

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



ANNUAL REPORT

2021-2022

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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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 over 60 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 over \$12 million in direct costs of NIH and private industry/foundation grants.

Education of students, post-doctoral trainees and visiting investigators continued to be a major priority in the Center. In 2021-2022, the CPET faculty continued to direct the training of sizable numbers of 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 and has now developed a CPET Pediatric Infectious Disease Pharmacy Fellowship. 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.

2021-2022 Annual Report

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ABOUT THE CENTER

2021-2022

Leadership



Jarrod R. Fortwendel, PhD

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



Glen E. Palmer, PhD

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



P. David Rogers, PharmD, PhD, FCCP

- Scientific Advisor
- Member, St. Jude Faculty
- Chair, Department of Pharmacy and Pharmaceutical Sciences
- Endowed Chair in Pharmaceutical Sciences



Jeremy S. Stultz, PharmD, BCPPS

- Scientific Advisor
- Coordinator, CPET Pediatric Infectious Disease Clinical Pharmacy Fellowship
- Associate Professor, Department of Clinical Pharmacy and Translational Science
- UTHSC / Le Bonheur Children's Hospital Infectious Diseases and Antimicrobial Stewardship Residency Mentor

Faculty

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

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

James B. Dale, M.D.

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

Jarrod R. Fortwendel, Ph.D. (Director)

- Associate Professor, Department of Clinical Pharmacy and Translational Science

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

- Assistant Professor, Department of Pharmaceutical Sciences

Camaron Hole, PhD

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

Santosh Kumar, Ph.D.

- Associate Professor, Department of Pharmaceutical Sciences

Bernd Meibohm, Ph.D.

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

Glen E. Palmer, Ph.D. (Scientific Advisor)

- 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

Todd B. Reynolds, Ph.D.

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

P. David Rogers, Pharm.D., Ph.D. (Scientific Advisor)

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

Jason W. Rosch, PhD

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

Jeffery Rybak, PharmD, PhD

- Instructor, Pharmacy and Pharmaceutical Science Department, St. Jude Children's Research Hospital

Jeremy Stultz, PharmD (*Fellowship Coordinator*)

- Associate Professor, Department of Clinical Pharmacy and Translation Science

Emeritus Faculty

Jeffrey M. Becker, Ph.D.

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

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.)

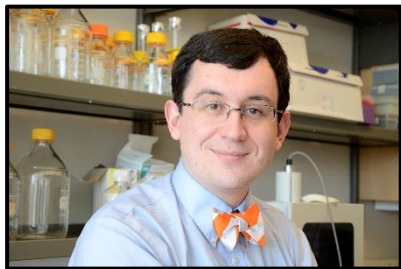
James B. Dale, M.D.

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

Faculty Research Activities

Theodore J. Cory, Pharm.D., Ph.D.
Assistant Professor of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center, Memphis

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

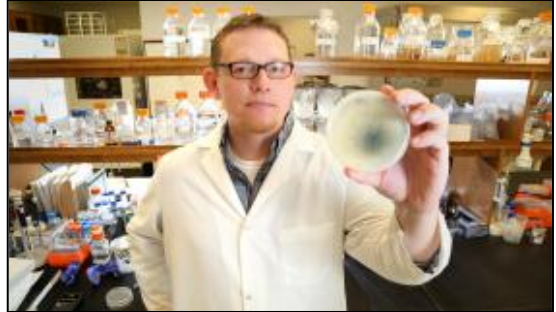
polarized subsets, the classically activated (M1) phenotype, which is pro-inflammatory and involved in the destruction of intracellular pathogens, and the alternatively activated (M2) phenotype, which is anti-inflammatory and involved in tissue repair. The role of these two subsets of macrophages in 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

Ivy Antwi, M.S. – Graduate Student (Pharmaceutical Sciences Graduate Program)

Jarrold R. Fortwendel, PhD.
Associate Professor, Clinical Pharmacy and Translational Science
Director, Center for Pediatric Experimental Therapeutics
University of Tennessee Health Science Center, Memphis

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:

Jarrold R. Fortwendel, PhD – Principal Investigator

Wenbo Ge – Research Associate

Adela Martin-Vicente, PhD – Postdoctoral Fellow

Xabier Guruçea Sierra, PhD – Postdoctoral Fellow

Ashley V. Nywening – Graduate Student, Integrated Program in Biomedical Sciences

Harrison Thorn – Graduate Student, Pharmaceutical Sciences Program

Jinhong Xie, MS – Graduate Student, Pharmaceutical Sciences Program

Christian H. Peevyhouse – PharmD/PhD Dual Enrollment Graduate Program

Kirk E. Hevener, Pharm.D., Ph.D.
Assistant Professor of Pharmaceutical Sciences
University of Tennessee Health Science Center, Memphis

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 – Lamy Alghanim, Rand Al-waqfi, Kristiana Avad.

Pharmacy Students – Humna Meer, Thao La

Camaron R. Hole, Ph.D.
Assistant Professor of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center, Memphis

Cryptococcus neoformans is the most common disseminated fungal pathogen in AIDS patients, with an estimated quarter million cases of cryptococcal meningitis each year resulting in ~200,000 deaths and remains the third most common invasive fungal infection in organ transplant recipients. Current antifungal therapy is hampered by toxicity and/or the inability of the host's immune system to aid in resolution of the disease; treatment is further limited by drug cost and availability in the resource-limited settings where this disease is rampant. Even with appropriate therapy, one third of patients with cryptococcal meningitis will undergo mycologic and/or clinical failure. Patients that do recover can be left with profound neurological sequelae, highlighting the urgent need for more effective diagnostics, therapies, and/or vaccines to combat cryptococcosis



Because host immune responses are so vital to the control of cryptococcosis, the focus of my research is to delineate the host: fungal interactions that impact *C. neoformans* pathogenesis or clearance. This can be driven by fungal components or by host response pathways. One of the main interfaces between the fungus and the host is the fungal cell wall. Most fungal cell walls contain chitin, however, the cryptococcal cell wall is unusual in that the chitin is predominantly deacetylated to chitosan. Why *Cryptococcus* converts chitin to chitosan and what advantages this conversion provides to the organism are not well understood. Chitosan deficient strains of *C. neoformans* are avirulent and rapidly cleared from the murine lung. Moreover, infection with a chitosan deficient *C. neoformans* strain lacking three chitin deacetylases (*cda1Δcda2Δcda3Δ*,) was found to confer protective immunity to a subsequent challenge with a virulent wild type counterpart. In addition to the chitin deacetylases, it was previously shown that chitin synthase 3 (Chs3) is also essential for chitin deacetylase mediated formation of chitosan. Mice inoculated with *chs3Δ* at a dose previously shown to induce protection with *cda1Δ2Δ3Δ* die within 36 hours after installation of the fungal organism. Using these chitosan deficient strains, as well as other strains that have defects in the fungal cell wall, we plan to study the pathways that drive the host response, the cryptococcal components that drive the immune response, and the bifurcation between protective and non-protective innate host responses.

