

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



ANNUAL REPORT

2022-2023

The Center for Pediatric Experimental Therapeutics



The Center for Pediatric Experimental Therapeutics
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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** unique, 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 ongoing or newly acquired funding totaling over \$19 million in NIH, NSF, DoD and private industry/foundation grants and contracts.

Education of students, post-doctoral trainees and visiting investigators continued to be a major priority in the Center. In 2022-2023, 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 a Pharmacy ID Fellow through the nascent 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.

2022-2023 Annual Report

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ABOUT THE CENTER

2022-2023

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.

- Associate Professor, Department of Clinical Pharmacy and Translational Science

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

- 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.

- Professor, Department of Pharmaceutical Sciences
- Assistant Dean, Scholarly Integration and Collaboration

Bernd Meibohm, Ph.D.

- Professor and 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.

- 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.

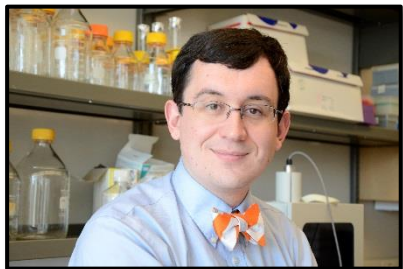
- Former Gene H. Stollerman Professor of Medicine, UTHSC
- Former Chief, Division of Infectious Diseases, UTHSC

Faculty Research Activities

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

**Associate 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.

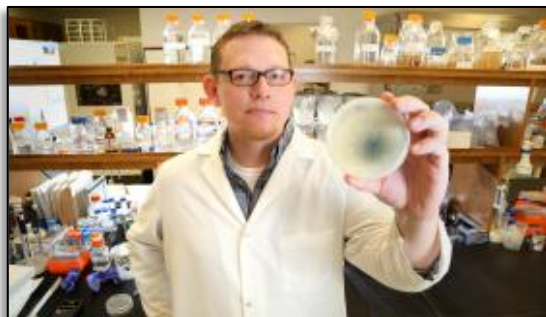
Current lab members

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

Jarrod R. Fortwendel, PhD.
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:

Jarrod R. Fortwendel, PhD – Principal Investigator

Adela Martin-Vicente, PhD – Postdoctoral Fellow

Xabier Gुरुceaga 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

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

Principal Investigator – Kirk E. Hevener, PharmD, PhD

Graduate Students – Fahad Bin Aziz Pavel, Kristiana Avad.

Pharmacy Students – Madeline Matheson

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

Graduate Student – Mikayla Harden

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 12 years Dr. Kumar's research projects are funded by several NIH grants. In the past 15 years, Dr. Kumar's group has published substantially in this field (~110 papers), with a total of ~150 papers in his career. Dr. Kumar has mentored nine graduate students and five post-doctorate fellows along with numerous other trainees. Currently, he is mentoring three graduate students. In addition to research, Dr. Kumar participates 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 Immediate Past-President 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 (2018 and 2023), 9) Full member of PDC fraternity, and 10) Nominated for the UTHSC-TLC Active learning teaching and SOTL awards.

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. HIV comorbidities with HPV/Cervical cancer, Alzheimer's disease, and stroke

Current Lab Personnel:

Mr. Sandip Godse, Ms. Lina Zhou, Dr. Golnoush Mirzahosseini, and Ms. Namita Sinha

Recently trained PDFs and graduated students

PDFs: Drs. PSS Rao, Narasimha Midde, Sunitha Kodidela, and Asit Kumar

Students: Drs. Sabina Ranjit, Mohammad A. Rahman, Sanjana Haque, and 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

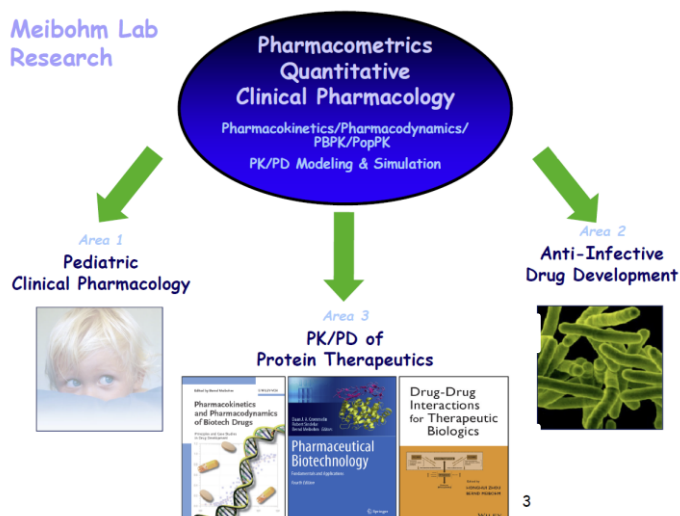
Dr. Meibohm's research is focused on the investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs with special emphasis on PK/PD-correlations.

