

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



ANNUAL REPORT 2019-2020

The Center for Pediatric Experimental Therapeutics



The Center for Pediatric Experimental Therapeutics
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Memphis, TN 38163
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This is a publication of:
The University of Tennessee
The Center for Pediatric Experimental Therapeutics.

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President

Steve Schwab
Chancellor, UTHSC

P. David Rogers, PharmD, PhD
Director (2019 – 2020)
Jarrod R. Fortwendel, PhD
Director (2020 – Present)

<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 over 85 peer-reviewed articles in leading medical or scientific journals.

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 \$7 million in NIH grants. This is at a time when NIH funding has never been more competitive, and many laboratories were faced with the challenge of COVID-19 pandemic-induced closures.

Education of students, post-doctoral trainees and visiting investigators continued to be a major priority in the Center. In 2019-2020, 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 continued to support 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.

2019-2020 Annual Report

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ABOUT THE CENTER

2019-2020

Leadership



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

Director (2019 – 2020)

- Member, St. Jude Faculty
- Chair, Department of Pharmaceutical Sciences
- Endowed Chair of Pharmaceutical Sciences

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



Jarrod R. Fortwendel, PhD

Director (2020 – Present)

- Associate Professor of Clinical Pharmacy and Translational Science
- Assistant Professor of Microbiology, Immunology, and Biochemistry

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.

Director (2020 -Present)

- 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.

- First Tennessee Endowed Chair of Excellence in Clinical Pharmacy
- Associate Professor, Department of Clinical Pharmacy and Translational Science

Joseph F. Pierre, PhD

- Assistant Professor, Department of Pediatrics-Obesity

Todd B. Reynolds, Ph.D.

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

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

Director (2019 – 2020)

- Member, St. Jude Faculty
- Chair, Department of Pharmaceutical Sciences

Jason W. Rosch, PhD

- Associate Member, Infectious Diseases Department, St. Jude Children's Research Hospital

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

Graduate Trainees

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

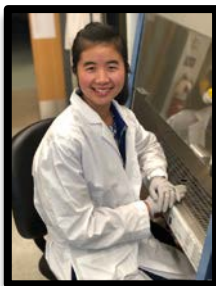
Ying Mu



“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

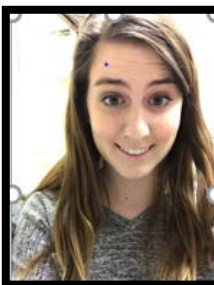
Parker Reitler



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

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

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

Postdoctoral Trainees

Jeffrey Rybak, Pharm.D., Ph.D.



“Novel Mechanisms of Triazole Resistance Among Clinical Isolates of *Candida auris*”

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

Faculty Research Activities

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

Director, Center for Pediatric Experimental Therapeutics (2019 – 2020)

Member, St. Jude Faculty

Chair, Department of Pharmaceutical Sciences

Endowed Chair in Pharmaceutical Sciences



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.

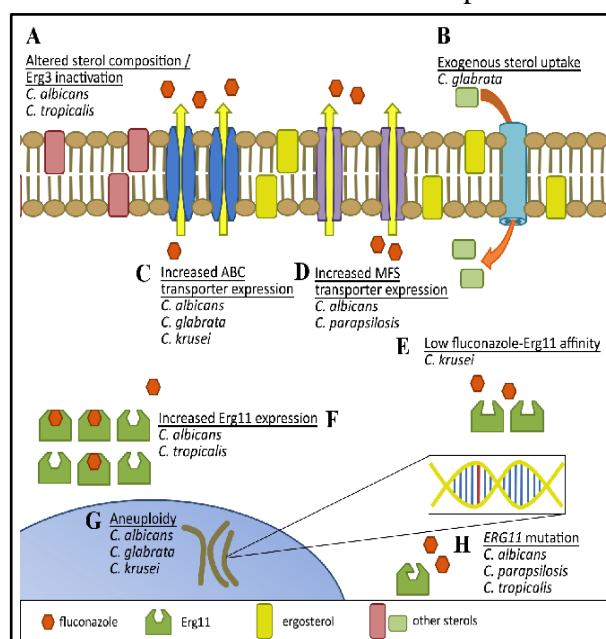


Figure 1. Comparison of documented fluconazole resistance mechanisms in *Candida* species. **A)** Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. **B)** Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased 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