Current lab members:

Lab Manager – Rebekah Watson

Technician – Elexis Allen

Santosh Kumar, Ph.D.
Professor of Pharmaceutical Sciences
Assistant Dean for Scholarly Integration and Collaboration
University of Tennessee Health Science Center, Memphis

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.

Bernd Meibohm, Ph.D., FCP, FAAPS
Professor of Pharmaceutical Sciences,
Associate Dean for Research and Graduate Programs
University of Tennessee Health Science Center, Memphis

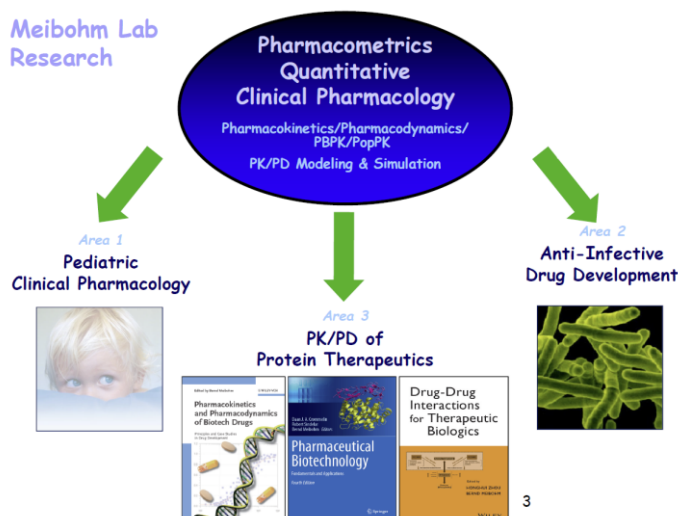
Dr. Meibohm's research is focused on the investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs with special emphasis on PK/PD-correlations.

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.

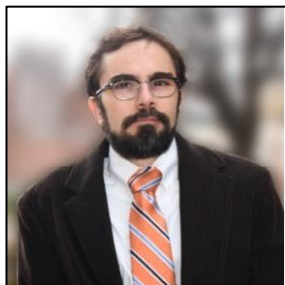


LAB PERSONNEL

- 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)

Glen E. Palmer, Ph.D.
Associate Professor of Clinical Pharmacy and Translational Science
Scientific Advisor, Center for Pediatric Experimental Therapeutics
University of Tennessee Health Science Center, Memphis

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:

Tracy Peters M.S - Lab Manager

Chun Cai – Technician

Katie Tucker - Technician

Jessica Regan - Graduate Student, Pharmaceutical Sciences Program

Parker Reitler – Graduate Student, Integrated Program in Biomedical Sciences

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

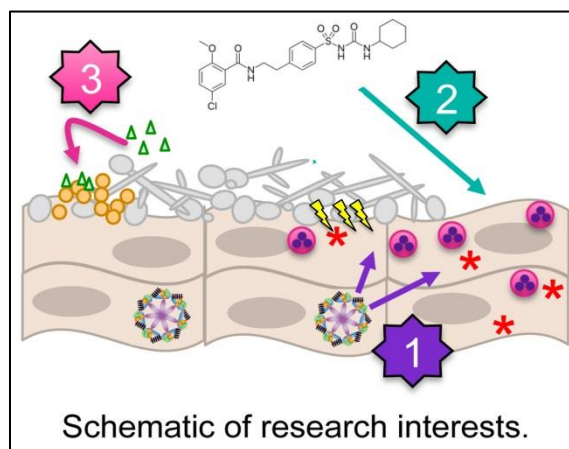
The Peters lab has two main foci of research: **1)** the host and fungal molecular mechanisms responsible for the immunopathogenesis of vulvovaginal candidiasis and **2)** quorum sensing and toxin regulation during fungal-bacterial intra-abdominal infection.

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 Members:

Gustavo Alvira-Arill, PharmD – Pharmacy Fellow, LeBonheur Hospital/UTHSC

Jian Miao, MS - Graduate Student, Pharmaceutical Sciences Program

Jennifer Carnahan – Technician

Saikat Paul – Postdoctoral Fellow

Todd B. Reynolds, Ph.D.
Professor of Microbiology
University of Tennessee, Knoxville

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 synthesize 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.

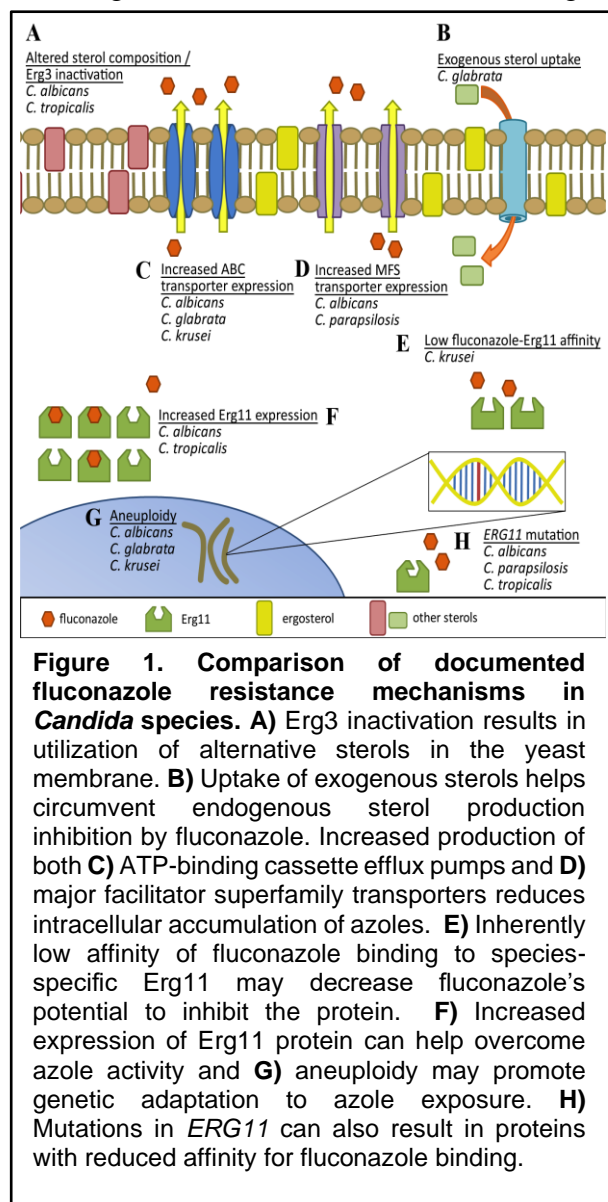
P. David Rogers, Pharm.D., Ph.D., FCCP
Member, St. Jude Faculty
Chair, Department of Pharmacy and Pharmaceutical Sciences
Endowed Chair in Pharmaceutical Sciences
Scientific Advisor, Center for Pediatric Experimental Therapeutics