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.

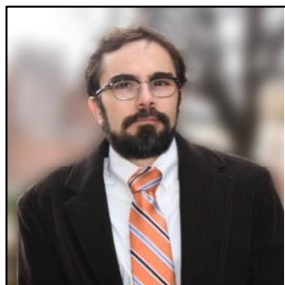


Lab members:

- Ashish Srivastava, PhD (postdoctoral fellow)
- Amarinder Singh, PhD (postdoctoral fellow)
- Paridhi Gupta, BPharm (PhD student, Pharmaceutical Sciences Program)
- Hyunseo Park, MS (PhD student, Pharmaceutical Sciences Program)
- Bhargavi Thalluri, MPharm (PhD student, Pharmaceutical Sciences Program)
- Christelle Mathieu, BS (PharmD/PhD student)

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:

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

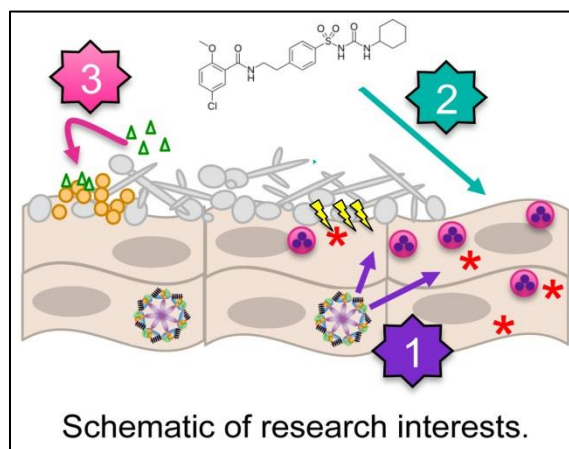
The Peters lab has two main foci of research: **1)** the host and fungal molecular mechanisms responsible for the immunopathogenesis of vulvovaginal candidiasis and **2)** quorum sensing and toxin regulation during fungal-bacterial intra-abdominal infection.

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

Amirhossein Davari – 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.

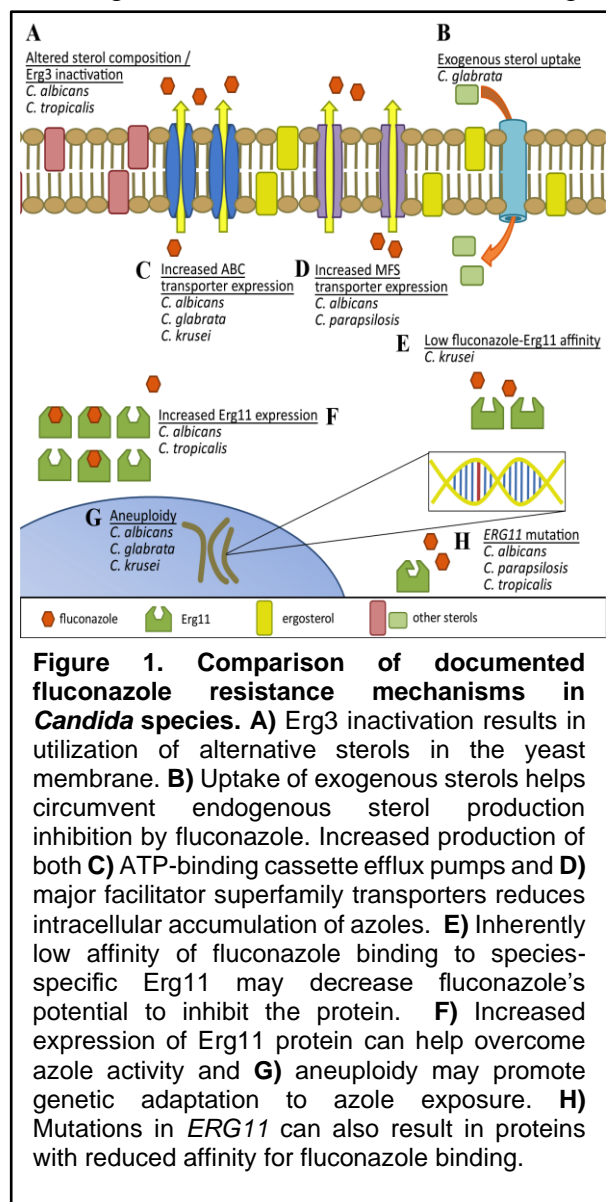
P. David Rogers, Pharm.D., Ph.D., FCCP
Member, St. Jude Faculty
Chair, Department of Pharmacy and Pharmaceutical Sciences
Endowed Chair in Pharmaceutical Sciences
Scientific Advisor, Center for Pediatric Experimental Therapeutics

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 two decades 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 including the emerging pathogen *Candida auris*, 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 antifungal resistance in *Candida auris*, 2) Delineating the genetic and molecular basis of triazole resistance in the fungal pathogen *Aspergillus fumigatus*, and 3) Discovering novel mechanisms of antifungal resistance in other non-albicans species of *Candida*.

