral trainees to Tennessee.

Research

1. To coordinate, integrate and enhance pediatric experimental therapeutics research programs, particularly in microbial pathogenesis and in new drug development, to yield highly focused and competitive research.
2. To integrate existing basic research programs and resources, including the Molecular Resource Center (MRC); Regional Bio-containment Laboratory (RBL); other UTHSC COREs; the Departments of Clinical Pharmacy and Translational Science, Microbiology, Immunology, and Biochemistry, and Pediatrics; and St. Jude Children's Research Hospital.
3. To establish the Center as an internationally recognized resources in pediatric experimental therapeutics.

Clinical Care

1. To coordinate pediatric experimental therapeutics research across the Health Science Center, the University, and State of Tennessee into a collaborative program functioning as one program, improving treatments for serious childhood diseases.
2. To recruit talented clinicians of national importance to the Center to broaden the specialized expertise in treating pediatric diseases, particularly infectious diseases and cancer.
3. To serve as a national and international resource for defining optimal pediatric treatment strategies.

Executive Summary

The Center for Pediatric Experimental Therapeutics (CPET) is the only state supported Center of Excellence that includes in its primary mission the health care and treatment of citizens of Tennessee. The University of Tennessee, Health Science Center, has a primary mission to improve human health through education, research, outreach and patient care. The CPET is an example of this effort. The University serves to coalesce programs in affiliated clinical institutions to form a dynamic Center focused on advancing the use of medication in children. The University brings together St. Jude Children's Research Hospital and Le Bonheur Children's Medical Center as both have clinical and laboratory faculty members who are internationally recognized as leaders in their field.

Since receiving accomplished center status in September of 1989, the CPET has not relented in its quest to remain one of the nation's premier centers for the improvement of therapeutics in children. Faculty comprising the CPET have sustained a high level of research productivity during the past year, having authored 75 peer reviewed articles in leading medical or scientific journals. In addition to their original research publications, CPET faculty authored 5 books or book chapters.

The CPET is dedicated to better understanding of microbial pathogenesis and antiinfectives in children. During the past year, CPET investigators have made substantial progress in their research programs related to improving antiinfective therapeutics in children, through a more complete understanding of infectious diseases and microbial pathogenesis, anti-infective pharmacotherapy, and antimicrobial resistance. Productivity is evidenced by the enclosed list of publications. These papers report the results of studies that will ultimately lead to improvements in the treatment of childhood infectious diseases. These studies are built on a substantial number of laboratory-based investigations that CPET faculty members are undertaking to define the biochemical and molecular basis for specific pediatric infectious diseases and to discover novel therapeutic targets and therapeutic agents for their treatment.

In the past academic year, CPET faculty disclosed \$6 million in NIH grants. This is at a time when NIH funding has never been more competitive.

Education of students, post-doctoral trainees and visiting investigators continued to be a major priority in the Center. In 2018-2019, the CPET faculty continued to direct the training of sizable numbers of post-doctoral fellows, graduate students, and professional students in the Colleges of Pharmacy and Medicine. In particular, the Center has supported a select group of exceptional students designated as CPET scholars. The hallmark of CPET teaching and research programs continues to be the integration of basic and translational sciences, with the goal of enhancing pharmacotherapeutic strategies for the treatment of pediatric illnesses.

2018-2019 Annual Report

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ABOUT THE CENTER

2018-2019



Leadership



P. David Rogers, Pharm.D., Ph.D.
Director

- First Tennessee Chair of Excellence in Clinical Pharmacy
- Professor of Clinical Pharmacy and Translational Science,
- Professor of Pediatrics

Richard E. Lee, Ph.D.
Scientific Advisor

- Member, Chemical Biology & Therapeutics
- Endowed Chair in Medicinal Chemistry, St. Jude Children's Research Hospital
- Adjunct Professor, University of Tennessee Health Science Center



Jeffrey Becker, Ph.D.
Scientific Advisor

- Chancellor's Professor and Chair Emeritus
- David and Sandra White Endowed Professor in Microbiology, UT Knoxville College of Arts and Sciences



James B. Dale, M.D.
Scientific Advisor

- Gene H. Stollerman Professor of Medicine
- Chief, Division of Infectious Diseases



Faculty

Jeffrey M. Becker, Ph.D.

Scientific Advisor

- Chancellor's Professor Emeritus
- David and Sandra White Endowed Professor of Microbiology, Department of Microbiology, College of Arts and Sciences

Theodore Cory, Pharm.D., Ph.D.

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

James B. Dale, M.D.

Scientific Advisor

- Gene H. Stollerman Professor of Medicine
- Chief, Division of Infectious Diseases

Jarrold R. Fortwendel, Ph.D.

- Associate Professor, Department of Clinical Pharmacy and Translational Science

Kirk E. Hevener, Pharm.D., Ph.D.

- Assistant Professor, Department of Pharmaceutical Sciences

Santosh Kumar, Ph.D.

- Associate Professor, Department of Pharmaceutical Sciences

Richard E. Lee, Ph.D.

Scientific Advisor

- Interim Chair and Member, Chemical Biology & Therapeutics
- Endowed Chair in Medicinal Chemistry, St. Jude Children's Research Hospital
- Adjunct Professor, University of Tennessee Health Science Center

Bernd Meibohm, Ph.D.

- Professor, Department of Pharmaceutical Sciences
- Associate Dean, Research and Graduate Programs, College of Pharmacy

Glen E. Palmer, Ph.D.

- Associate Professor, Department of Clinical Pharmacy and Translational Science

Brian M. Peters, Ph.D.

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

Todd B. Reynolds, Ph.D.

- Associate Professor, Department of Microbiology, College of Arts and Sciences

P. David Rogers, Pharm.D., Ph.D.

Director

- First Tennessee Chair of Excellence in Clinical Pharmacy
- Professor, Departments of Clinical Pharmacy and Pediatrics

Emeritus Faculty

Dennis D. Black, M.D.

- Director, Children's Foundation Research Institute, Le Bonheur Children's Hospital
- Vice-President for Research, Le Bonheur Children's Hospital
- Professor, Departments of Pediatrics and Physiology
- J.D. Buckman Endowed Professorship in Pediatrics at UTHSC

Steven C. Buckingham, M.D.

- Former Associate Professor, Department of Pediatrics, Division of Pediatric Infectious Diseases, Le Bonheur Children's Hospital
(Dr. Buckingham passed away November 24, 2015.)

Russell W. Chesney, M.D.

- Former Scientific Advisor and Past Director
- Former Professor, Department of Pediatrics, Le Bonheur Children's Hospital
Division of Pediatric Nephrology
(Dr. Chesney passed away April 2, 2015.)

William E. Evans, Pharm.D

- Member, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital
- Professor, Departments of Clinical Pharmacy and Translational Science, Pediatrics, and Pharmaceutical Sciences
- Endowed Chair in Pharmacogenomics
- Former Scientific Advisor and Inaugural Director

Richard A. Helms, Pharm.D.

- Former Scientific Advisor and Past Director
- Former Professor, Department of Clinical Pharmacy and Translational Science
- Former Professor, Department of Pediatrics

Sheldon B. Korones, M.D.

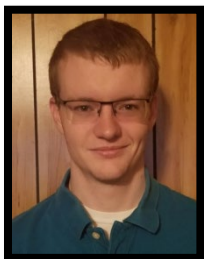
- Emeritus Professor, Department of Pediatrics, Division of Neonatology, Le Bonheur Children's Hospital
- Past Director, Newborn Center, The Regional Medical Center at Memphis
(Dr. Korones passed away July 3, 2013.)

John H. Rodman, Pharm.D.

- Former Vice Chair and Member, Pharmaceutical Sciences Department, St. Jude Children's Research Hospital
- Former Professor, Department of Clinical Pharmacy
(Dr. Rodman passed away April 29, 2006.)

CPET Scholars

Christian DeJarnette



“Identifying Fungal Fatty Acid Biosynthetic Inhibitors Using a Novel Drug Discovery Approach”

Advisor: Glen Palmer, Ph.D.
Integrated Biomedical Sciences

Laura Doorley



“Novel Mechanisms of Fluconazole Resistance in *Candida albicans* and *Candida parapsilosis*”

Advisor: P. David Rogers, Pharm.D., Ph.D.
Integrated Biomedical Sciences

Miranda Jarrett



“Developing Improved Antimicrobial Inhibitors of Folate Biosynthesis Through Evaluation of Sulfonamide Resistance Mechanisms and Exploration of the Cellular Fate of Next-generation Antifolates”

Advisor: Richard Lee, Ph.D.
Integrated Biomedical Sciences

Andrew Nishimoto, Pharm.D.



“Genomic and Transcriptomic Investigation of Azole Antifungal Resistance Mechanisms in *Candida albicans*”

Advisor: David Rogers, Pharm.D., Ph.D.
Pharmaceutical Sciences

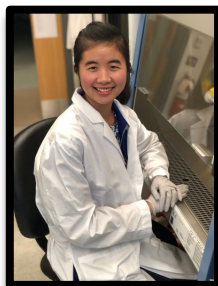
Ying Mu



“Effects of tobacco and alcohol on transporter expression and function in HIV infected macrophages”

Advisor: Ted Cory, Pharm.D., Ph.D.
Pharmaceutical Sciences

Tina Dao



“Immune constraints of antibiotic resistance development”

Advisor: Jason Rosch, Ph.D.
Integrated Biomedical Sciences

Jesse Jones



“Investigation of Narrow Spectrum Targets in Antibacterial Drug Discovery”

Advisor: Kirk Hevener, Ph.D.
Pharmaceutical Sciences

Benjamin Patters



“Effects of Ethanol Exposure on Neurotoxic Properties of Exosomes in the Central Nervous System”

Advisor: Santosh Kumar, Ph.D.
Integrated Biomedical Sciences

Parker Reitler



“Commonly Used Drugs Inducing Antifungal Resistance in *Candida* species”.

Advisor: Glen E. Palmer, Ph.D.
Integrated Biomedical Sciences

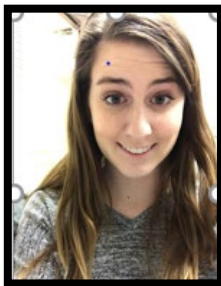
Jeffrey Rybak, Pharm.D.