Jeffery M. Rybak, Pharm.D., PhD – Post-doctoral Fellow
Laura Doorley – Graduate Student, Integrated Program in Biomedical Sciences
Yu Li – Graduate Student, Integrated Program in Biomedical Sciences

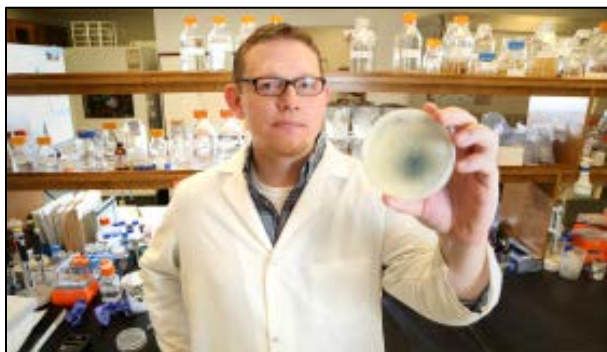
Key Collaborators:

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
Jarrod R. Fortwendel, PhD – University of Tennessee Health Science Center

Jarrod R. Fortwendel, PhD.

Director, Center for Pediatric Experimental Therapeutics (2020 – Pres)
Associate Professor of Clinical Pharmacy and Translational Science

Aspergillus fumigatus is among the most common causes of human fungal infection in immunocompromised individuals, including solid organ transplant recipients, those undergoing hematopoietic stem cell transplant, and patients receiving highly immunosuppressive chemotherapies. It is estimated that between 200,000 and 400,000 cases of invasive aspergillosis (IA) occur annually. If untreated, these infections are almost always fatal, and even with proper diagnosis and treatment, are associated with an overall 50% mortality rate. Furthermore, the estimated annual cost of these invasive *Aspergillus* infections in the U.S. approaches \$1 billion. In the non-immune suppressed patient, *Aspergillus* species can cause chronic, non-invasive infections that range from asymptomatic colonization of pre-formed cavitory lesions to inflammatory forms of disease. The inflammatory disease states, together known as Chronic Pulmonary Aspergillosis (CPA), are recently recognized by new diagnostic criteria and are actually a collection of syndromes known as chronic necrotizing, chronic cavitory and chronic fibrotic pulmonary aspergillosis depending on clinical manifestations. Prior mycobacterial infections, COPD and additional chronic lung complications are all major predisposing conditions for development of CPA, conditions that are often further complicated by the presence of the fungus. CPA is now considered a major under-recognized disease. Therapy options are extremely limited for the aspergilloses. Resistance to the triazole class of antifungals, the major class with anti-*Aspergillus* activity, 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. Our work addresses multiple questions directed at significant knowledge gaps concerning the elucidation of: 1) host-pathogen interactions during invasive and chronic fungal diseases; 2) molecular mechanisms of *A. fumigatus* pathogenic fitness; and 3) and mechanisms of triazole antifungal resistance in *Aspergillus* species.



Current Lab Members:

Wenbo Ge – Research Associate

Adela Martin-Vicente, PhD – Postdoctoral Fellow

Ana Camila Oliveira Souza, PhD – Postdoctoral Fellow

Ashley Nywening – Graduate Student

Past Lab Members:

Qusai Al Abdallah, PhD – Postdoctoral Fellow

Alba Perez Cantero – Visiting Research Scholar

Xabier Guruceaga – Visiting Research Scholar

Amy Hill – Research Technician

Rachael Lovingood – Research Associate

Tiffany Norton, PhD – Graduate Student

Brian M. Peters, Ph.D.
Associate Professor of Clinical Pharmacy and Translational Science
First Tennessee Endowed Chair of Excellence in Clinical Pharmacy