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.



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

Ana Camila Oliveira Souza – Staff Scientist

Laura Doorley – Graduate Student, Integrated Program in Biomedical Sciences

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

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

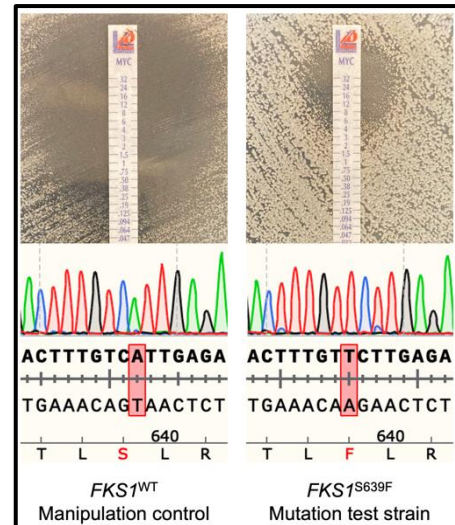
Jeffrey M. Rybak, Pharm.D., Ph.D.
Instructor, Department of Pharmacy and Pharmaceutical Sciences
St. Jude Children's Research Hospital



Fungal pathogens present a significant clinical challenge, particularly for immunocompromised patient populations, and are responsible for over one million life-threatening infections each year. While there are presently three distinct classes of primary antifungal agents available for clinical application, the efficacy of current standard of care therapies for the treatment of infections caused by fungal pathogens such as *Candida*, *Aspergillus*, and Mucorales remains unacceptably low, and mortality rates range from 30 to over 90%. Furthermore, the emergence of antifungal-resistant organisms, such as *Candida auris* and triazole-resistant *Aspergillus fumigatus*, continues to challenge clinicians and threatens the vulnerable populations of patients most affected by these infections. Thus, it is imperative that novel therapeutic strategies be developed to overcome infections caused by fungal pathogens.

The long-term objective of my research program is to advance the treatment of invasive fungal infections by developing new therapeutic strategies to overcome difficult-to-treat fungal pathogens. In pursuit of this objective, my lab focuses on three primary areas of study:

1) *Creating the tools needed to study and manipulate genetically intractable fungal pathogens.* Construction of these tools are essential to investigating the impact of genetic variations associated with therapeutic failures as well as to identifying and characterizing molecular weak-points which may represent new antifungal targets. My lab has recently devised a novel Episomal Plasmid Induced Ca9 (EPIC) gene-editing system which has advanced our ability to study the emerging fungal pathogen *C. auris*. Using the EPIC system it is now possible to perform genetic manipulations as precise as single base editing in *C. auris* clinical isolates, and my lab is working on devising similar systems in other fungal pathogens. 2) *Revealing the molecular mechanisms that drive antifungal resistance.* Identifying the genetic determinants of antifungal resistance and delineating their direct contributions to resistance greatly informs both the application of currently available antifungal agents and the development of next-generation antifungals. Using the EPIC system, I have been able to quantify the direct contribution of clinically derived mutations in the *C. auris FKS1* gene for the first time. 3) *Developing improved therapeutic approaches for the treatment of invasive fungal infections.* In a collaborative effort with other faculty at both UTHSC and St. Jude Children's Research Hospital, including multiple CPET investigators, my laboratory is currently utilizing molecular-genetic techniques, high-throughput screening, and *in vivo* models to identify both new antifungal therapeutics and approaches to advancing the treatment of fungal infections through novel applications of existing antifungal agents.



Lab members:

Jeffrey M. Rybak, Pharm.D., Ph.D. – Principal Investigator
Sarah Jones - Technician

Jeremy S. Stultz, PharmD, BCPPS
Associate Professor of Clinical Pharmacy and Translational Science
Coordinator, Pediatric Infectious Disease Clinical Pharmacy Fellowship
University of Tennessee Health Science Center, Memphis

Dr. Stultz practices as an Antimicrobial Stewardship Pharmacist at Le Bonheur Children's Hospital in Memphis, TN. He received a Doctor of Pharmacy degree from the University of Pittsburgh School of Pharmacy and completed a PGY-1 Residency at Le Bonheur and a 2-year Pediatric Pharmacotherapy Fellowship at The Ohio State University and Nationwide Children's Hospital in Columbus, Ohio. He was a faculty member at the Virginia Commonwealth University School of Pharmacy before returning to Tennessee. He has authored over 30 peer-reviewed journal publications focused primarily on pediatric infectious diseases, computerized clinical decision support, and medication safety. He is an active member of multiple national pharmacy organizations including the Pediatric Pharmacy Advocacy Group (PPAG) and the American College of Clinical Pharmacy (ACCP). He served as the PPAG Research Committee Chair and Co-chair from 2014-16 and received the 2012 ACCP Pediatric PRN Travel Award.



Lab Members:

Gustavo Alvira-Arill, PharmD – Pharmacy Fellow, LeBonheur Hospital/UTHSC

DIRECTION OF THE CENTER

2021-2022

Goals and Future Plans

In the coming year, the CPET will continue 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.