“Utilizing Next-generation Sequencing to Reveal Novel Mechanisms of Triazole Resistance Among Clinical Isolates of *Aspergillus fumigatus*”

Advisor: David Rogers, Pharm.D., Ph.D.
Integrated Biomedical Science

Olivia Todd



“Mechanisms of Synergistic Virulence during Polymicrobial Intra-Abdominal Infection”

Advisor: Brian M. Peters, Ph.D.
Integrated Biomedical Sciences

Ashley Nywening



“Illuminating network biology underpinning basal intracellular drug-induced stress responses and drug resistance in *Aspergillus fumigatus*”

Advisor: Jarrod Fortwendel, Ph.D.
Integrated Biomedical Sciences

Faculty Research Activities

P. David Rogers, Pharm.D., Ph.D., FCCP
First Tennessee Endowed Chair of Excellence
in Clinical Pharmacy and Pediatrics
Director, Center of Excellence for Pediatric Experimental Therapeutics
Professor of Clinical Pharmacy and Translational Science



The overarching long-term goal of the Rogers lab is to improve the safety and efficacy of antifungal pharmacotherapy. My interest in this area is driven by insights gained as an infectious diseases clinical pharmacist into the significant limitations that exist with regard to the treatment of serious fungal infections. Indeed, treatment of such infections is limited to only three antifungal classes. The polyene amphotericin B is effective for many fungal infections, but its use is hampered by significant infusion-related reactions and nephrotoxicity. It is also only available for intravenous administration. The triazole antifungals are effective and in some cases superior, yet much less toxic, inexpensive, and available both orally and intravenously. Unfortunately, resistance has emerged which limits the utility of this antifungal class. The echinocandins, such as caspofungin, are particularly useful for invasive candidiasis, but lack utility against other fungal pathogens and are only available for intravenous administration. Moreover, resistance to this antifungal class has begun to emerge, particularly in the fungal pathogen *Candida glabrata*. It must also be underscored that no new antifungal drug classes are on the horizon. Novel strategies are therefore urgently needed to preserve, improve, and expand the current antifungal armamentarium.

The overarching long-term goal of the Rogers lab is to improve the safety and efficacy of antifungal pharmacotherapy. My interest in this area is driven by insights gained as an infectious diseases clinical pharmacist into the significant limitations that exist with regard to the

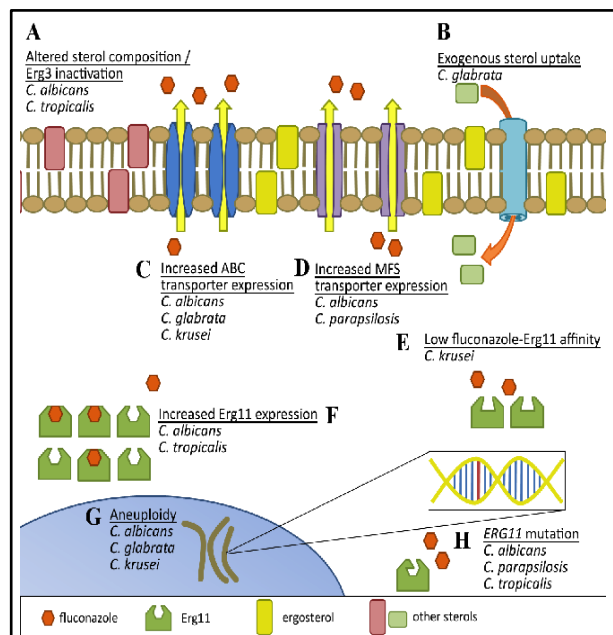


Figure 1. Comparison of documented fluconazole resistance mechanisms in *Candida* species. A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. B) Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production of both C) ATP-binding cassette efflux pumps and D) major facilitator superfamily transporters reduces intracellular accumulation of azoles. E) Inherently low affinity of fluconazole binding to species-specific Erg11 may decrease fluconazole's potential to inhibit the protein. F) Increased expression of Erg11 protein can help overcome azole activity and G) aneuploidy may promote genetic adaptation to azole exposure. H) Mutations in *ERG11* can also result in proteins with reduced affinity for fluconazole binding.

For over a decade our primary focus has been on understanding the molecular and cellular basis of resistance to the triazole class of antifungal agent in pathogenic fungi (overviewed in **Figure 1**). A long-term interest of my laboratory has been the use of genome-wide technologies to study antifungal stress responses in *Candida* species. We used microarray and proteomic analysis to identify changes in the gene expression and proteomic profiles of these organisms in response to the various classes of antifungal agents. This revealed both general and specific responses, some of which aligned with the mechanisms of action of these agents, and gave insight into factors that influence antifungal susceptibility (such as the azole-induction of the Cdr1 transporter). We also used this approach for genome-wide analysis of azole antifungal proteomic analysis to identify changes in the gene expression and proteomic profiles of these organisms in response to the various classes of antifungal agents. This revealed both general and specific responses, some of which aligned with the mechanisms of action of these agents, and gave insight into factors that influence antifungal susceptibility (such as the azole-induction of the Cdr1 transporter). We also used this approach for genome-wide analysis of azole antifungal resistance in *Candida* species, which has provided insight into this process (1-4).

My laboratory, working in collaboration with the laboratory of Joachim Morschhauser, discovered the transcriptional regulator Mrr1 and demonstrated that activating mutations in this transcription factor gene result in up-regulation of the Mdr1 transporter and fluconazole resistance in clinical isolates of *C. albicans*. In further work we have delineated the regulon of this transcriptional regulator and identified other regulators required for its activity (5-8). Working again in collaboration with the Morschhauser laboratory, we discovered that activating mutations in the transcription factor Upc2 leads to up-regulation of the gene encoding the azole target (*ERG11*), and increased azole resistance in clinical isolates. We have shown that this is a common and important mechanism of resistance among clinical isolates, identified additional regulators required for its activity, and have found it to be essential for azole resistance in clinical isolates exhibiting the major resistance mechanisms (9-12). More recently we have delineated the contribution of the putative lipid translocase Rta3 in azole resistance in this organism (13).

Our work has also explored the problem of triazole resistance in other fungal species. Working in collaboration with the laboratory of Thomas Edlind, we discovered that activating mutations in the transcription factor Pdr1 were responsible for azole resistance in *C. glabrata*. This led to further work by our group elucidating the role of this transcription factor, as well as the transcription factor Upc2, in azole antifungal resistance in this important *Candida* species (14-17). More recently we have begun to dissect this process in other non-albicans *Candida* species as well as the important fungal pathogen *Aspergillus fumigatus* (18, 19). Currently my research program maintains three focus areas: 1) Understanding the genetic and molecular basis of triazole antifungal resistance in *Candida albicans*, 2) Dissecting the Upc2A transcriptional pathway, protein interaction partners, and genetic network to overcome fluconazole resistance in *Candida glabrata*, and 3) Delineating the genetic and molecular basis of triazole resistance in the fungal pathogen *Aspergillus fumigatus*.

Lab Members:

P. David Rogers, Pharm.D., Ph.D., FCCP – Principal Investigator

Kathy Barker, Ph.D. – Senior Scientist

Qing Zhang – Laboratory Manager

Cheshta Sharma, Ph.D. – Post-doctoral Fellow

Sarah G. Whaley, Pharm.D. – Graduate Student, Pharmaceutical Sciences
Andrew T. Nishimoto, Pharm.D. - Graduate Student, Pharmaceutical Sciences
Jeffery M. Rybak, Pharm.D. – Graduate Student, Integrated Biomedical Sciences
Laura Doorley – Graduate Student, Integrated Program in Biomedical Sciences
Yu Li – Graduate Student, Integrated Program in Biomedical Sciences

Key Collaborators:

Joachim Morschhäuser, Ph.D. - Universität Würzburg
Steven Kelly, Ph.D., D.Sc. – Swansea University
Scott Moye-Rowley, Ph.D. – University of Iowa
Damian Krysan, M.D., Ph.D. – University of Rochester
Theodore White, Ph.D. – University of Missouri Kansas City
Nathan Wiederhold, Pharm.D. – University of Texas Health Science Center

Brian M. Peters, Ph.D.

Associate Professor of Clinical Pharmacy and Translational Science

The Peters lab has two main foci of research: **1)** the host and fungal molecular mechanisms responsible for the immunopathogenesis of vulvovaginal candidiasis and **2)** quorum sensing and toxin regulation during fungal-bacterial intra-abdominal infection.



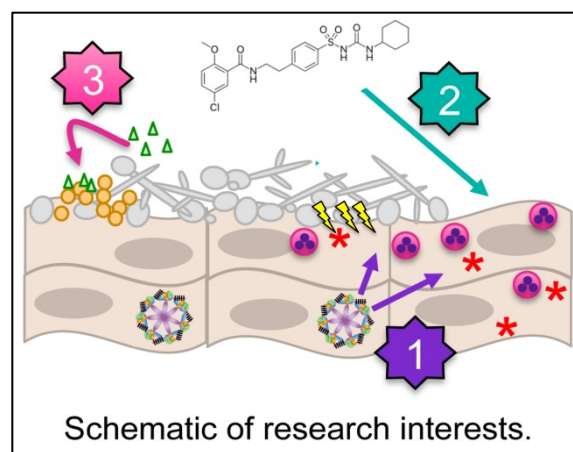
Immunopathogenesis of vulvovaginal candidiasis:

Candida albicans, an opportunistic human fungal pathogen, is the leading causative agent of vulvovaginal candidiasis (VVC) and presents major quality of life issues for women worldwide. It is estimated that nearly every woman of childbearing age will be afflicted by VVC at least once in her lifetime. Although these treatments are typically effective at reducing organism burden, static function of azole activity, fungal recalcitrance to clearance, and lack of comprehensive

understanding of disease pathology necessitates further insight into the host and fungal factors that contribute to vaginitis immunopathology.