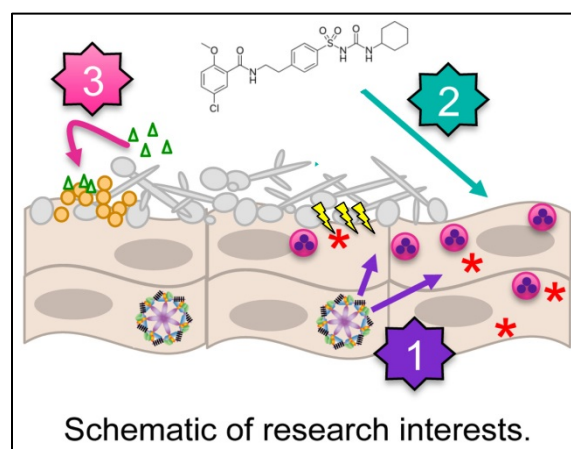
The Peters lab has two main foci of research: **1)** the host and fungal molecular mechanisms responsible for the immunopathogenesis of vulvovaginal candidiasis and **2)** quorum sensing and toxin regulation during fungal-bacterial intra-abdominal infection.



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. Current projects seek to identify relative pathogenicity of candidalysin alleles observed amongst clinical isolates and delineating mechanisms to explain inefficient toxin activity. We are also focused on determining the downstream signaling events relevant to disease pathogenesis, including activation those that contribute to neutrophil influx at the vaginal mucosa.



[2] We are also currently interrogating the sulfonamide 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 has led to the identification of 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, identifying host pathways that are substantially altered during co-infection, and devising strategies to treat downstream effects of α -toxin activity.

LAB PERSONNEL

Dr. David Lowes (Research Associate)

Dr. Zhenbo Xu (Visiting scholar, Associate Professor SCUT)

Dr. Junyan Liu (Postdoctoral fellow)

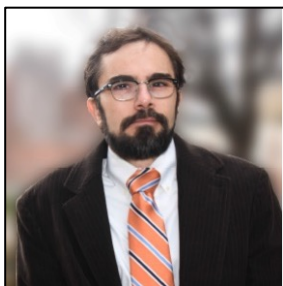
Olivia Todd (PhD Student, Integrated Biomedical Sciences Program)

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

Amanda Vogel (PhD Student, Integrated Biomedical 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.

Graduate Students – Jessica Regan B.S.; Parker Reitler B.S.

Santosh Kumar, Ph.D.

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 11 years, Dr. Kumar's group has published substantially in this field (~75 papers), with a total of >115 papers in his career. Dr. Kumar has mentored eight graduate students and three post-doctorate fellows along with numerous other trainees. Currently, he is mentoring three graduate students and two PDFs. 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

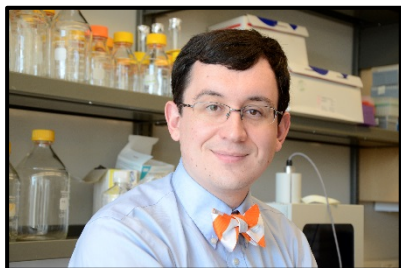
Dr. Sunitha Kodidela, Dr. Asit Kumar, Ms. Ahona Mukherji, Ms. Lina Zhou, Ms. Kelli Gerth, and Ms. Namita Sinha

Recently trained PDFs and graduated students

PDFs: Dr. PSS Rao, Dr. Narasimha Midde

Students: Dr. Sabina Ranjit, Dr. Mohammad A. Rahman, Dr. Sanjana Haque, Dr. Yuqing Gong.

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, nearly 3 million people are infected with drug-resistant bacteria and over 35,000 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*, & *Fusobacterium nucleatum* 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 digestive tract organisms, 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:

Postdoctoral Fellow – Afroza Akhtar, Ph.D.

Graduate Students – Lamyia Alghanim, Rand Al-waqfi, Kristiana Avad.