Lab Members:

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

Kathy Barker, Ph.D. – Managing Senior Scientist

Ana Oliveira Souza, Ph.D. – Scientist

Qing Zhang – Lead Researcher

Tracy Peters – Lead Researcher

Wenbo Ge – Senior Researcher

Laura Doorley, Ph.D. – Post-doctoral Fellow

Luisa Gomez Londono, Ph.D. – Post-doctoral Fellow

Gustavo Santiago-Collazo, Ph.D. – Postdoctoral Fellow

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

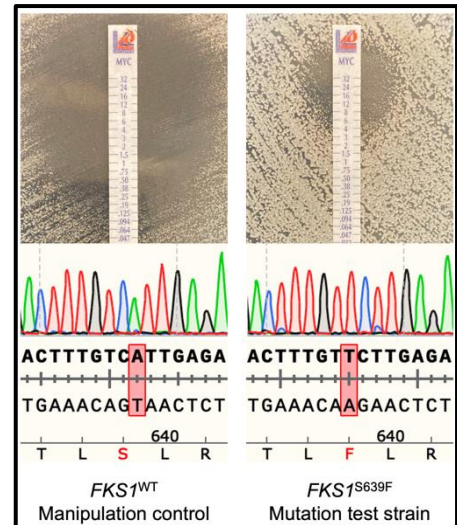
Jeffrey M. Rybak, Pharm.D., Ph.D.
Instructor, Department of Pharmacy and Pharmaceutical Sciences
St. Jude Children's Research Hospital



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

2022-2023

Goals and Future Plans

In the coming year, the CPET will continue its focus on the overarching themes of Pediatric Infectious Diseases and Anti-infective Pharmacotherapy.

The CPET Seed and Equipment Grant Program, originally implemented originally for the 2020-2021 cycle, is planned to be offered again for the coming 2023-2024 year as these programs have supported new faculty in submitting for federal funding and have increased the research infrastructure in the UTHSC CoP. For the coming 2023-2024 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 Career 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 2023-2024 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 Center plans to increase the number of Scholars supported for the next cycle to seven. For the first time, the Center will also provide competitive travel awards to Scholars to attend regional, national, and international conferences to disseminate findings and assist in the development of young scientists. The CPET Scholars trainees will again be further supported through the CPET support of the Tennessee Fungal Pathogens Group Retreat and Conference to be held in June 2024, as well as the CPET Seminar Series. For the Seminar series, Scholars Program trainees are offered first-choice of invited speakers. The Center has already lined up three speakers for the 2023-2024 cycle. 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.

The prior year investment in the 19th Annual South Central Medical Mycology Conference was deemed a huge success by all attendees. Although this conference typically travels between regional institutions, UTHSC and SJCRH have again been selected to host in the 2023 year due to our previous success. Therefore, the CPET plans to again offer sponsorship to the meeting to ensure the dissemination of research findings and the building of new collaborations for Center faculty at UTHSC, St. Jude Children's Research Hospital, Le Bonheur Children's Hospital and Rhodes College. This year, Center faculty will also be applying for NIH conference funding to grow this important conference.

Finally, the Center will be active in recruiting for the Pediatric Infectious Disease Pharmacy Fellowship in the 2023-2024 year, under the direction of Fellowship coordinator, Dr. Jeremy Stultz, PharmD.