[1] We are interested in exploring virulence mechanisms utilized by *C. albicans*, including the fungal toxin Candidalysin, to activate inflammasome signaling at the vaginal mucosa. We are also focused on determining the downstream signaling events relevant to disease pathogenesis, including activation of the NLRP3 inflammasome and related signaling at the vaginal mucosa.

[2] We are also currently interrogating the sulfonyleurea drug class as repurposed adjunctive therapeutic agents to more quickly arrest symptomatic disease. Recent work has demonstrated this class inhibits the NLRP3 inflammasome. Newer work with colleagues in the College of Pharmacy aims to create new inhibitors that demonstrate both antifungal and anti-inflammatory efficacy. Using a forward genetics approach, we are also interested in understanding how host genetic determinants alter symptoms of vaginal disease in the BXD recombinant inbred line. Follow-up studies to delineate molecular mechanisms are currently underway.



Polymicrobial intra-abdominal infection:

[3] Microorganisms rarely exist as single species communities but instead exist within multi-species consortia where mutually beneficial, parasitic, and antagonistic interactions may develop. However, relatively little is known about the functional consequences of these interactions as they relate to health and disease.

We aim to determine the complex inter-microbial signaling events that mediate infectious synergism observed during intra-abdominal infection with the ubiquitous bacterial pathogen *Staphylococcus aureus* and the fungus *C. albicans*. Prior studies have identified that the staphylococcal agr quorum sensing system is augmented during in vitro and in vivo growth

with *C. albicans*, leading to elevated levels of cytolytic α -toxin. Both genetic and passive immunization strategies against α -toxin significantly attenuate infectious synergism in vivo. The murine model of polymicrobial intra-abdominal infection serves as an excellent system for determining microbe-microbe induced virulence gene regulation in vivo. Current studies are aimed at delineating mechanisms by which *C. albicans* activates the *agr* system and devising strategies to treat downstream effects of α -toxin activity.

LAB PERSONNEL

Dr. David Lowes (Research Associate)

Dr. Emily Sansevere (Postdoctoral fellow, now at Finch Therapeutics)

Dr. Salman Ahmed (Postdoctoral fellow)

Dr. Marjoleine Willems (Postdoctoral fellow)

Olivia Todd (PhD Student, Integrated Biomedical Sciences Program)

Jian Miao, MS (PhD Student, Pharmaceutical Sciences Program)

Glen E. Palmer, Ph.D.
Associate Professor of Clinical Pharmacy and Translational Science

Title: Antifungal drug discovery and mechanisms of resistance.



An estimated 1.5 million people die each year from invasive fungal infections, and many millions more are afflicted by debilitating mucosal and subcutaneous mycoses. Current antifungal therapies have serious deficiencies including poor efficacy, limited spectrum of activity, patient toxicity and the emergence of resistant fungi. Consequently, mortality rates are disturbingly high. A major obstacle to developing effective new antifungal drugs is the fundamental similarity between the cells of these eukaryotic pathogens and their mammalian host. This presents a challenge in devising therapeutic agents with pathogen selective toxicity. A major long-term goal of my research program is to identify and validate new target proteins that can provide a basis to develop efficacious new antifungal therapies. Current investigations within my lab include the discovery and development of new classes of antifungal agents that target either: 1). The integrity of a sub-cellular organelle called the fungal vacuole; 2). Fungal fatty acid biosynthesis; and 3) aromatic amino acid biosynthesis. As part of these studies we have devised several high-throughput (HTP) chemical screening assays to identify compounds that target these cellular functions. This includes a new and broadly applicable type of target based whole-cell screen (TB-WCS) that combines the benefits of both traditional target-based and cell-based chemical screens into a single HTP assay. We anticipate our TB-WCS approach to chemical screening will greatly enhance the speed and efficiency with which new pre-therapeutic leads, with a defined mechanism of action can be identified. Through these efforts, I have become increasingly excited about the enormous potential of applying yeast based systems (which are highly amenable to HTP approaches) to the discovery of new pharmacotherapies that target human disease related proteins.

Current lab members:

Lab manager - Tracy Peters M.S.

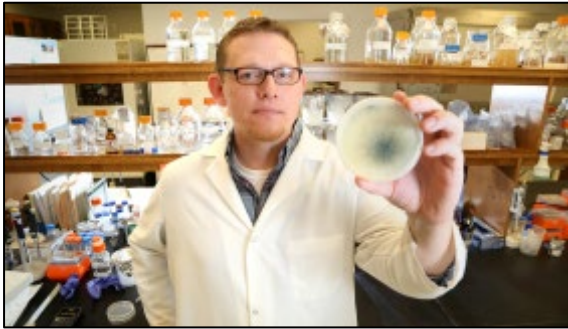
Postdoctoral researchers – Helene Tournu Ph.D; Arielle Butts Ph.D; Arturo Luna-Tapia Ph.D

Research Associate – Kathy Barker Ph.D

Graduate Students – Christian DeJarnette B.S.; Parker Reitler B.S.

Jarrod R. Fortwendel, PhD.
Associate Professor of Clinical Pharmacy and Translational Science

Control of Antifungal Drug Tolerance through the *Aspergillus fumigatus* Kinome



Invasive aspergillosis, caused mainly by *A. fumigatus*, is the most prevalent invasive mold infection of immunocompromised individuals and is associated with mortality rates of 35-90%. Therapy options are extremely limited for invasive aspergillosis and resistance to the triazole class of antifungals is on the rise. Although more than a decade of research has focused on characterizing the emerging threat

of triazole resistance in *A. fumigatus*, strategies for preventing or circumventing this increasingly grave phenomenon remain elusive. Significant knowledge gaps concerning how *A. fumigatus* adapts to drug-induced stress (i.e., drug tolerance) impair our ability to improve antifungal therapy and halt the rise in resistance. Without new resources to hasten discovery, progress in these areas is unlikely. In turn, we risk losing the most important class of drugs with anti-*Aspergillus* activity and endanger the lives of the increasing at-risk population. Our long-term goal is to improve antifungal therapy and to ensure the sustained clinical utility of the triazole class for treatment of invasive aspergillosis. The objective of this proposal is to delineate novel phospho-regulatory events utilized for antifungal tolerance by the major mold pathogen, *Aspergillus fumigatus*.

Reversible protein phosphorylation regulates the majority of eukaryotic cellular processes. A robust history of published research, including a recent functional analysis of the entire *Cryptococcus neoformans* kinome, implicates multiple protein kinases in the regulation of antifungal tolerance. To delineate novel roles for the *A. fumigatus* kinome in triazole tolerance, we have completed a preliminary phospho-proteomics analysis of the response to voriconazole treatment. Our preliminary data reveal significant changes in the phosphorylation status of ~1400 proteins, implying extensive kinase-mediated adaptation to drug-induced stress. Filtering this dataset for proteins known to mediate triazole tolerance, we identified voriconazole-induced phosphorylation state changes in HapB. The HapB protein is a subunit of the heterotrimeric CCAAT-binding complex (CBC), a crucial transcriptional repressor of ergosterol biosynthesis genes. Interestingly, clinical triazole resistance in select *A. fumigatus* isolates has been ascribed to mutations that alter functionality of the CBC. Therefore, delineation of CBC regulatory mechanisms could lead to novel interventions targeting antifungal tolerance and/or resistance. To identify kinases required for phosphorylation of the CBC, and to explore roles for *A. fumigatus* kinase networks in drug tolerance, an in-depth investigation of the *A. fumigatus* kinome is needed. A critical barrier to performing large-scale analysis of sizeable gene families in *A. fumigatus* has been the notoriously low homologous recombination rates of wild type strains. We have overcome this barrier by successfully adapting a novel CRISPR/Cas9-based mutational approach. We will utilize this facile system to test our hypothesis that the CBC is phospho-regulated in response to triazole stress through modification of the HapB subunit and to interrogate all 131 *A. fumigatus* protein kinases for networks modifying HapB and/or supporting triazole tolerance.

We are working now to test the working hypothesis that CBC-mediated regulation of triazole tolerance is controlled by differential phosphorylation of the HapB subunit. Unbiased

and targeted phosphoproteomics analyses will first be completed using multiple *Aspergillus*-active triazoles to confirm HapB phosphorylation state changes. Using directed mutagenesis combined with triazole sensitivity and Nanostring gene arrays, we will then systematically test each putative HapB phosphorylation event for regulation of CBC function in triazole tolerance and repression of ergosterol biosynthesis gene expression. Then, we aim to identify novel protein kinases supporting antifungal fitness in *A. fumigatus*. Using our novel CRISPR/Cas9 mutational approach, we will generate barcoded libraries of tetracycline-repressible and overexpression mutants representing each protein kinase in *A. fumigatus*. These libraries will be employed in pooled competitive fitness analyses to identify important components regulating fitness during stress induced by voriconazole. Kinase mutants with altered fitness will be further subjected to targeted phosphoproteomic analyses to identify the kinase(s) regulating HapB in response to inhibition of ergosterol biosynthesis.

Our expected outcome is that we will uncover multiple, novel contributions of protein kinases to *A. fumigatus* antifungal fitness. In addition, we will potentially delineate a phospho-regulatory mechanism controlling the CBC, a crucial transcriptional regulator of the triazole stress response. As they are considered the second largest class of proteins currently functioning as drug targets, identification of the protein kinases crucial to triazole tolerance could reveal novel targets for use in new stand-alone or combination therapies. Therefore, the potential **impact** of this work is the improvement of antifungal therapy and significant advance towards the sustained clinical utility of triazole antifungals against *Aspergillus*.