Pharmacy Students –Humna Meer, Thao La

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

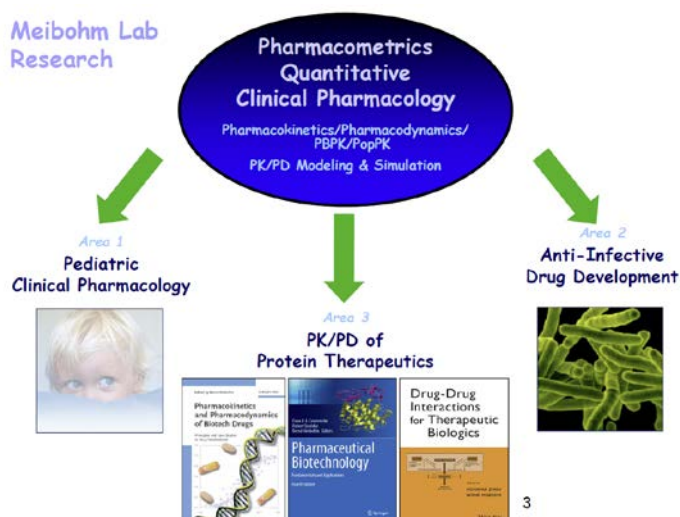
Dr. Meibohm's research is focused on the investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs with special emphasis on PK/PD-correlations.



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)
- Ashish Srivastava, 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)
- Paridhi 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.

Joseph F. Pierre, Ph.D.
**Assistant Professor of Pediatrics, Microbiology, Immunology, and
Biochemistry**

**Title: Contribution of Diet, Gut Microbes, and Microbial Metabolites in Host
Metabolism.**



My research program focuses on underlying microbiome mediated mechanisms of metabolic and immunologically driven diseases - including in obesity, liver disease, inflammatory bowel disease (IBD), and cancer. My experimental approaches include murine models of obesity, surgical intervention, and germ-free/gnotobiotic conditions to investigate microbial-host interactions and homeostasis. Specifically, our unique translational models include murine bariatric surgery and parenteral nutrition, which are common clinical modalities used in humans and lead to marked alterations in the gut microbiome and host metabolism. We also isolate and culture human and murine *in vitro* intestinal organoids (enteroids) as 3D and 2D microstructures, which are used to model gut epithelial interaction with microorganisms and the immune compartment. Growing evidence demonstrates that intestinal fungal species contribute to IBD and enterocolitis onset and progression. Enteroids, especially 2D monolayers, are useful for investigating the host mucosal interface with pathogen virulence. Along with colleagues, we are screening human enteroid cohort interactions with fungal pathobionts to gain deeper understanding of this nascent field. Another major area of research is the role of bile acids in metabolic regulation, and more recently cancer tumorigenesis. Our recent NIH award focuses on the role of intestinal microbes and bile acid enterohepatic circulation in regulating immunological response to the tumor microenvironment in breast cancer. To support many of our studies, our lab also supports next generation sequencing platforms and the computational strategies required to analyze complex (bacterial and fungal) microbial communities within the gut and other body sites.

Current lab members:

Lab manager – Qusai Al Abdallah, PhD

Research Technician – Tahliyah Mims, BS

Research Technician - TBD

Jason W. Rosch, Ph.D.
Associate Member, Department of Infectious Diseases
St Jude Children's Research Hospital

Host-Pathogen Interactions and Antibiotic Resistance in Pathogenic Streptococci



The overall goals of my research program are gain a greater understanding for the novel strategies to target invasive bacterial infections, particularly bacterial pneumonia and sepsis. My specific interest is gaining an understanding of infections and the development of antibiotic resistance in the context of high-risk hosts. Our lab has extensive experience with the genetic manipulation and characterization of Gram-positive pathogens including modeling bacterial pathogenesis and host response in the context of various murine models of infection including colonization, transmission, pneumonia, bacteremia, meningitis, and acute otitis media. This background in bacterial genetics and pathogenesis modeling has allows us to achieve mechanistic insights into host-pathogen interactions.

The primary emphasis of my research program is in three areas. 1) *Genetic approaches to delineate host-pathogen interaction in Streptococcus pneumoniae.* Mechanistic characterization of these virulence strategies provides insight into the intricacies underlying the various disease manifestations of the pneumococcus. Our most recent focus is modeling the impact of influenza co-infection on various aspects of pneumococcal host-pathogen interactions. We have a longstanding interest in therapeutic interventions based on these discoveries, both through vaccine development and tailored interventions to exploit specific virulence strategies. 2) *The dissection of the mechanisms underlying the heightened inflammation and infection susceptibility that manifests in the context of high-risk hosts.* Patients with sickle cell disease are at exceedingly high risk for invasive pneumococcal disease, though the factors underlying this susceptibility remain largely unknown. Using functional genomics and murine models of sickle cell disease we have been able to unravel previously unknown risk factors and tailor specific interventions to mitigate infection susceptibility. 3) *Understanding antibiotic resistance in the context of impaired immunity.* This work encompasses both basic research and translational projects dissecting molecular mechanisms of resistance that have emerged in our patient population and the impact of antibiotics and chemotherapy on antibiotic resistance in commensal bacteria. We have an active research program in understanding the immune constraints in the acquisition and development of antibiotic resistance in bacterial pathogens.