The CPET Seed and Equipment Grant Program, originally implemented for the 2020-2021 cycle, is planned to be implemented again for the coming 2022-2023 year. Through this program, CPET investigators receive seed monies for projects deemed competitive for extramural funding (e.g., NIH, DoD, etc.). For the coming 2022-2023 cycle, this Program is again aiming to fund collaborative work between UTHSC Center faculty and clinical research at Le Bonheur and St. Jude Childrens 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. The Seed Grant Program will also seek to invest in newly recruited faculty, focusing on young investigators to ensure success in laboratory setup and transitioning from Craeer Development-level to program-level NIH funding.

We will continue to train elite graduate students in the biomedical and pharmaceutical sciences with the support of the CPET Scholars Program. For the 2022-2023 Scholars program, Center support will again require scholars to generate at least one first-authored research publication in a peer-reviewed scientific journal (submitted) and to submit for external fellowship funding by the end of their second year in the program. These expectations will ensure that training in research remains rigorous. The CPET Scholars trainees will be further supported through the CPET support of the (now annual) Tennessee Fungal Pathogens Group Retreat and Conference as well as the CPET Seminar Series. For the Seminar series, Scholars Program trainees are offered first-choice of invited speakers. Through the combined synergy of each of these educational programs, the Center plans to continue the productive investments in the pathogenic mycology community at UTHSC and across the State.

As another major investment in the pathogenic mycology-heavy focus of the Center faculty, the CPET plans to offer support for the upcoming 19th Annual South Central Medical Mycology Meeting to be held in Memphis, TN on November 18-19, 2022. CPET faculty are hosting the meeting that is attended by over 80 people from the South-Central US region. This focused conference offers a unique opportunity to disseminate research findings and build new collaborations for Center faculty at UTHSC, St. Jude Children's Rerearch Hospital, Le Bonheur Children's Hospital and Rhodes College.

Finally, the CPET will continue to support newly conceived Pediatric Infectious Disease Pharmacy Fellowship. The current fellow, Dr. Alvira-Arill, has been immensely successful in his current position. In collarboration with Fellowship coordinator, Dr. Jeremy Stultz, we plan to begin recruitment for a new Fellow to join the program beginning in the Summer of 2023. Through this exciting new program, the Center is working to positively and immediately impact therapeutic advances in children.

Schedule 7

CENTERS OF EXCELLENCE ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution: **University Of Tennessee Health Science Center** Center: **Pediatric Pharmacokinetics**
R079700142

	FY 2021-22 Actual			FY 2022-23 Proposed			FY 2023-24 Requested		
	Matching	Appropriation	Total	Matching	Appropriation	Total	Matching	Appropriation	Total
Expenditures									
Salaries (Exclude Longevity from Salaries and report separately)									
Faculty	\$1,214,773	\$9,000	\$1,223,773	\$1,232,995	\$9,000	\$1,241,995	\$1,232,995	\$9,000	\$1,241,995
Other Professional	\$220,235		\$220,235	\$223,539		\$223,539	\$223,539		\$223,539
Clerical/ Supporting	\$232,978	\$133,992	\$366,970	\$236,473	\$125,000	\$361,473	\$236,473	\$130,000	\$366,473
Assistantships	\$169,076		\$169,076	\$171,612		\$171,612	\$171,612		\$171,612
Total Salaries	\$1,837,062	\$142,992	\$1,980,054	\$1,864,618	\$134,000	\$1,998,618	\$1,864,618	\$139,000	\$2,003,618
Longevity (Excluded from Salaries)	\$7,707	\$30	\$7,737	\$7,823	\$30	\$7,853	\$7,823	\$30	\$7,853
Fringe Benefits	\$438,723	\$13,779	\$452,502	\$445,304	\$12,500	\$457,804	\$445,304	\$12,500	\$457,804
Total Personnel	\$2,283,492	\$156,800	\$2,440,292	\$2,317,744	\$146,530	\$2,464,274	\$2,317,744	\$151,530	\$2,469,274
Non-Personnel									
Travel		\$5,382	\$5,382		\$11,500	\$11,500		\$10,000	\$10,000
Software			\$0			\$0			\$0
Books & Journals		\$329	\$329			\$0			\$0
Other Supplies		\$112,030	\$112,030		\$64,234	\$64,234		\$66,303	\$66,303
Equipment		\$19,474	\$19,474		\$30,000	\$30,000		\$30,000	\$30,000
Maintenance			\$0			\$0			\$0
Scholarships			\$0			\$0			\$0
Consultants		\$6,565	\$6,565			\$0			\$0
Renovation			\$0			\$0			\$0
Other (Specify):		\$313	\$313			\$0			\$0
TFP Annual Conference Support		\$14,555	\$14,555		\$14,666	\$14,666		\$14,666	\$14,666
SCMM Conference Support			\$0		\$12,000	\$12,000		\$12,000	\$12,000
			\$0			\$0			\$0
Total Non-Personnel	\$0	\$158,649	\$158,649	\$0	\$132,400	\$132,400	\$0	\$132,969	\$132,969
GRAND TOTAL	\$2,283,492	\$315,449	\$2,598,941	\$2,317,744	\$278,930	\$2,596,674	\$2,317,744	\$284,499	\$2,602,243
Revenue									
New State Appropriation		\$262,144	\$262,144		\$270,951	\$270,951		\$284,499	\$284,499
Carryover State Appropriation		\$61,284	\$61,284		\$7,979	\$7,979			\$0
New Matching Funds	\$2,283,492		\$2,283,492	\$2,317,744		\$2,317,744	\$2,317,744		\$2,317,744
Carryover from Previous Matching			\$0			\$0			\$0
Total Revenue	\$2,283,492	\$323,428	\$2,606,920	\$2,317,744	\$278,930	\$2,596,674	\$2,317,744	\$284,499	\$2,602,243

YEAR-IN-REVIEW

2021-2022

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 millions of dollars in grants and contracts each year to the Health Science Center (HSC), its affiliated programs, and the State of Tennessee. For the 2021-2022 cycle, Center faculty reported over \$12 million in total funding. 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. Again for the 2021-2022 cycle, exceptional students enrolled in graduate education at UTHSC under the direction of Center faculty have been selected for partial support from the Center through either stipend relief or support for attendance to scientific meetings and publication of research findings in peer-reviewed journals (See CPET Scholar section).