Systematic Functional Analysis *Aspergillus fumigatus* Kinases

To cause invasive disease, *A. fumigatus* must be able to sense and utilize tissue-specific nutrient sources and effectively handle host-induced stress. A strong history of published research implicates protein kinases as essential for orchestration of a wide variety of nutrient sensing/utilization and stress response networks in pathogenic fungi. Reversible protein phosphorylation regulates almost all eukaryotic processes and, on average, about 30% of cellular proteins are modified by phosphorylation. Although no systematic analysis has yet been accomplished in *A. fumigatus*, the relatively few protein kinases that have been characterized play diverse roles in cellular stress responses and virulence. Furthermore, *kinases are considered the second largest protein class currently functioning as drug targets*, as their inhibition can be readily accomplished by small molecules. Unfortunately, the vast majority of *A. fumigatus* protein kinases remain unstudied. We have successfully adapted a novel CRISPR/Cas9-based mutational approach for use in wild type strains of *A. fumigatus*. Our preliminary data show that this facile system increases the typically low levels of gene targeting in wild type *A. fumigatus* to as high as 90%. With this new tool, we propose to systematically delete and functionally analyze all putative protein kinases in the wild type *A. fumigatus* genetic background, Af293. The CRISPR/Cas9 components are being designed based on our preliminary results and purchased from commercial vendors. The necessary ribonucleotide complexes will be assembled via a short, *in vitro* reaction and then mixed with microhomology repair templates before protoplast transformation. Repair templates will be designed to incorporate signature tags into each kinase mutant, barcoding the strains for competitive fitness analyses. Essential kinases will be confirmed by tetracycline-regulatable promoter replacement using a modification our CRISPR/Cas9 approach. We will then perform competitive fitness analyses employing signature-tagged pools of kinase mutants to identify novel roles for the kinome during pathogenic growth. To identify kinases that may regulate fitness in response to host immune status, we will utilize two highly characterized models of invasive aspergillosis that re-capitulate the immune dysfunction in both

neutropenic and non-neutropenic hosts. We will also perform *in vitro* competitive fitness assays using culture conditions that mimic pathobiologically relevant stress. A subset of the least-fit mutants from both *in vivo* and *in vitro* studies will be complemented and employed in single infection/inoculation studies to confirm roles in fitness. We expect to discover multiple, novel contributions of protein kinases to the pathobiology of invasive aspergillosis. The information generated by completion of this work will support future applications exploring novel aspects of *A. fumigatus* virulence.

New Tools for *Aspergillus fumigatus* Molecular Analyses: CRISPR/Cas9 gene editing using *in Vitro*-Assembled Cas9-Guide RNA Ribonucleoproteins Coupled with Microhomology Repair Templates

Tackling the multifactorial nature of virulence and antifungal drug resistance in *A. fumigatus* requires the mechanistic interrogation of a multitude of genes, sometimes across multiple genetic backgrounds. Classical fungal gene replacement systems can be laborious and time-consuming and, in wild-type isolates, are impeded by low rates of homologous recombination. CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9 is a novel genome-editing system that has been successfully established in *Aspergillus fumigatus*. However, the current state of the technology relies heavily on DNA-based expression cassettes for delivering Cas9 and the guide RNA (gRNA) to the cell. Therefore, the power of the technology is limited to strains that are engineered to express Cas9 and gRNA. To overcome such limitations, we developed a simple and universal CRISPR-Cas9 system for gene deletion that works across different genetic backgrounds of *A. fumigatus*. The system employs *in vitro* assembly of dual Cas9 ribonucleoproteins (RNPs) for targeted gene deletion. Additionally, our CRISPR-Cas9 system utilizes 35 to 50 bp of flanking regions for mediating homologous recombination at Cas9 double-strand breaks (DSBs). As a proof of concept, we first tested our system in the \DeltaakuB (\DeltaakuB^{ku80}) laboratory strain and generated high rates (97%) of gene deletion using 2 μ g of the repair template flanked by homology regions as short as 35 bp. Next, we inspected the portability of our system across other genetic backgrounds of *A. fumigatus*, namely, the wild-type strain Af293 and a clinical isolate, *A. fumigatus* DI15-102. In the Af293 strain, 2 μ g of the repair template flanked by 35 and 50 bp of homology resulted in highly efficient gene deletion (46% and 74%, respectively) in comparison to classical gene replacement systems. Similar deletion efficiencies were also obtained in the clinical isolate DI15-102. Taken together, our data show that *in vitro*-assembled Cas9 RNPs coupled with microhomology repair templates are an efficient and universal system for gene manipulation in *A. fumigatus*. Our simple and universal CRISPR-Cas9 system for gene manipulation generates efficient gene targeting across different genetic backgrounds of *A. fumigatus*. We anticipate that our system will simplify genome editing in *A. fumigatus*, allowing for the generation of single- and multigene knockout libraries. In addition, our system will facilitate the delineation of virulence factors and antifungal drug resistance genes in different genetic backgrounds of *A. fumigatus*.

Santosh Kumar, Ph.D.

Associate Professor in Pharmaceutical Sciences Assistant Dean for Scholarly Integration and Collaboration

Dr. Kumar graduated from the Indian Institute of Technology (IIT)-Bombay, India. Dr. Kumar did his post-doctorate fellowship from the University of Missouri-Kansas City (UMKC) followed by joined as a junior faculty at the University of Texas Medical Branch. He then went back to UMKC as an Assistant Professor before coming to UTHSC in 2014. Dr. Kumar is trained as a biochemist and enzymologist with expertise in drug metabolism, HIV, and substance abuse. His laboratory works in the field of HIV/AIDS, neuroAIDS, and substance use/abuse, especially alcohol and smoking, and extracellular vesicles. For the past 8 years Dr. Kumar's research projects are funded by several NIH grants. In the past 10 years, Dr. Kumar's group has published substantially in this field (~65 papers), with a total of >100 papers in his career. Dr. Kumar has mentored six graduate students and three post-doctorate fellows along with numerous other trainees. Currently, he is mentoring three graduate students and one PDF. In addition to research, Dr. Kumar participate significantly in classroom teaching to both professional pharmacy students and graduate students.



Dr. Kumar has been actively engaged in serving the Society on Neuroimmune Pharmacology (SNIP), not only as a member, but also as Chair of "Early Career Investigator Committee, as well as Secretary and President-elect of the society. As a result of his distinguished contributions to research, teaching, mentoring, and service, Dr. Kumar has received numerous awards and honors. In the past five years

Dr. Kumar has received: 1) Mahatma Gandhi Pravasi (Non-resident Indian (NRI)) Samman (Honor) from NRI, India, 2) Teacher of the Year Award from UMKC-SOP, 3) Distinguish Service Award from the SNIP, 4) Postdoctoral Fellow Outstanding Junior Mentoring Academy Award from the Post-doctorate Association, UTHSC, 5) Phi Delta Chi (PDC) "Professor of the Year Award" from UTHSC-COP (2018 and 2019), 6) UT Alumni Association "Outstanding Teacher Award", from the University of Tennessee, 7) Inducted in Phi Lambda Sigma society, UTHSC-COP, 8) The Student Government Association Executive Council (SGAEC) "Excellence in Teaching Award", from UTHSC-GCHS, 9) Full member of PDC fraternity.

Research Projects

1. Alcohol, HIV, antiretroviral therapy (ART), extracellular vesicles, and cytochrome P450
2. Tobacco/nicotine, HIV, and extracellular vesicles, and cytochrome P450
3. Antiretroviral therapy (ART) and nanoformulations
4. HPV/Cervical cancer and HIV/AIDS

Current lab personnel

Dr. Sunitha Kodidela, Ms. Sanjana Haque, Ms. Yuqing Gong, Ms. Kelli Gerth, Ms. Namita Sinha

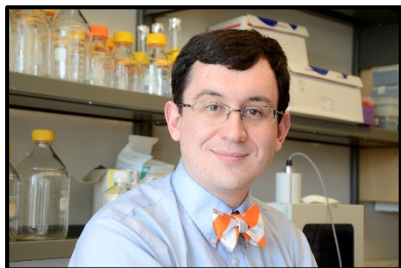
Recently trained PDFs and graduated students

PDFs: Dr. PSS Rao, Dr. Narasimha Midde

Students: Dr. Sabina Ranjit, Dr. Mohammad A. Rahman

Theodore J. Cory, Pharm.D., Ph.D.

Assistant Professor, Department of Clinical Pharmacy and Translational Science



Viral persistence is a critical barrier to the eradication of HIV-1 in infected individuals. One hypothesis is that HIV resides in cells in locations with subtherapeutic antiretroviral concentrations, which are insufficient to fully inhibit viral replication, making elimination of the virus from these sites impossible. These sites include the brain, lymph nodes, and secondary lymphoid tissues. While CD4+ T cells are the primary target of HIV, macrophages are infected early, and remain an important infected cell population. These two host cells interact in lymph nodes and secondary lymphoid tissue. Macrophages exist in two phenotypically dissimilar polarized subsets, the classically activated (M1) phenotype, which is pro-inflammatory and involved in the destruction of intracellular pathogens, and the alternatively activated (M2) phenotype, which is anti-inflammatory and involved in tissue repair. The role of these two subsets of macrophages in HIV is uncertain, as is the disposition of antiretrovirals in the cells. Our goal is to define the mechanisms by which intracellular antiretroviral concentrations are altered in macrophage subsets, and the effect of this on viral replication and spread, and do develop strategies to increase antiretroviral concentrations in the macrophage reservoir of HIV. Additionally, we are interested in how drugs of abuse including nicotine and alcohol influence concentrations of the drugs used in HIV inside of cells, and are aiming to develop new strategies to increase the concentrations of these drugs inside of cells.

Current lab members

Graduate Student: Ying Mu, M.S.

Kirk E. Hevener, Pharm.D., Ph.D.
Assistant Professor of Pharmaceutical Sciences

Title: Narrow-Spectrum Antibacterial Target Validation & Drug Discovery



Every year in the United States, over 2 million people are infected with drug-resistant bacteria and over 23,000 people die as a direct result of these infections. The overuse of broad-spectrum antibacterial agents has been linked to the alarming rise in drug-resistant bacteria we are currently seeing. Further, we are continuing to understand the role of the human microbiome in health and disease and the adverse effects on human health that can result from the disruption to the microbiome caused by broad spectrum antibacterials. Therefore, there is an urgent need to validate and characterize novel antibacterial targets, particularly those that may result in a narrow-spectrum antibacterial effect against pathogenic, invasive organisms that can spare the human microbiota, and to develop therapeutic agents that affect these validated targets. The Hevener laboratory is currently investigating two such targets: the enoyl-acyl carrier protein (ACP) reductase enzyme (FabK) in *Clostridioides difficile* & *Porphyromonas gingivalis*, and the topoisomerase I enzyme in *Streptococci*. FabK is an essential enzyme in the bacterial fatty acid synthesis pathway (FAS-II) of certain pathogenic organism, such as *C. difficile* and *P. gingivalis*, which are responsible for GI and oral infections. FabK is a unique isozyme at this essential step that is distinct from the FabI isozyme found at this step in many of the non-pathogenic gut organism, which makes it an attractive target for narrow-spectrum antibacterial design. The type 1A topoisomerase found in *Streptococci* presents another potential narrow-spectrum antibacterial target as many non-pathogenic organisms express additional, redundant topoisomerase enzymes that pathogenic species of *Streptococci* do not. My laboratory is using a variety of microbiological, biochemical and structural biology approaches to validate and characterize these targets and is concurrently using structure-based design strategies to identify novel and potent inhibitors of these targets for further use as chemical probes and potential drug discovery leads.