Current lab members:

Lab manager – Amy Iverson, B.S.

Research Associate – Haley Echlin, PhD.

Graduate Student – Tina Dao, B.S

Postdoctoral Fellow – Andy Nishimoto, PhD, PharmD.

Animal Research Technician – Aaron Poole

Todd B. Reynolds, Ph.D.
Associate Professor of Microbiology

Title: Cell envelope proteins as novel antifungal drug targets.



Fungi cause over 1 billion infections world-wide, and the most common cause genus of fungi that causes these infections are yeast of the genus *Candida*. The most frequently isolated *Candida* species from infectious sites is *C. albicans*, and it, along with other *Candida* species, are natural commensals of the human gut, vaginal, tract, and skin. However, they can become pathogenic under conditions that compromise immune protection and cause painful mucosal infections and life-threatening invasive infections. Mucosal infections can range from vaginal infections in women to oropharyngeal infections in immunocompromised patients that have AIDS, use corticosteroids, take broad spectrum antibiotics, or take certain drugs. Life threatening infections are associated with cancer and organ transplant chemotherapies as well as the use of intravascular catheters. In fact, *Candida* species are the 3rd-4th most common cause of catheter associated invasive infections in intensive care units. A major concern with *Candida* infections is that there are only three classes of antifungals commonly used for invasive infections, and these are limited in their efficacy by a combination of drug toxicity, drug resistance, and only a few can be taken orally. My lab is exploring this through two major foci that both involve components of the cell envelope (cell wall and plasma membrane). 1) We have found that the *C. albicans* phosphatidylserine (PS) synthase enzyme has great potential as a drug target. PS is plasma membrane lipid, and the fungal PS synthase is the sole source for PS in fungi, and is required for virulence of *C. albicans* in mouse models of both oral and invasive infection. Moreover, it is essential for viability in the fungal pathogen *Cryptococcus neoformans*. In addition, PS synthase is conserved throughout fungi, and the human PS synthase uses a completely different mechanism to synthase PS and bears little sequence similarity to the fungal enzyme. Altogether, this indicates that inhibitors of fungal PS synthase would prevent virulence, have broad applicability to other fungi, and have low toxicity. My lab is exploring the structure of *C. albicans* PS synthase with a goal of developing small molecule inhibitors of this enzyme. 2) A second major direction of my lab is to explore the role of immunotherapy against *Candida* species. Oral and invasive infections do not occur as often in the immunocompetent, so enhancing the residual immune response in immunocompromised patients should improve health outcomes. We have found that hyperactivation of some signaling pathways in *C. albicans* leads to greater exposure of the fungus to immune cells and a reduction in virulence during infection. We are working to discover how these pathways cause this reduction in virulence with the long-term goal of exploiting this to improve immunotherapy. Altogether, these two foci in my lab complement one another as they both focus on aspects of the cell envelope that can be exploited to improve antifungal therapies.

Current lab members:

Graduate students – Andrew Wagner, B. S.; Elise Phillips, B. S.; Yue Zhou, M. Sc.; Jordan Cannon, B.S.

Research Specialist – Stephen Lumsdaine, B. S.