Schedule 7

CENTERS OF EXCELLENCE ACTUAL, PROPOSED, AND REQUESTED BUDGET

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

Expenditures	FY 2022-23 Actual			FY 2023-24 Proposed			FY 2024-25 Requested		
	Matching	Appopr.	Total	Matching	Appopr.	Total	Matching	Appopr.	Total
Salaries									
Faculty	\$1,232,995	\$9,000	\$1,241,995	\$1,251,490	\$9,000	\$1,260,490	\$1,251,490	\$9,000	\$1,260,490
Other Professional	\$223,539		\$223,539	\$226,892		\$226,892	\$226,892		\$226,892
Clerical/ Supporting	\$236,473	\$105,970	\$342,443	\$240,020	\$10,000	\$250,020	\$240,020	\$10,500	\$250,520
Assistantships	\$171,612		\$171,612	\$174,186	\$97,500	\$271,686	\$174,186	\$102,375	\$276,561
Total Salaries (exclude Longevity)	\$1,864,618	\$114,970	\$1,979,588	\$1,892,587	\$116,500	\$2,009,087	\$1,892,587	\$121,875	\$2,014,462
Longevity (Excluded from Salaries)	\$7,823	\$36	\$7,859	\$7,940	\$40	\$7,980	\$7,940	\$50	\$7,990
Fringe Benefits	\$445,304	\$9,711	\$455,015	\$451,983	\$10,000	\$461,983	\$451,983	\$10,500	\$462,483
Total Personnel	\$2,317,744	\$124,717	\$2,442,461	\$2,352,511	\$126,540	\$2,479,051	\$2,352,511	\$132,425	\$2,484,936
Non-Personnel									
Travel		\$5,024	\$5,024		\$18,000	\$18,000		\$18,900	\$18,900
Software			\$0		\$8,500	\$8,500		\$9,000	\$9,000
Books & Journals			\$0			\$0			\$0
Other Supplies		\$27,600	\$27,600		\$56,418	\$56,418		\$38,174	\$38,174
Equipment			\$0		\$75,000	\$75,000		\$30,000	\$30,000
Maintenance			\$0			\$0			\$0
Scholarships			\$0		\$14,000	\$14,000		\$14,000	\$14,000
Consultants			\$0			\$0			\$0
Other (Specify):									
Printing, Duplicating, Binding		\$451	\$451		\$500	\$500		\$500	\$500
Postage, Freight, & Telephone			\$0			\$0			\$0
Professional Serv & Memberships		\$21,691	\$21,691		\$20,000	\$20,000		\$20,000	\$20,000
Computer Services			\$0			\$0			\$0
Rentals		\$260	\$260			\$0			\$0
Grants & Subsidies		\$4,747	\$4,747		\$5,000	\$5,000		\$6,000	\$6,000
Contractual & Special Services		\$7,722	\$7,722		\$8,000	\$8,000		\$8,000	\$8,000
Other Expenditures		\$12,194	\$12,194		\$16,000	\$16,000		\$18,000	\$18,000
Entertainment, Food & Housing			\$0			\$0			\$0
Facilities & Admin			\$0			\$0			\$0
Direct Cost Sharing			\$0			\$0			\$0
Total Non-Personnel	\$0	\$79,689	\$79,689	\$0	\$221,418	\$221,418	\$0	\$162,574	\$162,574
GRAND TOTAL	\$2,317,744	\$204,406	\$2,522,150	\$2,352,511	\$347,958	\$2,700,469	\$2,352,511	\$294,999	\$2,647,510
Revenue									
New State Appropriation		\$271,413	\$271,413		\$280,951	\$280,951		\$294,999	\$294,999
Carryover State Appropriation			\$0		\$67,007	\$67,007			\$0
New Matching Funds	\$2,317,744		\$2,317,744	\$2,352,511		\$2,352,511	\$2,352,511		\$2,352,511
Carryover from Previous Matching Funds			\$0			\$0			\$0
Total Revenue	\$2,317,744	\$271,413	\$2,589,157	\$2,352,511	\$347,958	\$2,700,469	\$2,352,511	\$294,999	\$2,647,509

YEAR-IN-REVIEW

2022-2023

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 2022-2023 cycle, Center faculty reported over \$45 million in total funding that was either newly acquired or maintained from previous funding cycles. 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 has continued to support graduate education through the CPET Scholars Program. For the 2022-2023 cycle, exceptional students enrolled in graduate education at UTHSC, UTK and St. Jude Childrens Research Hospital under the direction of Center faculty have been selected for partial support from the Center through stipend relief. This year, the Center increased the number of Scholars support to five (See CPET Scholar section).

This CPET further supported faculty and trainee development through the CPET Seminar Series. Although six speakers were originally invited, the Center ended up supporting four (due to cancellations) external speakers representing leading experts in the field of 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 2022-2023 involved speakers focused on genetic determinants of invasive fungal disease, covering both systemic and ocular 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 July of 2022. In addition, The CPET provided financial support for the South Central Medical Mycology Conference the was co-convened by Center faculty and hosted at the Hyatt Centric Hotel in Memphis, TN in November, 2022. A full description of these activities is found below.

Originally started in the 2021-2022 academic year, the CPET Pediatric Infectious Disease Pharmacy Fellowship continued its success in the 2022-2023 year providing support to Gustavo Alvira-Arill, PharmD as our first fellow (see activities report below). Dr. Alvira-Arill's position was also 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. Dr. Alvira-Arill completed his Fellowship in June 2023 and the CPET is currently recruiting the next candidate.

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 continue to be 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 2022-2023 retreat was attended by almost 40 individuals



and was held at Evins Mill Retreat Center, where trainees provided updates on research progress. The keynote lecture was provided by Dr. Kevin Fuller, PhD, Assistant Professor in the Department of Microbiology and Immunology and the Department of Ophthalmology at Oklahoma University

Health Science Center. Presentations were also provided by two trainees of the Fuller lab, Manali Kamath and Becca Wells.