This CPET further supported faculty and trainee development through the CPET Seminar Series. The Center supported six external speakers representing 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. The seminar series for 2021-2022 involved speakers focused on genetic determinants of invasive fungal disease, as well as fungal/bacterial co-infections. In support of the world-class medical mycology unit that comprises a major component of the membership, the CPET was also again instrumental in supporting the annual Tennessee Fungal Pathogens Group Conference that took place in September of 2021. A full description of these activities are found below.

As a major new initiative for the 2021-2022 year, the CPET established the CPET Pediatric Infectious Disease Pharmacy Fellowship and successfully recruited Gustavo Alvira-Arill, PharmD as our first fellow (see activities report below). Dr. Alvira-Arill's position is partially funded by an NIH R21 award to Center members, Dr. Brian Peters, PhD and Dr. Jeremy Stultz, PharmD. Dr. Alvira-Arill has been incredibly productive in his first year, having used CPET support to acquire two external grants from private foundations.

In the coming year the CPET will continue to direct its efforts to focus on 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 Trainee Opportunities

A major priority of the CPET is to train the next generation of basic and clinical research scientists to tackle the ever-evolving therapeutic challenges faced by children across the state of Tennessee. Through these priorities, the CPET expects to make the greatest impact on true “bench-to-bedside” discoveries. Current Center faculty support this mission by identifying high-caliber graduate and post-graduate trainees to develop the skills and research prowess for addressing future problems of antimicrobial resistance and infectious disease. Currently, the Center supports faculty in these endeavors through three programs: the CPET Tennessee Fungal Pathogens Group (TFPG) Annual Retreat, the CPET Scholars Program, and the CPET Pediatric Infectious Disease Pharmacy Fellowship.

CPET TFGP Annual Retreat

Beginning the 2020-2021 cycle, the Center offered support for a conference that was designed to bring together research laboratories across the state of Tennessee to share ideas for addressing the critical issues of invasive fungal disease among children. A significant proportion of the CPET faculty membership are world renowned leaders in the fields of fungal pathogenesis,



antifungal drug development, and antifungal drug resistance. As such, this initial state-wide conference served to solidify the nascent “Tennessee Fungal Pathogens Group” into one of the the strongest and most influential medical mycology centers in the world. This initial conference was,



therefore, deemed an outstanding success and has now become an annual retreat/conference that brings together researchers from UTHSC (Memphis), St. Jude Children’s Research Hospital (Memphis), Rhodes College (Memphis), Vanderbilt University (Nashville), UTK (Knoxville), and East Tennessee State University (Johnson City). The 2021-2022 retreat was attended by more than 40 individuals and was held at Evins Mill Retreat Center, where trainees provided



updates on research progress and keynote lectures were provided by the two newest CPET faculty members, Dr. Camaron Hole and Dr. Jeffery Rybak.

CPET Scholars Program

Amanda K. Vogel, MS officially joined the Peters laboratory in January 2020 and successfully defended her Master's thesis to complete her MS degree requirements in July 2022. She was integral in establishing several new areas of research focus for the laboratory. Work highlighted in her thesis led to the development of a new cloning-free and recyclable marker system that leverages the power of CRISPR-Cas9 gene editing for manipulation of the fungal pathogen *Candida albicans*. Construction of a hygromycin-flipper cassette, paired with the long used *SAT1*-flipper cassette, allows for facile PCR-mediated generation of repair templates for homozygous gene deletion with very high efficiency. A modular system for gene reversion was also established by gene complementation at a neutral locus. Amanda's contributions have streamlined mutant construction in the Peters lab and this system will touch multiple current and future projects.



Amanda also began to unravel mechanisms that contribute the immunopathogenesis of vulvovaginal candidiasis—a major focus of the Peters lab. She found that IL-1R signaling orchestrates responses to *C. albicans* at the vaginal mucosa through the virulence factor and peptide toxin candidalysin that impact both control of fungal burden and neutrophil recruitment. This work has opened up new avenues for exploration as to necessary and sufficient roles of IL-1 α and IL-1 β for driving protection and disease pathology and to identify cell types that make and respond to these cytokines during vaginitis. Aside from these studies, she also participated in collaborations with other labs across the state of TN to share her expertise.

Since leaving the Peters lab this summer, Amanda has joined Meridian Bioscience in Memphis, TN where she will focus on product and process development of life science tools and reagents.

Manuscripts:

Rapid Hypothesis Testing in *Candida albicans* Clinical Isolates Using a Cloning-Free, Modular, and Recyclable System for CRISPR-Cas9 Mediated Mutant and Revertant Construction. Liu J, Vogel AK, Miao J, Carnahan J, Lowes DJ, Rybak JM, Peters BM. *Microbiol Spectr.* 2022 Jun 29;10(3):e0236021. PMID: 35612314.

Mucosal infection with unmasked *Candida albicans* cells impacts disease progression in a host niche specific manner *Candida albicans* unmasking impacts mucosal infection. Wagner AS, Vogel AK, Lumsdaine SW, Phillips EK, Willems HME, Peters BM, Reynolds TB. *Infect Immun.* UNDER REVIEW.

Presentations:

“Delineating a role for IL-1R signaling in the immunopathogenesis of vulvovaginal candidiasis”. South Central Medical Mycology Meeting. San Antonio, TX. Apr 1-2, 2022.

“Delineating the role of IL-1 signaling during VVC”. 5th Annual Tennessee Fungal Pathogens Retreat at Evins Mill. Smithville, TN. Sep 29-Oct 1, 2021.

Grants:

Data solely generated solely by Amanda led to a Dean’s Enhancement Seed Grant Award from the College of Pharmacy (to Dr. Peters). 12/2021 – 06/2022. \$15,000.

Parker Reitler is a sixth-year graduate student in the Palmer lab.

Project description. Currently, there is approximately 30-50% treatment failure rate for patients with *Candida albicans*-related blood stream infections; however, only a small percentage of clinical isolates are classified as resistant to the drugs used to treat these infections on standard antifungal susceptibility testing. This disparity highlights that many treatment failures remain unexplained. My project focuses on the idea that the co-administered medications taken by patients may alter fungal physiology and/or antifungal sensitivity, and thus the outcome of infection. Indeed, our previous research shows that several anti-schizophrenic medications (Ex. Aripiprazole) as well as heart-related medications (Ex. Amiodarone), can cause induce azole resistance, through activation of mechanisms of antifungal resistance.