DIRECTION OF THE CENTER

2019-2020

Goals and Future Plans

In the coming year, the CPET will continue to refine its focus on the overarching themes of Pediatric Infectious Diseases and Antiinfective Pharmacotherapy. We will continue to expand our work specifically in the areas of fungal pathogens, HIV/AIDS, and anti-infective drug discovery and development. In addition, we aim to expand our expertise with the recruitment of new faculty to the UTHSC campus, as well as to the CPET. Specifically, the CPET will look to add core faculty focused on childhood asthma, co-infections, and research-active clinical faculty with high potential for collaborative research interactions with current CPET members. To support this goal, a new “CPET Seed Grant Program” is currently under development for implementation in either the 2020-2021 or 2021-2022 cycle. Through this program, CPET investigators would be able to receive seed monies for projects deemed competitive for collaborative extramural funding (e.g., NIH multi-PI R01 applications, program project grants, etc.) within the core Center research focus domains outlined above. This Program aims to facilitate truly translational discoveries and to support the generation and dissemination of new knowledge regarding the treatment of childhood diseases throughout UTHSC, the state of Tennessee, and the nation. 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 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 2019-20 Actual			FY 2020-21 Proposed			FY 2021-22 Requested		
	Matching	Appopr.	Total	Matching	Appopr.	Total	Matching	Appopr.	Total
Salaries									
Faculty	\$1,190,838	\$15,841	\$1,206,679	\$1,202,746	\$12,000	\$1,214,746	\$1,214,773	\$12,000	\$1,226,773
Other Professional	215,895	0	215,895	218,054	0	218,054	220,235		220,235
Clerical/ Supporting	228,387	0	228,387	230,671	15,000	245,671	253,738	15,000	268,738
Assistantships	165,745	136,730	302,475	167,402	153,000	320,402	174,148	153,000	327,148
Total Salaries (Excluding Longevity)	\$1,800,865	\$152,571	\$1,953,436	\$1,818,873	\$180,000	\$1,998,873	\$1,862,894	\$180,000	\$2,042,894
Longevity (Exclude from Salaries)	\$7,555	\$319	\$7,874	\$7,631	\$0	\$7,631	\$7,707	\$0	\$7,707
Fringe Benefits	430,080	12,568	442,648	434,380	25,125	459,505	465,723	25,125	490,848
Total Personnel	\$2,238,500	\$165,458	\$2,403,958	\$2,260,884	\$205,125	\$2,466,009	\$2,336,324	\$205,125	\$2,541,449
Non-Personnel									
Travel	\$19,869	\$5,172	\$25,041	\$7,000	\$5,000	\$12,000	\$16,000	\$5,000	\$21,000
Software			0		5,000	5,000		5,000	5,000
Books & Journals			0			0			0
Other Supplies	4,676	7,130	11,806	5,000	32,702	37,702	13,660	26,151	39,811
Equipment			0		20,000	20,000			0
Maintenance			0			0			0
Scholarships		1,485	1,485		0	0			0
Consultants			0			0			0
Renovation			0			0			0
Other (Specify):			0			0			0
Media Processing	1,000		1,000	1,000		1,000	1,000		1,000
Communication	1,500	16	1,516	480	0	480	1,500		1,500
Professional Services & Memberships	2,900	18,689	21,589	3,000	15,000	18,000	5,000	15,000	20,000
Rentals & Insurance		3,425	3,425		5,000	5,000	2,000	5,000	7,000
Insurance & Interest		6,244	6,244		0	0	6,000		6,000
Contractual & Special Services	9,500	1,015	10,515	5,000	5,000	10,000	15,000	5,000	20,000
Other Services & Expenditures		5,240	5,240		0	0			0
UT Direct Cost Sharing			0			0			0
Total Non-Personnel	\$39,445	\$48,416	\$87,861	\$21,480	\$87,702	\$109,182	\$60,160	\$61,151	\$121,311
GRAND TOTAL	\$2,277,945	\$213,874	\$2,491,819	\$2,282,364	\$292,827	\$2,575,191	\$2,396,484	\$266,276	\$2,662,760
Revenue									
New State Appropriation		\$253,105	\$253,105		\$253,596	\$253,596		\$266,276	\$266,276
Carryover State Appropriation		0	0		39,231	39,231		0	0
New Matching Funds	2,277,945	0	2,277,945	2,282,364	0	2,282,364	2,396,484	0	2,396,484
Carryover from Previous Matching Funds		0	0		0	0		0	0

YEAR-IN-REVIEW

2019-2020

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 \$7 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).