South Central Medical Mycology Conference

The importance of scientific conferences to the development of young scientists cannot be overstated. The South Central Medical Mycology (SCMM) conference is unique in that it is a regional US conference focused primarily on presentations of unpublished work by graduate students and postdoctoral fellows of all levels from laboratories of successful Principal Investigators (PI). The meeting rotates among cities that are home to participating PIs' universities (New Orleans, Houston, San Antonio, Memphis, Albuquerque, Stillwater, and Oklahoma City). The regional setting also



facilitates development of PI collaborations and is an excellent venue to recruit graduate students for post- doctoral positions. The SCMM also provides strong developmental groundwork for the trainees who attend as all presentations are oral, followed by a question/answer session, and later, informal discussions with presenters. Hence, the impact and significance of the meeting has and continues to be high. SCMM prides itself on bringing a critical mass of medical mycology researchers together from the south central region of the United States to share the latest research being conducted in the various labs, provide opportunities for collaboration, and promote the



development of junior trainees in participating laboratories. The primary objectives of the meeting are to 1) bring regionally-based medical mycologists together to share research, initiate collaborations, and provide a venue for trainees to present their latest work, and 2) promote the development of young/junior scientists as a mentoring tool to facilitate their transition into academic scientists or their chosen career path. The 19th Annual

SCMM conference was held in Memphis, TN on November 18-19, 2022 at the Hyatt Centric Hotel and was co-convened by CPET member faculty, Brians Peters, PhD and Jarrod Fortwendel, PhD (CPET Director). CPET funds were provided in partial support for the meeting. The keynote speaker for this year's meeting was Robert A. Cramer, PhD, Professor in the Department of Microbiology and Immunology at the Dartmouth College, Geisel School of Medicine.

CPET Scholars Program

Harrison Thorn is a third-year graduate student in the Fortwendel lab

Project description:

Harrison has been studying the regulatory components of the *Aspergillus fumigatus* septation initiation network (SIN), which may represent novel drug targets to increase the clinical efficacy of the echinocandins. His research has focused on components thought to be essential for activation of the three SIN kinases (*SepH*, *SepL* and *SidB*). These kinases have been shown to be essential for septation, and as septation has been shown to be essential for withstanding echinocandins and virulence, they represent potential novel drug targets. Because the SIN has well-conserved components across the tree of life, further study of the pathway is crucial for determining the ideal drug target for use in combination with the echinocandins. Using a CRISPR/Cas9 system, Harrison has targeted the *SepH*-activating GTPase *SpgA*, its two-component GAP of *ByrA* and *BubA*, the *SepL* activator *SepM*, and the *SidB* activator *MobA*. Through a combination of fluorescent microscopy experiments, drug susceptibility tests and in-vivo studies, Harrison has identified that, contrary to data in other fungi, *SpgA* and its GAP appear not to be heavily involved in septation. *SepM* and *MobA* were both identified as important SIN components, with the *mobA* deletion strain being the most comparable to previously studied SIN kinase mutants in echinocandin susceptibility and avirulence. He is currently writing a manuscript on the project for submission. His future work will focus on the function of the SIN to maintain cell wall integrity under stress. He also plans to screen kinase inhibitors to find novel antifungals.



Publications:

Jeffrey M. Rybak, Jinhong Xie, Adela Martin-Vicente, Xabier Guruceaga, **Harrison I. Thorn**, Ashley V. Nywening, Wenbo Ge, Ana C. O. Souza, Vincent M. Bruno, Josie E. Parker, Steven L. Kelly, Hannah M. Snell, Christina A. Cuomo, P. David Rogers and Jarrod R. Fortwendel. “A novel secondary mechanism of action for triazole antifungals: induction of negative feedback regulation of HMG-CoA Reductase.” *Nature Communications*. Under Review.

Presentations:

Tennessee Fungal Pathogens Group Presentation: “Phenotypic characterization of *Aspergillus fumigatus* SIN regulators SepM and MobA.” October 14, 2022.

The 19th Annual South Central Medical Mycology Meeting: “The *Aspergillus fumigatus* Septation Initiation Network regulator, MobA, is essential for hyphal septation and survival under echinocandin stress.” November 18, 2022.

The 19th International Asperfest meeting: “The *Aspergillus fumigatus* Septation Initiation Network regulator, MobA, is essential for septation, survival under echinocandin stress, and virulence.” March 5, 2023.

Pharmaceutical Sciences departmental seminar: “The role of the *Aspergillus fumigatus* SIN kinase regulators in septation and cell wall stress response.” April 18, 2023.

2023 Tennessee Fungal Pathogens Group Annual Retreat: “The role of the *Aspergillus fumigatus* SIN kinase regulators in septation, cell wall stress response and virulence.” July 26-28, 2023.