Project status. Over the course of 2021-2022, I have made several steps in expanding my research to be able to better identify the impact of human medications on fungal physiology, virulence and antifungal drug sensitivity.

First is that we began expanding our chemical-screening to identify additional antifungal antagonists. Over the course of 2021-2022, we have identified a number of drugs that induce *C. albicans* resistance to several azoles (Fluconazole, Itraconazole, Voriconazole), as well as several echinocandins (Caspofunin, Anidulafungin, and Micafungin) to uncover the scope of antifungal antagonism. We have also conducted additional studies with our collaborating partners at the National Center for Advanced Translational Sciences Center (NCATS). To analyze the huge screening datasets, we are collaborating with the Shelat lab at St Jude, applying a model they developed (Bivariate Response to Additive Interacting Doses or BRAID) to categorize and identify novel types of drug-drug interaction on the fungus. This will allow us to look at more complex surface interactions to identify both antifungal antagonists, as well as antifungal sensitizers.

Furthermore, we begun testing the impact of our selected antifungal antagonists on their impact in a mouse model of disseminated candidiasis. We were able to successfully replicate human plasma concentrations of these medications in mice, and over this year we discovered that one of our most prominent antifungal antagonists, Aripiprazole, induced hyper virulence compared to vehicle treated mice, though the mechanism is currently unknown.

Future. Over the course of 2022-2023, we aim to investigate why certain medications are appearing as hits in these screens, as well as to better understand their impact on fungal physiology. We also aim to identify the mechanism of Aripiprazole-induced hyper mortality, as well as identify how other medications beyond Aripiprazole, affect fungal virulence.

Active societies

Journal club for the College of Graduate Health Sciences at University of Tennessee Health Science Center

Presentations

2022 TFGP Retreat Program (oral presentation)

Yue “Aeric” Zhou is a graduate student in the Reynolds lab.

Project Description / Status: During the past year, I have been working on solubilizing and purifying the phosphatidylserine synthase from *Candida albicans*, which is a potential drug target for developing a new class of antifungals against *C.albicans*. I have worked with a couple of detergents and protein purification techniques, and have successfully purified the membrane-bound phosphatidylserine synthase in the native *C.albicans* host. I can then proceed to the next steps which are structure determination and small molecule screening. I have also developed a malachite green-based screening assay for the purified phosphatidylserine synthase to identify inhibitors. During the past year, I have presented this work at two conferences (listed below), and have published an abstract about this topic. Also, I have wrapped up and published the previous research topic in the *Frontiers in cellular and infectious disease Journal* about the identification of the substrate-binding sites in the *C.albicans* phosphatidylserine synthase. Besides, I have gone to Dr. Melanie Ohi’s lab at the University of Michigan, Ann Arbor, from June 11th to August 31st to conduct the structure work.



Publications

Zhou, Y., Bruce, B., and Reynolds, TB (2022). Solubilization and purification of phosphatidylserine synthase from *Candida albicans*. *The FASEB Journal* 36.

Zhou, Y., Cassilly, CD., Reynolds, TB* (2021). Mapping the Substrate Binding Sites in the Phosphatidylserine Synthase in *Candida albicans*. *Front. Cell. Infect. Microbiol.* 11 (2021): 765266-765266

Conference Proceedings

Yue Zhou. “Solubilization and purification of phosphatidylserine synthase from *Candida albicans*” with poster presentation, ASBMB 2022 Conference, Convention center, Philadelphia, Pennsylvania. April 2nd – 5th, 2022.

Yue Zhou. “Solubilization and purification of phosphatidylserine synthase from *Candida albicans*” with public presentation, 5th Annual Tennessee Fungal Pathogens Group Research Conference, Evins Mill, Smithville, Tennessee. Sept 29th – Oct 1st, 2021.

“The C-24 sterol methyltransferase encoding gene, *erg6*, is essential for *Aspergillus fumigatus* viability”

Jinhong Xie is a first-year graduate student in the Fortwendel laboratory. Jinhong obtained her Master’s degree working on bacterial resistance mechanisms at South China University of Technology in Guangzhou, China. Her current research focuses on a potential novel antifungal drug target, *Erg6*, the C-24 sterol methyltransferase in *Aspergillus fumigatus* ergosterol synthesis

pathway. Ergosta-type sterols are essential for fungal survival and are highly conserved in fungi. Therefore, ergosterol and its biosynthesis are targets for most currently available antifungal drugs used to treat human fungal infections. Originating from the observation that *erg6* responds to antifungals in transcriptional level, she has validated that *erg6* is essential for *A. fumigatus* viability and obtained a comprehensive understanding of *erg6* characteristics. Based on this important work, Jinhong already has an initial manuscript ready for submission titled, “The C-24 sterol methyltransferase encoding gene, *erg6*, is essential for *Aspergillus fumigatus* viability”. Next, she plans to identify novel and potent inhibitors of *erg6* to improve antifungal therapies. As a graduate trainee, Jinhong participates in academic events actively including Pharmaceutical Sciences weekly Journal Club and Seminar Series, Center for Pediatric Experimental Therapeutics Seminar Series and Tennessee Fungal Pathogens Group Research Conference.



Presentations at scientific conferences:

The 6th Annual Tennessee Fungal Pathogens Group Research Conference (Oral presentation)
Title: “The C-24 sterol methyltransferase encoding gene, *erg6*, is essential for *Aspergillus fumigatus* viability”

Academic activities:

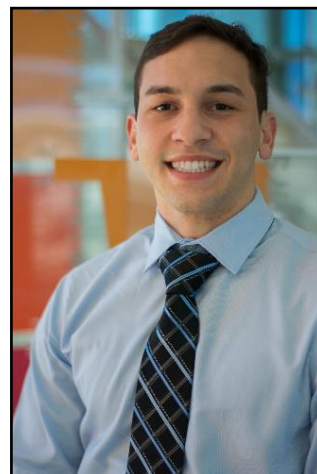
Pharmaceutical Sciences Program Journal club presentation
“Reducing *Aspergillus fumigatus* Virulence through Targeted Dysregulation of the Conidiation Pathway” mBio vol. 11,1 e03202-19.