Current lab members:

Graduate Students – Jesse A. Jones, Pharm.D.

Pharmacy Students – Rebecca Wahrmund, B.S.; Hoang P. Nguyen, B.S., B.A.; Kristiana Watson, B.S.

Bernd Meibohm, Ph.D., FCP, FAAPS
Professor of Pharmaceutical Sciences,
Associate Dean for Research and Graduate Programs

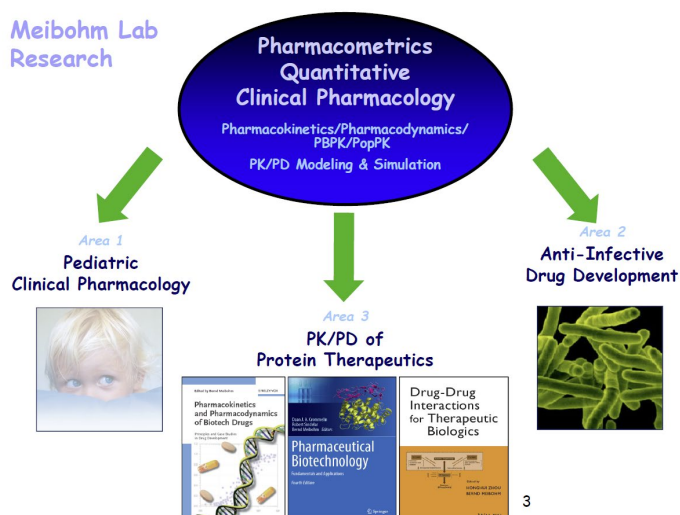
Dr. Meibohm's research is focused on the investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs with special emphasis on PK/PD-correlations.



Pharmacokinetic/pharmacodynamic (PK/PD)-modeling bridges the gap between dynamic dose-concentration relationships and static concentration-effect relationships of drugs. By combining information provided by pharmacokinetics and by pharmacodynamics, it facilitates the description and prediction of the time course of drug effects that are resulting from a certain dosing regimen. The application of these PK/PD-modeling concepts has been identified as beneficial in all phases of preclinical and clinical drug development as well as in applied clinical pharmacotherapy, where it provides a more rational basis for patient-specific dosage individualization. Thus, the ultimate goal of the research in Dr. Meibohm's lab is to contribute to the optimization of dosing regimens for increased efficacy and reduced toxicity and to modulate pharmacotherapy according to the needs of the individual patient.

Special areas of interest are:

1. Pharmacokinetics and pharmacodynamics of small molecule drugs and biologics in pediatric patients and their dependency on developmental changes.
2. Pharmacokinetics and pharmacodynamics of anti-infective drugs with specific focus on development of therapies against tuberculosis and alphavirus infections.
3. Application of pharmacometrics and quantitative pharmacology concepts in preclinical and clinical drug development, with specific focus on therapeutic proteins.



LAB PERSONNEL

- Pradeep Lukka, PhD (postdoctoral fellow)
- Santosh Wagh, MS (PhD student, Pharmaceutical Sciences Program)
- Keyur Parmar, MS (PhD student, Pharmaceutical Sciences Program)
- Zaid Temrikar, MS (PhD student, Pharmaceutical Sciences Program)
- Parish Gupta, BPharm (PhD student, Pharmaceutical Sciences Program)

James B. Dale, M.D.
Gene H. Stollerman Professor of Medicine
Chief, Division of Infectious Diseases



James B. Dale, MD is the Gene H. Stollerman Professor of Medicine and Chief of the Division of Infectious Diseases at the University of Tennessee Health Sciences Center in Memphis. He received his undergraduate degree from the University of Tennessee in Knoxville and his MD degree from the University of Tennessee, Memphis. He has achieved a national and international reputation for research on group A streptococcal infections. He has published over 135 original scientific articles and reviews in the area of infectious diseases. Dr. Dale has received continuous U.S. federal research funding for 36 years and has devoted his entire research career to the study of the pathogenesis of group A streptococcal infections and the design, development and clinical testing of streptococcal vaccines.

DIRECTION OF THE CENTER 2018-2019



Annual Report 2018-2019

Goals and Future Plans

In the coming year the CPET will continue to refine its focus on the overarching theme of Pediatric Antiinfective Pharmacotherapy. We will expand our work specifically in the areas of fungal pathogens, HIV/AIDS, and anti-infective drug discovery and development. CPET investigators will compete for new extramural funding within these domains and continue to facilitate discovery and generate and disseminate new knowledge. We hope to expand our expertise with the recruitment of new faculty to the UTHSC campus as well as to the CPET. We will continue to train elite graduate students in the biomedical and pharmaceutical sciences with the support of the CPET Scholars Program. Dissemination of our discoveries and sharing and exchange of new ideas will be facilitated through CPET support of events such as the annual UTHSC Fungal Pathogens Group Research Conference, the annual CPET Research Day, and the CPET Seminar Series.

Schedule 7

CENTERS OF EXCELLENCE ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution:

UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Center:

PEDIATRIC PHARMACOKINETICS

Expenditures	FY 2017-18 Actual			FY 2018-19 Proposed			FY 2019-20 Requested		
	Matching	Appropriations	Total	Matching	Appropriations	Total	Matching	Appropriations	Total
Salaries									
Faculty	\$1,261,352	\$17,746	\$1,279,098	\$1,184,039	\$17,746	\$1,201,785	\$1,184,039	\$17,800	\$1,201,839
Other Professional	\$290,389	\$34,068	\$324,437	\$217,718	\$14,716	\$232,434	\$227,718	\$14,500	\$242,218
Clerical/ Supporting	\$214,512	\$0	\$214,512	\$258,387	\$0	\$258,387	\$358,387	\$0	\$358,387
Assistantships	\$45,900	\$135,049	\$180,949	\$161,758	\$157,504	\$319,262	\$161,758	\$155,000	\$316,758
Total Salaries	\$1,812,133	\$186,863	\$1,998,996	\$1,821,902	\$189,966	\$2,011,868	\$1,931,902	\$187,300	\$2,119,202
Longevity (Exclude from Salaries and include in Benefits)	\$7,000	\$403	\$7,403	\$7,480		\$7,480	\$7,980		\$7,960
Fringe Benefits	\$452,102	\$23,187	\$475,289	\$421,606	\$11,819	\$433,425	\$421,606	\$11,000	\$432,606
Total Personnel	\$2,271,235	\$210,453	\$2,481,688	\$2,250,988	\$201,785	\$2,452,773	\$2,361,468	\$198,300	\$2,559,768
Non-Personnel									
Travel	\$20,466	\$11,082	\$31,548	\$0	\$5,000	\$5,000	\$0	\$5,000	\$5,000
Software	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Books & Journals	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Other Supplies	\$0	\$12,824	\$12,824	\$0	\$15,000	\$15,000	\$0	\$58,370	\$58,370
Equipment	\$30,391	\$5,121	\$35,512	\$0	\$15,000	\$15,000	\$0	\$0	\$0
Maintenance	\$0	\$4,075	\$4,075	\$0	\$5,000	\$5,000	\$0	\$0	\$0
Scholarships	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Consultants	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Renovation	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Other (Specify):	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Media Processing	\$1,658	\$1,175	\$2,833	\$0	\$4,099	\$4,099	\$0	\$0	\$0
Communication	\$4,815	\$352	\$5,167	\$0	\$3,000	\$3,000	\$0	\$0	\$0
Professional Services & Memberships	\$3,136	\$14,572	\$17,708	\$0	\$9,000	\$9,000	\$0	\$0	\$0
Insurance & Interest	\$0	\$6,631	\$6,631	\$0	\$6,000	\$6,000	\$0	\$0	\$0
Grants & Subsidies	\$0	\$1,335	\$1,335	\$0	\$0	\$0	\$0	\$0	\$0
Contractual & Special Services	\$17,689	\$7,524	\$25,213	\$0	\$20,000	\$20,000	\$0	\$0	\$0
Other Services & Expenditures	\$0	\$8,524	\$8,524	\$0	\$40,000	\$40,000	\$0	\$0	\$0
Total Non-Personnel	\$78,155	\$73,215	\$151,370	\$0	\$122,099	\$122,099	\$0	\$63,370	\$63,370
GRAND TOTAL	\$2,349,390	\$283,668	\$2,633,058	\$2,250,988	\$323,884	\$2,574,872	\$2,361,468	\$261,670	\$2,623,138
Revenue									
New State Appropriation	\$0	\$244,518	\$244,518	\$0	\$249,235	\$249,235	\$0	\$261,670	\$261,670
Carryover State Appropriation	\$0	\$113,799	\$113,799	\$0	\$74,649	\$74,649	\$0	\$0	\$0
New Matching Funds	\$2,349,390	\$0	\$2,349,390	\$2,250,988	\$0	\$2,250,988	\$2,361,468	\$0	\$2,361,468
Carryover from Previous Matching Funds	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Total Revenue	\$2,349,390	\$358,317	\$2,707,707	\$2,250,988	\$323,884	\$2,574,872	\$2,361,468	\$261,670	\$2,623,138

YEAR-IN-REVIEW

2018-2019



Program Overview and Accomplishments

The Center for Pediatric Experimental Therapeutics (CPET) has been continuously funded for over 30 years. It achieved accomplished status early, and has been among the best Centers statewide when one considers return on investment. The CPET is among the smallest Centers by total annual appropriations, but consistently brings grant and contract dollars in excess of \$6 million per year to the Health Science Center (HSC), its affiliated programs, and the State of Tennessee. The Center has been multidisciplinary, interprofessional, multi-institutional, multi-college and multi-departmental from its beginning, and has had translational science at its core (from bench-top to patient and back again). It is the only state-funded Center of Excellence with improvement in children's health as its primary mission. The CPET has accomplished its mission over the years through research, education, outreach, and patient care.