Other academic activities:

Pharmaceutical Sciences Journal Club presentation: January 5, 2023.

Jian Miao is a 4th year student in the Peters lab.

Jian earned his master’s degree working on *Staphylococcus aureus* biofilm and rapid pathogen detection at South China University of Technology in Guangzhou, China. Jian then joined the Pharmaceutical Sciences PhD Program and Peters laboratory in July 2019. His current research focuses on how glycogen metabolism in *Candida albicans* impacts fitness in the host and host-pathogen interactions. As a graduate trainee, Jian actively attended academic conferences (South Central Mycology Meeting, GRC fungal immunology, ASM Microbe, etc.) and to present his research. Jian also participates in other academic events including the UTHSC Graduate Research Day, Pharmaceutical Sciences weekly Journal Club and Seminar Series, CPET Seminar Series and Tennessee Fungal Pathogens Group Annual Research Conference.



Project Description:

Title: The Impact of *Candida albicans* Glycogen Metabolism on the Fitness and Host-Pathogen Interactions. As it exists at a variety of host mucosal surfaces, the opportunistic fungal pathogen *C. albicans* is able to adapt to various microenvironments. Carbohydrate catabolism confers fitness advantages at anatomical site-specific host niches. *C. albicans* possesses the capacity to accumulate and store carbohydrate as glycogen and can consume intracellular glycogen stores when nutrients become limiting. Recently, it’s been showed that glucan and glycogen exist as a covalently linked macromolecular complex in *C. albicans* cell wall. Jian’s research has demonstrated that impaired glycogen metabolism synthesis and catabolism significantly impacts *C. albicans* fitness in the host during murine vulvovaginal and systemic candidiasis. Exploring how the cell wall glucan-glycogen macromolecular complex affects the host-*Candida* interaction, Jian has revealed that loss of cell wall glycogen enhances immune responses through augmented β -(1→3)-glucan display in the cell wall, and partially mediated by the Dectin-1 receptor. Future work will focus on revealing if the glucan-glycogen macromolecular complex acts as a novel fungal PAMP important for governing the host-*Candida* interaction.

Honors/Awards (July 2022-present):

The MMSA Pete T. Magee Award. First awardee, Medical Mycological Society of the Americas. July 2023.

John Autian Student Enrichment Fund Awardee. College of Graduate Health Sciences, UTHSC. March 2023.

Travel Award (student). GRC on Immunology of Fungal Infections 2023. Galveston, TX. January 2023.

John Autian Student Enrichment Fund Awardee. College of Graduate Health Sciences, UTHSC. November 2022.

Publications (July 2022-present):

Glycogen metabolism in *Candida albicans* impacts fitness and virulence during vulvovaginal and invasive candidiasis. Jian Miao, Jessica Regan, Chun Cai, Glen E. Palmer, David L. Williams, Michael D. Kruppa, Brian M. Peters. mBio. Feb 2023. DOI: 10.1128/mbio.00046-23

Antimicrobial Resistance, SCCmec, Virulence and Genotypes of MRSA in Southern China for 7 Years: Filling the Gap of Molecular Epidemiology. Junyan Liu, Tengyi Huang, Thanapop Soteyome, Jian Miao, Guangchao Yu, Dingqiang Chen, Congxiu Ye, Ling Yang, Zhenbo Xu. Antibiotics. Feb 2023. DOI: 10.3390/antibiotics12020368

Candidalysin: connecting the pore forming mechanism of this virulence factor to its immunostimulatory properties. Charles M. Russell, Jennifer A. Rybak, Jian Miao, Brian M. Peters, Francisco N. Barrera. Journal of Biological Chemistry. Dec 2022. DOI: 10.1016/j.jbc.2022.102829

Oral presentations:

“Dysregulated Glycogen Metabolism in *Candida albicans* Impacts Fitness, Virulence, And Innate Immune Signaling Via β -(1 \rightarrow 3)-glucan Unmasking”. Rapid Fire Session. ASM Microbe 2023. Houston, TX. June 16, 2023. (Invited)

“Dysregulated glycogen metabolism in *Candida albicans* impacts innate immune signaling via β -(1 \rightarrow 3)-glucan unmasking”. Student session. Asia-Pacific Biofilms 2022. Guangzhou, China. October 22, 2022. (Invited)

“Dysregulated Glycogen synthesis in *Candida albicans* Impacts Innate Immune Signaling via β -(1 \rightarrow 3)-glucan Unmasking”. The 19th South Central Medical Mycology Meeting. Memphis, TN. November 18, 2022.

Posters and Abstracts

Dysregulated Glycogen Metabolism in *Candida albicans* Impacts Fitness, Virulence, And Innate Immune Signaling Via β -(1 \rightarrow 3)-glucan Unmasking (2023). Miao J, Kruppa MD, Ma Z, Lowman DW, Regan J, Palmer GE, Williams DL, Peters BM. ASM Microbe. Houston, TX.