In a year cut short by a global pandemic, the CPET maintained high productivity. This year, in addition to the CPET Scholars Program, the Center supported six speakers as part of the CPET Seminar Series. These speakers are invited by Center faculty and represent leading experts in the fields of pediatrics, clinical pharmacy, and infectious diseases. The CPET Seminar Series serves to promote research conducted by Center faculty and to engage leading experts for future research collaborations, as well as for networking opportunities for trainees in the CPET Scholars Program. Although the CPET was slated to again be instrumental in supporting the Annual UT Fungal Pathogens Group Retreat, taking place each year in the month of July, plans for this essential activity were postponed. The planned programming included focused research presentations from graduate students and post-doctoral fellows from each laboratory as well as basic science and clinical keynote lectures. This year, invited keynote speakers were John C. Panepinto, Ph.D., Professor and Director of Recruiting and Admissions, PhD Program in Biomedical Sciences from the University at Buffalo and Cornelius (Neil) J. Clancy, M.D., Associate Professor of Medicine, Associate Chief of VA Pittsburgh Health System and Opportunistic Pathogens, Chief of Infectious Diseases, University of Pittsburgh. Assuming a return to normal activities by July 2021, the retreat will be re-scheduled.

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.

CPET Seminar Series (2019-2020)



Scott Filler, MD
Investigator, The
Lundquist Institute
Professor of Medicine,
David Geffen School of
Medicine at UCLA
Principal, NovaDigm
Technologies



**Kevin W. Garvey,
PharmD, MS, FASHP**
Professor and Chair,
Dept of Pharmacy
Practice and
Translational Research,
University of Houston



Joseph F. Pierre, PhD
Assistant Professor of
Pediatrics
Assistant Professor of
Microbiology,
Immunology and
Biochemistry
UTHSC, Memphis



W. Scott Moye-Rowley, PhD
Professor, Molecular
Physiology and Biophysics,
Carver College of Medicine,
University of Iowa



Damian Krysan, MD, PhD
Professor of Pediatrics –
Infections Disease,
Professor of Microbiology
and Immunology
Director, Division of Pediatric
Infectious Disease, Carver
College of Medicine,
University of Iowa



Kevin K. Fuller, PhD
Assistant Professor
Dept. of Microbiology and
Immunology
Dept. of Ophthalmology,
College of Medicine,
The University of
Oklahoma Health Sciences
Center

Extramural Funding

Extramural Funding

Federal Funding (including NIH)

Investigator: **Cory TJ** (MPI **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 6/30/23
Total Direct: \$960,000
Annual Direct: \$225,000

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 6/30/22
Total Direct: \$2,768,850
Annual Direct: \$528,426

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 10/31/21
Total Direct: \$418,000
Annual Direct: \$125,000

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 6/30/21
Total Direct: \$418,000
Annual Direct: \$125,000

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: **Fortwendel JR (MPI Rogers PD)**
Title: Non-Cyp51A Mutation Mediated Triazole Resistance in *Aspergillus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI143197
Dates: 3/1/20 to 2/28/25
Total Direct: \$2,472,220
Annual Direct: \$492,444

Investigator: **Hevener KE**
Title: Development and Evaluation of Inhibitors of the *C. difficile* Enzyme, FabK, as Microbiome-Sparing Antibacterials
Source: Department of Defense (DoD), CDMRP
W81XWH-20-1-0296
Dates: 8/1/2019 to 7/31/2024
Total Direct: \$1,397,074
Annual Direct: Not Provided

Investigator: **Kumar S (MPI Cory TJ, subcontract Lee R)**
Title: Monocytic and plasma exosomal cytochrome P450s in smoking-mediated HIV-1 pathogenesis
Source: National Institute of Drug Abuse (NIDA)
5R01DA047178
Dates: 9/30/18 to 6/30/23
Total Direct: \$1,700,000
Annual Direct: \$225,000

Investigator: **Kumar S**
Title: Targeted Nano-Chemosensitization of Breast Cancers
Source: National Cancer Institute (NCI)
1R15CA213232-01
Dates: 9/1/17 to 8/31/21
Total Direct: \$289,354
Annual Direct: \$289,354

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: \$634,513

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: 6/14/18 to 5/31/22
 Total Direct: Not Provided
 Annual Direct: \$452,681