Extramural funding and research publications from faculty supported by the Center are outlined in the following pages. In addition to this grant support and research productivity, the Center supports graduate education through the CPET Scholars Program. Exceptional students enrolled in graduate education at UTHSC under the direction of Center faculty have been selected for partial support from the center (See CPET Scholar section).

This year the Center was instrumental in supporting the 4th Annual UT Fungal Pathogens Group Retreat which was July 15-17 at the Grand Bohemian Hotel in Mountain Brook, Alabama. Programming included focused research presentations from graduate students and post-doctoral fellows from each laboratory as well as basic science and clinical keynote lectures supported in the form of the First Tennessee Distinguished Visiting Professorship. This year we were delighted to have as our keynote speakers Jennifer Lodge, Ph.D., Vice Chancellor for Research and Professor of Molecular Microbiology from Washington University and Jatin (Jay) M. Vyas, M.D., Ph.D., Associate Professor of Medicine, Harvard Medical School, and Internal Medicine Residency Program Director, Massachusetts General Hospital.

In the coming year the CPET will continue to direct its efforts to the focus of pediatric infectious diseases and finding ways to overcome them. Infectious diseases are a leading cause of death in the pediatric population world-wide. This has been complicated by increases in resistance to existing antimicrobial agents. New therapeutic strategies are desperately needed. The CPET has evolved to include leading investigators focused on the bacteria, fungi, and viruses that cause many of the most significant infectious diseases including tuberculosis, pneumonia, blood stream infections, HIV/AIDS, and fungal infections. We expect the years to come to be filled with novel and important research, thus invigorating CPET faculty, transforming the care of patients, and building new connections with the communities we touch. The CPET serves as a unifying force for scientists within these domains and connects the resources and efforts of our faculty through pivotal relationships with Le Bonheur Children's Medical Center and St. Jude Children's Research Hospital. In addition to our efforts in the laboratory, CPET scientists, clinicians, and educators have developed professional curriculum course materials, innovative interprofessional educational programs, scientific seminars and conferences, and train the next generation of pediatric biomedical scientists through our graduate and postdoctoral training programs.

The important work, both papers and funded projects, of CPET member faculty who shape our continuing story of innovative science, education, and patient care, are outlined in the following pages. Combined with our established investigators, the CPET is a potent force in improving the health of children in Tennessee, the country, and the world.

Extramural Funding

Extramural Funding

Federal Funding (including NIH)

Investigator: **Cory TJ, Kumar S** (subcontract **Meibohm B**)
Title: Monocytic and Exosomal Cytochrome P450 in Smoking-Mediated HIV-1 Pathogenesis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01DA047178
Dates: 9/30/18 to 8/30/23
Total Direct: \$960,000
Annual Direct: \$250,000

Investigator: **Dale JB**
Title: Structure-Based Design of a Broadly Protective Group A Streptococcal Vaccine
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI132117
Dates: 6/8/17 to 6/30/20
Total Direct: \$2,768,850
Annual Direct: \$614,095

Investigator: **Fortwendel JR**
Title: Control of Antifungal Drug Tolerance through the *Aspergillus fumigatus* Kinome
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R21AI142509
Dates: 11/13/18 to 10/31/20
Total Direct: \$418,000
Annual Direct: \$214,000

Investigator: **Fortwendel JR**
Title: Systematic Functional Analysis of the *Aspergillus fumigatus* Kinome
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R21AI139388
Dates: 7/1/18 to 6/30/20
Total Direct: \$418,000
Annual Direct: \$214,000

Investigator: **Fortwendel JR**
Title: Fungal Ras-Mediated Invasive Growth Mechanisms
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R21AI139388
Dates: 2/1/14 to 1/31/20

Total Direct: \$1,513,250
Annual Direct: \$252,208

Investigator: **Hevener KE**
Title: Investigation of FAS-II enzyme, FabK, as a druggable target for *C. diff*

Source National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI126755

Dates: 6/25/16 to 11/30/19
Total Direct: \$275,000
Annual Direct: Not Provided

Investigator: **Kumar S**
Title: Exosomes in tobacco- and HIV-mediated neurotoxicity
Source National Institute of Drug Abuse (NIDA)

5R21DA042374-02
Dates: 6/1/14 to 5/31/19
Total Direct: \$418,000
Annual Direct: Not Provided

Investigator: **Kumar S**
Title: Role of cytochrome P450 in alcohol-mediated HIV-1 pathogenesis and antiretroviral therapy
Source National Institute of Alcohol Addiction and Alcoholism (NIAAA)

5R01AA022063-06
Dates: 6/1/14 to 8/31/19
Total Direct: \$1,700,000
Annual Direct: \$70,000 (in no cost extension)

Investigator: **Kumar S** (transferred)
Title: Targeted Nano-Chemosensitization of Breast Cancers
Source National Cancer Institute (NCI)

1R15CA213232-01
Dates: 6/1/19 to 9/31/19
Total Direct: \$235,000
Annual Direct: \$235,000

Investigator: **Lee RE**
Title: Developing therapeutics to treat chronic infections
Source National Institute of Allergy and Infectious Diseases (NIAID)

5R01AI110578-05
Dates: 3/1/14 to 2/29/20
Total Direct: \$1,215,645
Annual Direct: (in no cost extension)

Investigator: **Lee RE** (PI Perfect J)
Title: Transdisciplinary Program to Identify Novel Antifungal Targets and Inhibitors

Source National Institute of Allergy and Infectious Diseases (NIAID)

5P01AI104533-03
 Dates: 6/25/15 to 5/31/20
 Total Direct: \$279,020
 Annual Direct: Not Provided

Investigator: **Lee RE** (PI White S)
 Title: Training in the Design and Development of Infectious Disease Therapeutics
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 5T32AI106700-03
 Dates: 7/1/10 to 6/30/20
 Total Direct: Not Provided
 Annual Direct: Not Provided

Investigator: **Lee RE** (subcontract **Meibohm B**)
 Title: Development of Novel Proteins Synthesis Inhibitors for MDR Tuberculosis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 2R01AI090810-06
 Dates: 7/6/10 to 2/28/23
 Total Direct: \$3,997,590
 Annual Direct: Not Provided

Investigator: **Lee RE** (PI Bulitta JB)
 Title: Combating resistant superbugs by understanding the molecular determinants of target site penetration and binding
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI136803-01
 Dates: 3/1/18 to 2/28/23
 Total Direct: \$839,671
 Annual Direct: Not Provided

Investigator: **Lee RE** (PI Haecker H)
 Title: Discovery of small molecules inhibiting Toll-like receptor-mediated inflammation
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI139014-01
 Dates: 9/1/18 to 8/31/22
 Total Direct: \$302,446
 Annual Direct: Not Provided

Investigator: **Lee RE** (PI Lafleur M, Lee RSY)
 Title: Development of Ureadepsipetides for Drug-resistant Infections
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI141193-01
 Dates: 12/3/18 to 12/2/23
 Total Direct: \$1,291,231
 Annual Direct: Not Provided

Investigator: **Lee RE** (PI Hurdle JG)
Title: High Throughput Screening for Non-antibiotic Inhibitors of *Clostridium difficile* Pathophysiology
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI144459-01
Dates: 4/1/19 to 3/31/23
Total Direct: \$692,959
Annual Direct: Not Provided

Investigator: **Lee RE** (subcontracts **Meibohm B** and **Rosch JW**)
Title: Development of Aminospectinomycins for Biodefense
Source National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI111449-05
Dates: 6/4/14 to 5/31/19
Total Direct: \$1,237,511
Annual Direct: \$247,502

Investigator: **Lee RE** (PI Jackson M)
Title: Mechanisms of Susceptibility and Resistance of *Mycobacterium tuberculosis* to Isoxyl and Thiacetazone
Source National Institute of Allergy and Infectious Diseases (NIAID)
5R21AI130929-02
Dates: 2/10/17 to 1/31/19
Total Direct: \$21,267
Annual Direct: Not Provided

Investigator: **Lee RE** (PI Lafleur M)
Title: Bactericidal antibiotic for Vancomycin Resistant Enterococci
Source National Institute of Allergy and Infectious Diseases (NIAID)
5R44AI122426-03
Dates: 3/15/16 to 2/20/19
Total Direct: \$382,930
Annual Direct: Not Provided

Investigator: **Meibohm B**, Braunstein MS, Gonzalez-Juarrero M, Hickey AJ
Title: Aerosol spectinamide-1599 therapy against tuberculosis
Source National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI120670-04
Dates: 6/16/16 to 5/31/21
Total Direct: \$3,570,230
Annual Direct: \$714,046

Investigator: **Meibohm B** (PI Li W)
Title: Selective Targeting Survivin for Cancer Therapy
Source National Cancer Institute (NCI)
5R01AI120670-04
Dates: 5/1/16 to 4/30/21
Total Direct: \$1,913,635
Annual Direct: Not Provided

Investigator: **Meibohm B** (PI Lowe TL)
Title: Nanogels for Drug Delivery across the BRB to Treat Diabetic Retinopathy
Source National Eye Institute (NEI)
5R01EY023853-04
Dates: 9/01/16 to 8/30/21
Total Direct: \$1,900,000
Annual Direct: Not Provided

Investigator: **Meibohm B** (PI Jonsson CB)
Title: Center of Excellence for Encephalitic Alphavirus Therapeutics
Source National Eye Institute (NEI)
1U19AI142762-01
Dates: 3/01/19 to 2/29/24
Total Direct: \$21,104,316
Annual Direct: Not Provided