The Cell Wall Glucan-glycogen Complex: A Novel Determinant of the *C. albicans* Host-pathogen Interaction (2023). Miao J, Kruppa MD, Ma Z, Lowman, DW, Ozment TR, Williams DL, Peters BM. Candida and Candidiasis 2023. Montreal, Canada.

Uridine Auxotrophy in *Candida albicans* Disrupts Cell Wall Architecture but Attenuates Virulence by Slowing Growth in mice. Mikayla Mangrum, Andrew Wagner, Jian Miao, Elise Phillips, Brian Peters, Todd Reynolds. Candida and Candidiasis. Montreal, Canada.

The Cell Wall Glucan-glycogen Complex: A Novel Determinant of the *C. albicans* Host-pathogen Interaction (2023). Miao J, Kruppa MD, Ma Z, Lowman, DW, Ozment TR, Williams DL, Peters BM. UTHSC Graduate Research Day. Memphis, TN.

Dysregulated glycogen metabolism in *Candida albicans* impacts fitness, virulence, and innate immune signaling via β -(1 \rightarrow 3)-glucan unmasking (2023). Miao J, Kruppa MD, Ma Z, Lowman DW,

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

Project description:

Approximately 30-50% of patients with *Candida albicans*-related blood stream infections fail antifungal therapy – resulting in very high rates of mortality; however, only a small percentage of clinical isolates are classified as resistant to the drugs used to treat these infections. This disparity highlights that many treatment failures remain unexplained. My project focuses on the idea that the 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 alter antifungal sensitivity by activating mechanisms of antifungal resistance.



Project status:

Over the course of 2022-2023, I have continued to expand my research to examine the impact of human medications on fungal physiology, virulence, and antifungal drug sensitivity. First, we expanded chemical-screens to identify medications which alter fungal physiology as well as antifungal resistance. Over the course of 2022-2023, we identified several drugs that induce *C. albicans* resistance to several azoles (Fluconazole, Itraconazole, Voriconazole), as well as several echinocandins (Caspofungin, Anidulafungin, and Micafungin). In addition, we identified human medications that alter cell wall stress tolerance and potentially recognition by the immune system, a crucial step during infection. Additionally, we have been performing chemoinformatic analysis to determine if there are common structural or physical properties of the approximately 1% of drugs that affect fungal physiology and antifungal sensitivity. We also tested if select medications that alter antifungal sensitivity also affect *C. albicans* growth and stress tolerance, finding that of those tested so far, there is little impact on fungal fitness beyond altering antifungal sensitivity. Thus, while they modulate antifungal sensitivity, they do not obviously affect *C. albicans* fitness or viability. Finally, we continued testing the impact of selected antifungal antagonists upon the outcome of infection in a mouse model of disseminated candidiasis. This has revealed that treatment with therapeutically relevant concentrations of aripiprazole, a medication that not only causes increased azole, echinocandin, and cell wall stress resistance, significantly increases mortality compared to untreated mice. Further testing has confirmed that this mechanism is dependent upon immune response to the fungus, as in the difference is not observed in immunosuppressed mice. Currently, we are investigating the underlying mechanisms.

Future:

Over the course of 2023-2024, we aim to identify the mechanism of aripiprazole-associated worsened outcome. We will also test how other azole and echinocandin antagonists affect fungal physiology and virulence. Finally, we are currently working with collaborators to determine if the use of drugs we have found to be antifungal antagonists are associated with altered clinical outcomes.

Active societies:

Presentations:

2022 TFPG Retreat Program (oral)

2022 SCMM (oral)

2023 TFPG Retreat Program (oral)

Yue “Aeric” Zhou is a 6th year student in the Reynolds lab.

Project description:

During the past year, I have finished the PS synthase solubilization and purification project. We were able to purify PS synthase as a hexameric form, which is unique because all the other proteins with known structures within the same family are dimers. I have also performed kinetic study on the purified hexameric PS synthase and confirmed its overall shape using transmission electron microscopy, which led to my recent publication in the Journal of Biological Chemistry. Using the purified protein, I then moved on to screen about 8,000 bioactive molecules with known biological targets to identify potential inhibitors to PS synthase using a high-throughput assay. Seven inhibitors were found to completely inhibit PS synthase at a low concentration, and one molecule is particularly interesting because it was shown to inhibit PS synthase both *in vitro* and *in vivo*. I am currently wrapping up this project and will get it published soon. For the conferences I have attended since last July, I went to the annual Biophysical Society meeting 2023 in San Diego in February and presented a poster on the structure work done in Dr. Melanie Ohi’s lab at the University of Michigan, Ann Arbor. I also went to Candida and Candidiasis 2023 conference held at Montreal, Canada in May, and presented a poster on the small molecule screening project.