CPET Pediatric Infectious Diseases Pharmacy Fellowship

Gustavo Alvira-Arill, PharmD

Pediatric Infectious Diseases Pharmacy Fellow
Department of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center, Memphis

Dr. Alvira's fellowship position is hosted jointly by the University of Tennessee Health Science Center and Le Bonheur Children's Hospital (LBCH) with a focus on clinical care, education, and translational research. The primary focus of his research program is to examine differences in catheter-related bloodstream infection (CR-BSI) rates in pediatric patients receiving parenteral nutrition (PN) with different intravenous fat emulsions (IFE) and investigate in vitro mechanisms for pathogens associated with varying infection rates. As part of this endeavor, he was awarded with the American College of Clinical Pharmacy (ACCP) Foundation's Futures Grant to examine differences in biofilm formation and CR-BSI rates for *Staphylococcus* spp. Preliminary results examining differences in proportions and rates of CR-BSIs caused by *C. albicans* based on receipt of either soybean oil-based IFE (SO-IFE) or mixed oil IFE (MO-IFE) were presented at the 31st Annual Pediatric Pharmacy Association (PPA) Meeting and 24th Annual Making a Difference in Infectious Disease (MAD-ID) Meeting, respectively. Preliminary results for his main work with *Staphylococcus* spp. was accepted for platform and poster presentation at the ACCP Global Conference this October and was selected as one of four finalists for ACCP's Best Resident/Fellow poster presentation. Lastly, his single-center analysis of differences in CR-BSI rates in pediatric patients receiving PN with SO-IFE or MO-IFE was submitted for publication and is currently under review.



His program's second focus is on acute kidney injury (AKI) prevalence in pediatric patients based on antimicrobial dosing practices and presence of congenital anomalies of the kidneys and urinary tract (CAKUT). To the former, he was awarded with PPA's Pediatric Small Research Grant to further investigate differences on AKI prevalence in pediatric patients that received vancomycin using different pharmacodynamic targets. The basis for that investigation is to combine claims data from the Pediatric Health Information System (PHIS) database- a comparative pediatric database that includes clinical and resource utilization data for more than 49 academic medical centers and freestanding children's hospitals in the U.S.- with a survey distributed to pediatric infectious diseases pharmacists located at these sites to identify the monitoring strategy used for vancomycin dosing. Regarding AKI prevalence and CAKUTs, Dr. Alvira is mentoring a pharmacy residency research project at Le Bonheur Children's examining differences in AKI prevalence in critically ill neonates receiving nephrotoxic medications with CAKUTs to those without.

Aside from his research activities, Dr. Alvira provides antimicrobial stewardship and clinical pharmacy services at LBCH. He has teaching responsibilities at UTHSC for the infectious diseases section of the Introduction to Therapeutics course and varied sections for the Pediatrics Elective course. He is an active member of ACCP, MAD-ID Communications Committee, and PPA.

CPET Seminar Series



“Site Matters: Non-classical β -glucan recognition induces organ-specific responses during candidiasis”

Marc Swidergall, PhD

Assistant Professor, David Geffen School of Medicine, UCLA
Investigator, The Lundquist Institute
Harbor-UCLA Medical Center



“Dissecting *Candida albicans* virulence traits using naturally occurring variation”

Matthew Anderson, PhD

Assistant Professor
Department of Microbiology
Department of Microbial Infection and Immunity
The Ohio State University



“Induction of protective immunity against pulmonary cryptococcosis – an AIDS defining disease”

Floyd L. Wormley Jr., PhD

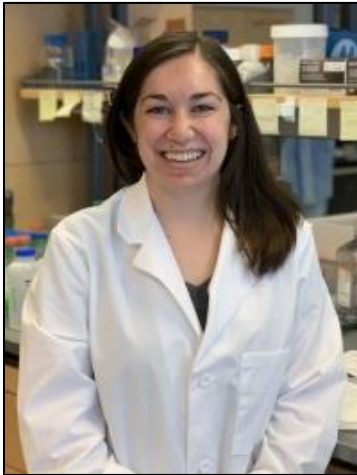
Associate Provost for Research
Dean of Graduate Studies
Texas Christian University



“*Aspergillus fumigatus* & tissue damage: Fungus and host perspectives”

David S. Askew, PhD

Professor
Department of Pathology and Laboratory Medicine
College of Medicine
University of Cincinnati



“A toxic relationship: Exploring *C. albicans*-*S. aureus* interactions during polymicrobial infection”

Kara Eichelberger, PhD

Postdoctoral Fellow
Division of Pediatric Infectious Disease
Department of Pediatrics
Department of Pathology, Microbiology and Immunology
Vanderbilt University



“Bone Ap tit: Host-pathogen interactions during osteomyelitis”

Jim Cassat, MD

Assistant Professor
Division of Pediatric Infectious Disease
Department of Pediatrics
Department of Pathology, Microbiology and Immunology
Vanderbilt University

CPET Seed Grant Program

Awardee: Dr. Camaron Hole, PhD

Project Description: Dr. Hole has been awarded a CPET seed grant, renewable for four years, as laboratory setup support. Dr. Hole was hired as an Assistant Professor in the Department of Clinical Pharmacy and Translational Science in July of 2021. Dr. Hole's recruitment represented a major commitment of the UTHSC CoP to the pathogenic mycology core that is an existing strength in the Department and of the CPET. Dr. Hole's research focus is on immunopathologies associated with *Cryptococcus* pulmonary infections, as well as vaccine development against this deadly fungal infection. Data generated with the 2020-2021 Seed Grant Funds includes the development of a novel system for facile genetic manipulations of *Cryptococcus neoformans*. This new genetic approach is expected to revolutionize the fungal genetic field for a historically genetically intractable organism.



CPET Capital Equipment Grant Program

The CPET is committed to supporting joint research endeavors among Center faculty. For the 2021-2022 cycle, this support included the purchase of new Thermo Scientific MTX150 ultracentrifuge. This equipment is housed in a shared equipment space within the UTHSC College of Pharmacy where it is directly accessible to the CoP Center faculty. This equipment seed grant was awarded to Dr. Glen Palmer and Dr. Jarrod Fortwendel (Director) to support the development of *in vitro* assays for novel target-based antifungal drug screens.