Investigator: **Palmer GE**
Title: Molecular and chemical validation of the vacuole as a new antifungal target
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI099080-01A1
Dates: 5/20/14 to 4/30/20
Total Direct: \$1,804,354
Annual Direct: \$360,871

Investigator: **Palmer GE** (subcontracts **Lee RE** and **Meibohm B**)
Title: Broad spectrum antifungals targeting fatty acid biosynthesis
Source National Institute of Allergy and Infectious Diseases (NIAID)
4R33AI127607-03
Dates: 12/1/17 to 11/30/21
Total Direct: \$355,000
Annual Direct: \$88,750

Investigator: **Palmer GE** (PI Reiter LT)
Title: An *in vivo* chemical screen for seizure suppression in Duplication 15q syndrome
Source Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD)
1R21HD091541-01
Dates: 4/1/17 to 3/31/19
Total Direct: \$418,000
Annual Direct: Not Provided

Investigator: **Palmer GE**
Title: Broad spectrum antifungals targeting fatty acid biosynthesis
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI127607-01

Dates: 12/8/16 to 11/30/18
Total Direct: \$449,622
Annual Direct: \$224,811

Investigator: **Peters BM**
Title: Candidalysin: a key mediator of *Candida* vaginitis immunopathology
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI134796-02

Dates: 9/1/18 to 8/31/20
Total Direct: \$380,000
Annual Direct: \$76,000

Investigator: **Peters BM**
Title: Sulfonyleureas as repurposed agents against vulvovaginal candidiasis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R21AI127942-02

Dates: 1/1/18 to 12/31/20
Total Direct: \$228,000
Annual Direct: Not Provided

Investigator: **Peters BM**
Title: Host and microbial factors promoting synergistic mortality during polymicrobial intra-abdominal infections with *Candida albicans* and *Staphylococcus aureus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI141829-01

Dates: 11/13/18 to 10/31/19
Total Direct: \$190,000
Annual Direct: Not Provided

Investigator: **Peters BM (PI Noverr MC)**
Title: Targeted and forward genetic approaches to decipher the pathogenesis of symptomatic vulvovaginal candidiasis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI116025-01

Dates: 12/1/14 to 11/30/19
Total Direct: \$90,000
Annual Direct: Not Provided

Investigator: **Reynolds TS**
Title: Identification of CDP-DAG and serine binding sites in *Candida albicans* phosphatidylserine synthase, an antifungal drug target
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI130895-01

Dates: 1/16/17 to 12/31/18
Total Direct: \$185,880
Annual Direct: Not Provided

Investigator: **Reynolds TS** (PI Wilhelm S)
Title: EDGE CT: Genetic tools to study giant viruses
Source: National Science Foundation, IOS Division Of Integrative Organismal Systems
IOS 1922958
Dates: 10/01/19 to 9/30/22
Total Direct: \$1,009,308
Annual Direct: Not Provided

Investigator: **Rogers PD**
Title: Novel Azole Resistance Mechanisms in *Candida albicans*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI058145-13
Dates: 6/21/17 to 5/31/22
Total Direct: \$2,122,820
Annual Direct: \$454,854

Investigator: **Rogers PD**
Title: Upc2A: A Central Regulator and 'Achilles' Heel' of Fluconazole Resistance in *Candida glabrata*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI131620-03
Dates: 2/07/17 to 1/31/22
Total Direct: \$2,706,949
Annual Direct: \$589,278

Investigator: **Rosch JW**
Title: Pneumococcal pathogenesis in sickle cell disease
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI131620-03
Dates: 12/1/14 to 11/31/19
Total Direct: \$1,250,000
Annual Direct: \$250,000

Investigator: **Rosch JW** (PI Van Opijnen T)
Title: Predicting the emergence of antibiotic resistance through multi-omics approaches and Immune System-surveillance
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5U01AI124302-04
Dates: 3/1/16 to 2/28/21
Total Direct: \$9,892,074
Annual Direct: \$291,009

Investigator: **Rosch JW** (PI Rock CO)
Title: Regulation of lipid metabolism in bacteria
Source: National Institute of Allergy and Infectious Diseases (NIAID)
2R01GM034496-35
Dates: Not Provided

Total Direct: Not Provided
Annual Direct: Not Provided

Foundation and Industry Funding

Investigator: **Cory TJ**
Title: Overcoming Ethanol Dependent Modulation of Transporter Expression in the HIV Macrophage Reservoir
Source: UTHSC New Grant Support Program
Dates: 9/1/18 to 8/3/19
Total Direct: Not Disclosed
Annual Direct: Not Disclosed

Investigator: **Dale JB**
Title: Strengthening the Health System Response to Rheumatic Heart Disease: Developing Evidence-Based Strategies For Prevention
Source: AHA Strategically Focused Research Network Award
Dates: 7/1/17 to 6/30/21
Total Direct: \$1,000,000
Annual Direct: \$316,691

Investigator: **Dale JB**
Title: Strengthening the Health System Response to Rheumatic Heart Disease: Developing Evidence-Based Strategies For Prevention
Source: AHA Strategically Focused Research Network Award
Dates: 7/1/17 to 6/30/21
Total Direct: \$1,000,000
Annual Direct: \$316,691

Investigator: **Fortwendel JR**
Title: Novel Mechanisms of Triazole Antifungal Resistance in Clinical Isolates of *Aspergillus fumigatus*
Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
Dates: 2019 Cycle
Total Direct: \$15,000
Annual Direct: NA

Investigator: **Kumar S**
Title: Exosomes in Smoking mediated HIV-1 pathogenesis
Source: UTHSC New Grant Support Program
Dates: 3/1/18 to 12/31/18
Total Direct: \$30,000
Annual Direct: NA

Investigator: **Kumar S**

Title: Nanoparticle-based targeted delivery of antiretroviral drugs to HIV-infected macrophages
Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
Dates: 1/1/19 to 6/30/20
Total Direct: \$45,000
Annual Direct: \$30,000

Investigator: **Kumar S**
Title: Exosomes in alcohol-induced HIV-1 pathogenesis and neuronal damage
Source: UTHSC Bridge Grant Program
Dates: 3/1/19 to 2/28/21
Total Direct: \$75,000
Annual Direct: \$37,500

Investigator: **Lee RE** (PI Jackowski S)
Title: Small Molecule Modulators of Pantothenate Kinase
Source: CoA Therapeutics INC
Dates: 4/1/17 to 4/30/20
Total Direct: \$1,024,821
Annual Direct: Not Provided

Investigator: **Palmer GE**
Title: Targeting the aromatic amino acid synthesis pathway to develop a new class of broad spectrum antimicrobial agents.
Source: UTHSC CORNET Award Program
Dates: 9/1/17 to 8/31/18
Total Direct: \$100,000
Annual Direct: Not Provided

Investigator: **Palmer GE**
Title: Modulation of *Candida* biofilm formation and catheter lock efficacy by total parenteral nutrition
Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
Dates: 2019 Cycle
Total Direct: \$15,000
Annual Direct: Not Provided

Investigator: **Pierre JF** (PI Davenport)
Title: Unraveling the role of microbial dysbiosis in breast cancer health disparities
Source: Tennessee Clinical and Translational Science Institute
Dates: 2019 Cycle
Total Direct: Not Provided
Annual Direct: Not Provided

Investigator: **Pierre JF** (PI Puchowicz)

Title: Role of Phosphorylation in Microbial Short Chain Fatty Acid Production in a Defined Microbial Community
Source: Tennessee Clinical and Translational Science Institute
Dates: 2019 Cycle
Total Direct: Not Provided
Annual Direct: Not Provided

Investigator: **Pierre JF** (PI Rao)
Title: Role of Microbial Metabolites and Phosphorylation in Diet-Induced Obesity
Source: Le Bonheur Hospital Grant
Dates: 2019 Cycle
Total Direct: Not Provided
Annual Direct: Not Provided

Investigator: **Pierre JF**
Title: Not Provided
Source: UTHSC Department of Pediatrics, Tennessee Governor's Pediatric Recruitment Fund
Dates: 2019 Cycle
Total Direct: Not Provided
Annual Direct: Not Provided

Investigator: **Rosch JW** (PI McDevitt)
Title: Hitting the wall: Harnessing metal-antibiotic synergies
Source: Not Provided
APP1122742
Dates: Not Provided
Total Direct: Not Provided
Annual Direct: Not Provided

Investigator: **Willis KA**
Title: Gastrointestinal microbiome influence on the development of bronchopulmonary dysplasia in very low birthweight neonates
Source: UTHSC Department of Pediatrics
Dates: 2017-Present
Total Direct: Not Provided
Annual Direct: \$15,000

Investigator: **Willis KA**
Title: Gastrointestinal microbiome influence on the development of bronchopulmonary dysplasia in mice
Source: UTHSC Department of Pediatrics and the Marshall Klaus Award
Dates: 2017-Present
Total Direct: Not Provided
Annual Direct: \$20,000

Investigator: **Willis KA**
Title: Metagenomic influence of perinatal antibiotics exposure on growth in the newborn
Source: Not Provided
Dates: 2017-Present
Total Direct: Not Provided
Annual Direct: \$50,000

Publications

Book Chapters

1. **Cory, TJ**. Pathology and Pathophysiology. The APhA Complete Review for the FPGEE, 2nd ed., Boucher B, Ed. American Pharmacist's Association: Washington, DC, 2018.
2. **Hevener KE**. Medicinal Chemistry. The APhA Complete Review for the FPGEE, 2nd ed., Boucher B, Ed. American Pharmacist's Association: Washington, DC, 2018.
3. **Hevener KE**, Ren JH, Pesavento R, Ratia K, Lee H, Johnson ME. Hit-to-Lead: Hit Validation, Assessment, and Improvement of Drug-Like Properties. Modern Advances in Drug Discovery, Lesburg C, Ed. Elsevier: New York, NY, 2018.
4. **Kumar S**. Cytochrome P450 Biocatalysts - Current Applications and Future Prospects. Industrial Biocatalysis, Grunwald P, Ed. Pan Stanford Publishing, Singapore (USA: Boca Raton, FL), 2019.
5. Haque S, Gong Y, Kodidela S, Rahman MA, Ranjit S, **Kumar S**. Cytochrome P450 Enzymes for the Synthesis of Novel and Known Drugs and Drug Metabolites. Industrial Biocatalysis, Grunwald P, Ed. Pan Stanford Publishing, Singapore (USA: Boca Raton, FL), 2019.