Investigator: **Lee RE**
 Title: Spectinomycin Analogs for NTM Infections
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI157312

Dates: 9/17/20 to 8/31/25
 Total Direct: Not Provided
 Annual Direct: \$599,062

Investigator: **Meibohm B** (MPI Lei W, Li Z)
 Title: Dual inhibition of MDM2 and XIAP as a therapeutic strategy in cancer
 Source: National Cancer Institute (NCI)
 5R01CA240447

Dates: 7/1/20 to 6/30/25
 Total Direct: \$2,720,508
 Annual Direct: \$462,561

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: \$582,610

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: \$250,000

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: \$2,830,169

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: Not Provided
Annual Direct: \$379,500

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 8/31/22
Total Direct: \$1,000,000
Annual Direct: \$250,000

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: \$275,000
Annual Direct: \$125,000

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 10/31/20

Total Direct: \$275,000

Annual Direct: \$125,000

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 11/30/20

Total Direct: \$365,000

Annual Direct: \$90,000

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: **Reynolds TS**

Title: Regulation of $\beta(1,3)$ -glucan exposure in *Candida albicans*

Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI153599

Dates: 5/8/20 to 4/30/25

Total Direct: \$2,533,727

Annual Direct: \$361,932

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: \$312,303

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: \$381,416

Investigator: **Rogers PD (MPI Fortwendel JR)**
Title: Non-Cyp51A Mutation Mediated Triazole Resistance in *Aspergillus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI143197
Dates: 3/1/20 to 2/28/25
Total Direct: \$2,472,220
Annual Direct: \$492,444

Investigator: **Rosch JW**
Title: Pneumococcal pathogenesis in sickle cell disease
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI131620
Dates: 12/1/14 to 11/31/20
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: **Pierre JF (MPI Makowski)**
Title: Role of microbial-modulated bile acid receptor signaling in breast cancer
Source: National Cancer Institute (NCI)
R01CA253329
Dates: 8/1/20 – 4/30/25
Total Direct: \$2,100,000
Annual Direct: \$274,540

Investigator: **Pierre JF (PI Sumida K)**
Title: Circulating microbiome and premature mortality in hemodialysis patients
Source: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
R01DK125586
Dates: 7/1/20 – 6/30/25
Total Direct: \$3,100,000
Annual Direct: \$450,027

Investigator: **Pierre JF (PI Gosain A)**
Title: Dysbiosis in Hirschsprung Associated Enterocolitis

Source Pathogenesis
National Institute of Diabetes and Digestive and Kidney
Diseases (NIDDK)
R01DK125047
Dates: 6/1/20 – 5/30/25
Total Direct: \$2,700,000
Annual Direct: \$287,987

Foundation and Industry Funding

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: *Aspergillus fumigatus* kinase-driven inflammasome activation
Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
Dates: 2019 Cycle
Total Direct: \$15,000
Annual Direct: N/A

Investigator: **Peters BM (MPI Hevener K)**
Title: Dual function inhibitors to suppress host inflammation and
fungal growth
Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
Dates: 2019 Cycle
Total Direct: \$15,000
Annual Direct: N/A

Investigator: **Peters BM (MPI Stultz J)**
Title: Lipid emulsion composition as a determinant of fungal biofilm
formation and incidence of candidemia
Source: UTHSC CoP Dean's Enhancement Program for Seed
Research Grant
Dates: 2019 Cycle
Total Direct: \$15,000
Annual Direct: N/A

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: 2019 Cycle
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: **Hevener K (MPI Peters BM)**
 Title: Dual function inhibitors to suppress host inflammation and fungal growth
 Source: UTHSC CoP Dean's Enhancement Program for Seed Research Grant
 Dates: 2019 Cycle
 Total Direct: \$15,000
 Annual Direct: N/A

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: **Willis KA**
 Title: Gastrointestinal microbiome influence on the development of bronchopulmonary dysplasia in very low birthweight neonates
 Source: UTHSC Department of Pediatrics
 Dates: 2017-2020
 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: 2017-2020
 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: 2017-2020
 Total Direct: Not Provided
 Annual Direct: \$50,000

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