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 (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: **Fortwendel JR**
Title: Unlocking the cidal activity of echinocandins against *Aspergillus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI143197
Dates: 3/1/20 to 2/28/25
Total Direct: \$1,552,025

Annual Direct: \$310,405

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 PR191438
 Dates: 7/21/09 to 6/2023
 Total Direct: \$1,200,000
 Annual Direct: Not Provided

Investigator: **Hole CR**
 Title: Cryptococcal Chitin Synthase 3 and Host Immune Responses
 Source: National Institute of Allergy and Infectious Diseases (NIAID) 1K22AI148724
 Dates: 08/27/21 to 07/31/23
 Total Direct: \$275,000
 Annual Direct: \$150,000

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) R01DA047178
 Dates: 9/01/18 to 8/31/23
 Total Direct: \$1,700,000
 Annual Direct: \$227,000

Investigator: **Kumar S**
 Title: Extracellular vesicle-based drug delivery of antiretroviral regimen to target CNS HIV reservoirs
 Source: National Institute of Mental Health (NIMH) 1R21MH125670
 Dates: 04/01/2021 to 03/31/2023
 Total Direct: \$275,000
 Annual Direct: \$150,000

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: **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: Inhaled tigecycline therapy for pulmonary *M abscessus* infections
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 5R01AI155922

Dates: 6/24/21 to 5/30/2026
 Total Direct: \$3,343,775
 Annual Direct: \$668,755

Investigator: **Meibohm B** (PI Lowe TL)
 Title: Nanogels for Drug Delivery across the BRB to Treat Diabetic Retinopathy
 Source: National Eye Institute (NEI)
 5R01EY023853

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

Dates: 3/01/19 to 2/29/24
 Total Direct: \$21,104,316
 Annual Direct: \$2,830,169

Investigator: **Palmer GE** (subcontract to **Meibohm B**)
 Title: Broad spectrum antifungals targeting fatty acid biosynthesis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 4R33AI127607

Dates: 12/1/17 to 11/30/21
 Total Direct: \$800,000
 Annual Direct: \$379,500

Investigator: **Palmer GE**
 Title: Examining the importance of folate biosynthetic enzymes in infectious fungi
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R21AI156611

Dates: 11/25/20 – 10/31/22
 Total Direct: \$275,000
 Annual Direct: \$150,000

Investigator: **Palmer GE**

Title: Antifungal antagonism as a cause of treatment failure for invasive mycoses
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI152067
 Dates: 03/25/21 – 02/28/26
 Total Direct: \$2,059,240
 Annual Direct: \$411,848

Investigator: **Peters BM (MPI Stultz JS)**
 Title: Lipid emulsion composition as a determinant of fungal biofilm formation and incidence of candidemia
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R21AI153768
 Dates: 04/09/21 to 03/31/2022
 Total Direct: \$275,000
 Annual Direct: \$150,000

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: **Reynolds TB (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 TB**
 Title: Regulation of β -(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: **Reynolds TB**
 Title: Integrated Membrane Program (IMP)
 Source: National Institute of General Medical Sciences (NIGMS)
 1T32GM142621
 Dates: 06/02/21 to 05/30/26
 Total Direct: \$840,000
 Annual Direct: \$139,008

Investigator: **Rogers PD**
Title: Novel Azole Resistance Mechanisms in *Candida albicans*
Source National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI058145
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
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: Consequences of Direct Viral-Bacterial Interactions
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R56AI155614
Dates: 07/20/21 to 06/30/22
Total Direct: \$339,210
Annual Direct: \$339,210

Investigator: **Rosch JW**
Title: Consequences of Direct Viral-Bacterial Interactions
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI168214
Dates: 01/05/22 to 12/31/26
Total Direct: \$1,673,305
Annual Direct: \$334,661

Investigator: **Rosch JW**
Title: Evolvable Essenitality of in the pan-genome of *Streptococcus pneumoniae* and its mechanistic and evolutionary consequences
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI168214
Dates: 07/01/22 to 06/30/27
Total Direct: \$1,673,305

Annual Direct: \$334,661

Investigator: **Rosch JW (PI Rock)**
Title: Regulation of lipid metabolism in bacteria
Source: National Institute of General Medical Sciences (NIGMS)
5R011GM034496
Dates: 11/19/20 to 11/30/22
Total Direct: \$1,200,000
Annual Direct: \$402,779

Investigator: **Rosch JW (PI Orihuela)**
Title: PspA binds necroptotic cells to cause disease and transmit
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI156898
Dates: 12/01/20 to 11/30/25
Total Direct: \$1,409,185
Annual Direct: \$281,837

Investigator: **Rosch JW (PI Van Opijnen)**
Title: Attacking failure of antibiotic treatment by targeting antimicrobial
resistance enabler cell-states
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1U19AI158076
Dates: 09/12/22 to 06/30/26
Total Direct: \$1,675,232
Annual Direct: \$418,808

Investigator: **Stultz JS (MPI Peters BM)**
Title: Lipid emulsion composition as a determinant of fungal biofilm
formation and incidence of candidemia
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI153768
Dates: 04/09/21 to 03/31/2022
Total Direct: \$275,000
Annual Direct: \$150,000

Foundation and Industry Funding

Investigator: **Kumar S**
Title: Role of extracellular vesicles in HPV-induced HIV pathogenesis
Source: UTHSC CORNET award in Health Disparities
Dates: 03/01/20 to 02/28/22
Total Direct: \$25,000
Annual Direct: \$12,500

Investigator: **Kumar S**
Title: Development of extracellular vesicles-based drug delivery platform
for HIV-associated neuronal diseases
Source: UTHSC Plough Center award

Dates:	03/01/20 to 02/28/23
Total Direct:	\$300,000
Annual Direct:	\$100,000

Publications

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Wagh S, Rathi C, Lukka PB, Parmar K, Temrikar Z, Liu J, Scherman MS, Lee RE, Robertson GT, Lenaerts AJ, **Meibohm B**. Model-Based Exposure-Response Assessment for Spectinamide 1810 in a Mouse Model of Tuberculosis. *Antimicrob Agents Chemother*. 2021 Oct 18;65(11):e0174420. doi: 10.1128/AAC.01744-20. Epub 2021 Aug 23.

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