Publications

6. Mu Y, Kodidela S, Wang Y, **Kumar S**, and **Cory TJ**. The Dawn of Precision Medicine in HIV: State of the art of Pharmacotherapy. Expert Opinion on Pharmacotherapy. 2018;19(14):1581-1595.
7. Mu Y, Patters BJ, Midde NM, He H, **Kumar S**, and **Cory TJ**. Tobacco and antiretrovirals modulate transporter, metabolic enzyme, and antioxidant enzyme expression and function in polarized macrophages. Current HIV Research. 2018;16(5):354-363.
8. Gong Y, Rao PSS, Sinha N, Ranjit S, **Cory TJ**, and **Kumar S**. The role of cytochrome P450 2E1 on ethanol-mediated oxidative stress and HIV replication in human monocyte-derived macrophages. Biochemistry and Biophysics Reports. 2019;17:65-70.
9. Hatami E, Mu Y, Shields DN, Chauhan SC, **Kumar S**, **Cory TJ**, and Murali Yallapu. Mannose-decorated hybrid nanoparticles for enhanced macrophage targeting. Biochemistry and Biophysics Reports. 2019;17:197-207.
10. Gong Y, Haque S, Chowdhury P, **Cory TJ**, Kodidela S, Yallapu MM, Norwood JM, and Kumar S. Pharmacokinetics and pharmacodynamics of cytochrome p450 inhibitors for HIV treatment. Expert opinion on Drug Metabolism and Toxicology. 2019;15(5):417-427.
11. Haydar D, **Cory TJ**, Birket SE, Murphy BS, Pennypacker KR, Sinai AP, and Feola DJ. Azithromycin Polarized Macrophages to an M2 phenotype via Inhibition of the

- STAT1 and NF- κ B Signaling Pathways. *The Journal of Immunology*. 2019;203:1021-1030
12. Gong Y, Chowdhury P, Bhusetty Nagesh P, **Cory TJ**, Dezfuli C, Kodidela S, Singh A, Yallapu MM, and Kumar S. Nanotechnology approaches for delivery of cytochrome P450 substrates in HIV treatment. *Expert Opinion on Drug Delivery*. 2019;16(8):869-882.
 13. Kodidela S, Wang Y, Patters B, Gong Y, Sinha N, Ranjit S, Girth K, Haque S, **Cory TJ**, McArthur C, Kumar A, Wan JY, **Kumar S**. Proteomic profiling of exosomes derived from plasma of HIV-infected alcohol drinkers and cigarette smokers, *J Neuroimm Pharmacol*. 2019 [Epub ahead of print].
 14. **Dale JB**, Shulman ST. Caution Indicated in Extrapolating Carditis in Rats to Rheumatic Heart Disease in Humans. *J Infect Dis*. 2018;219(4):674-675.
 15. García PC, Paillavil BA, Scioscia N, **Dale JB**, Legarraga P, Salazar-Echegarai FJ, Bueno SM, Kalergis AM, Wozniak A. Clinical and microbiological response of mice to intranasal inoculation with *Lactococcus lactis* expressing Group A *Streptococcus* antigens, to be used as an anti-streptococcal vaccine. *Microbiol Immunol*. 2018;62(11):711-719.
 16. Salehi S, Hohn CM, Penfound TA, **Dale JB**. 2019. Development of an opsonophagocytic killing assay using HL-60 cells for detection of functional antibodies against *Streptococcus pyogenes*. *mSphere*. 2018;3(6) pii: e00617-18.
 17. Osowicki J, Azzopardi KI, Baker C, Waddington CS, Pandey M, Schuster T, Grobler A, Cheng AC, Pollard AJ, McCarthy JS, Good MF, Walker MJ, **Dale JB**, Batzloff MR, Carapetis JR, Smeesters PR, Steer AC. Controlled human infection for vaccination against *Streptococcus pyogenes* (CHIVAS): Establishing a group A *Streptococcus* pharyngitis human infection study. *Vaccine*. 2019;37(26):3485-3494.
 18. Rybak JM, **Fortwendel JR**, **Rogers PD**. Emerging threat of triazole-resistant *Aspergillus fumigatus*. *J Antimicrob Chemother*. 2019;74(4):834-842.
 19. Martin-Vicente A, Souza ACO, Al Abdallah Q, Ge W, **Fortwendel JR**. SH3-class Ras Guanine Nucleotide Exchange Factors are essential for *Aspergillus fumigatus* invasive growth. *Cell Microbiol*. 2019;21(6):e13013.
 20. Rybak JM, Ge W, Wiederhold NP, Parker JE, Kelly SL, **Rogers PD**, **Fortwendel JR**. Mutations in *hmg1*, Challenging the Paradigm of Clinical Triazole Resistance in *Aspergillus fumigatus*. *mBio*. 2019; 10(2) pii: e00437-19.
 21. Souza ACO, Al Abdallah Q, DeJarnette K, Martin-Vicente A, Nywening AV, DeJarnette C, Sansevere EA, Ge W, **Palmer GE**, **Fortwendel JR**. Differential Requirements of Protein Geranylgeranylation for the Virulence of Human Pathogenic Fungi. *Virulence*. 2019;10(1): 511-526.
 22. Zhang M, Prior A, Maddox M, Shen WJ, **Hevener KE**, Bruhn D, Lee REB, Singh A, Reinicke J, Simmons C, Hurdle JG, **Lee RE**, Sun D. Pharmacophore Modeling, Synthesis, and Antibacterial Evaluation of Chalcone and Derivatives. *ACS Omega*. 2018;3(12): 18343-60.
 23. Marreddy RKR, Wu X, Sapkota, M, Prior AM, Jones JA, Sun D, **Hevener KE**, Hurdle JG. The Fatty Acid Synthesis Protein Enoyl-ACP Reductase II (FabK) is a Target for Narrow Spectrum Antibacterials for *Clostridium difficile* Infection. *ACS Infect Dis*. 2019;5(2): 208-217.

24. Luna-Tapia A, DeJarnette C, Sansevere E, Reitler P, Butts A, **Hevener KE**, **Palmer GE**. The Vacuolar Ca²⁺ ATPase Pump Pmc1p is Required for *Candida albicans* Pathogenesis. *mSphere*. 2019;4(1): e00715-18.
25. Lee H, Boyle-Vavra S, Ren J, Jarusiewicz J, Sharma LK, Hoagland DT, Yin S, Zhu T, **Hevener KE**, Ojeda I, Daum RS, Johnson ME. Identification of small molecules exhibiting oxacillin synergy through a novel assay for inhibition of vraTSR expression in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2019;63(9): e02593-18.
26. Jones JA, **Hevener KE**. Crystal structure of the 65-kilodalton amino-terminal fragment of DNA topoisomerase I from the Gram-positive model organism *Streptococcus mutans*. *Biochem Biophys Res Commun*. 2019;516(2): 333-338.
27. Jones JA, Prior A, Mareddy RKR, Wahrmund R, Hurdle JG, Sun D, **Hevener KE**. Small-molecule inhibition of the *Clostridioides difficile* FAS-II enzyme, FabK, results in selective activity. *ACS Chem Biol*. 2019;14(7): 1528-1535.
28. Rahman MA, Kodidela S, Sinha N, Haque S, Shukla PK, Rao RK, **Kumar S**. Plasma exosomes exacerbate alcohol- and acetaminophen-induced toxicity via CYP2E1 pathway. *Sci Rep*. 2019;9(1): 571.
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30. Vaddady PK, Trivedi A, Rathi C, Madhura DB, Liu J, **Lee RE**, **Meibohm B**. Dynamic time-kill curve characterization of spectinamide antibiotics 1445 and 1599 for the treatment of tuberculosis. *Eur J Pharm Sci*. 2019;127: 233-239.
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32. Brewer CT, Yang L, Edwards A, Lu Y, Low J, Wu J, **Lee RE**, Chen T. The Isoniazid Metabolites Hydrazine and Pyridoxal Isonicotinoyl Hydrazone Modulate Heme Biosynthesis. *Toxicol Sci*. 2019;168(1): 209-224.
33. Rathi C, Lukka PB, Wagh S, **Lee RE**, Lenaerts AJ, Braunstein M, Hickey A, Gonzalez-Juarrero M, **Meibohm B**. Comparative pharmacokinetics of spectinamide 1599 after subcutaneous and intrapulmonary aerosol administration in mice. *Tuberculosis (Edinb)*. 2019;114: 119-122.
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39. Polli JW, McCurdy CR, Wurster DE, DeSilva BS, Bak A, Bendayan R, **Meibohm B**, Templeton AC, Weiser W; AAPS Leadership. The Journey to AAPS 2020: a Reflection from Strategic Planning to PharmSci 360. *AAPS Journal*. 2018: 21(1): 2.
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41. Polli JW, McCurdy CR, Wurster DE, DeSilva BS, Bak A, Bendayan R, **Meibohm B**, Templeton AC, Weiser W; AAPS Leadership. The Journey to AAPS 2020: a Reflection from Strategic Planning to PharmSci 360. *AAPS Open*. 2018: 4:8.
42. Donnenberg VS, Chaikin P, Mandic M, **Meibohm B**, van den Anker J, Rhinehart E, Nafziger AN, Burris JF. Core Entrustable Professional Activities in Clinical Pharmacology for Entering Residency: Common Problem Drugs and How to Prescribe Them. *Journal of Clinical Pharmacology*. 2019;59: 915-22.
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44. Walz A, Lukka PB, Pearce C, Crissen E, Braunstein M, Hickey A, **Meibohm B**, Gonzalez-Juarrero M. Sterilization of *Mycobacterium tuberculosis* infected samples using methanol preserves anti-tuberculosis drugs for subsequent pharmacological testing studies. *Tuberculosis*. 2019;117: 52-55
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