Publications:

Zhou, Y., Syed, J. H., Semchonok, D. A., Wright, E., Kyrilis, F. L., Hamdi, F., ... & Reynolds, T. B. (2023). Solubilization, purification, and characterization of the hexameric form of phosphatidylserine synthase from *Candida albicans*. *J. Biol. Chem.* 299 (6): 104756

Ancajas, C., Carr, A. J., Lou, J., Sagar, R., **Zhou, Y.**, Reynolds, T., & Best, M. D. (2023). Harnessing Clickable Acylated Glycerol Probes as Chemical Tools for Tracking Glycerolipid Metabolism. *Chemistry—A European Journal*, e202300417.

Phillips, E. K., Cannon, J. A., **Zhou, Y.**, Bonifer, K. S., & Reynolds, T. B. (2023). Conjugation-Mediated Plasmid Transfer Enables Genetic Modification of Diverse Bacillus Species. *Microbiology Spectrum*, e03700-22.

Ancajas, C. F., Alam, S., Alves, D. S., **Zhou, Y.**, Wadsworth, N. M., Cassilly, C. D., ... & Best, M. D. (2023). Cellular Labeling of Phosphatidylserine Using Clickable Serine Probes. *ACS Chemical Biology*, 18(2), 377-384.

Conferences:

Yue Zhou, Gregory Phelps, Jeffrey Rybak, Richard Lee, Todd Reynolds. “Identification of small molecule inhibitors to *Candida albicans* phosphatidylserine synthase using a target-based screening” with poster presentation, Candida and Candidiasis 2023, Le Centre Sheraton Montreal Hotel, Montreal, Canada. May 13th -17th, 2023

Yue Zhou, Jacquelyn Roberts, Melanie Ohi, Todd Reynolds. “Reconstitution of purified hexameric phosphatidylserine synthase from *Candida albicans* into lipid nanodisc for structure determination” with poster presentation, Annual Biophysical Society meeting 2023, Convention center, San Diego, California. February 18th– 22nd, 2023.

Ivy Antwi is a 3rd year student in the Cory lab.

Project description:

Over the past year, I have been assessing Azithromycin's role in macrophages' response to *Aspergillus fumigatus*. I have successfully characterized inflammatory cytokines associated with Azithromycin-induced macrophage polarization and also determined Azithromycin's role in the phagocytic activity of *Aspergillus fumigatus*. The successful completion of this work has positioned me to proceed to determine the rate and extent of Azithromycin-aided intracellular killing of *A. fumigatus* by macrophages. I also had the opportunity to present this work at the Autumn Immunology Conference and published an abstract as well. In the course of the year, I put together a review article on the topic: ‘Substances of Abuse and their Effect on SARS-CoV-2 Pathogenesis’ which has been accepted for publication in the *NeuroImmune Pharmacology and Therapeutic* journal.



Publications:

Ivy Antwi, Destiny Watkins, Alahn Pedawi, Atheel Ghayeb, Christine Van de Vuurst, and Theodore J. Cory. Substances of Abuse and Their Effect on SAR-CoV-2 Pathogenesis. *NeuroImmune Pharm Ther.* 2023

Pence B, Zhang Y, **Antwi I**, Cory TJ. Senescent macrophages alter fibroblast fibrogenesis in response to SARS-CoV-2 infection. *NeuroImmune Pharm Ther.* 2022;1(1):37-42. doi: 10.1515/nipt-2022-0003. Epub 2022 Aug 5. PMID: 36534613; PMCID: PMC9726213.

Presentations:

Oral - Ivy Antwi, Jarrod Fortwendel, Theodore J. Cory (2022) “Assessing the role of Azithromycin in Macrophage responses to *Aspergillus*” 50th Autumn Immunology Conference. Chicago, IL. Nov 18- Nov 21, 2022.

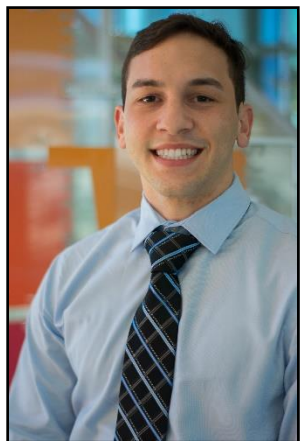
Poster - Ivy Antwi, Jarrod Fortwendel, Theodore J. Cory (2022) “Assessing the role of Azithromycin in Macrophage responses to *Aspergillus*” 50th Autumn Immunology Conference. Chicago, IL. Nov 18- Nov 21, 2022.

CPET Pediatric ID 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 (UTHSC) and Le Bonheur Children's Hospital (LBCH) with a focus on clinical care,



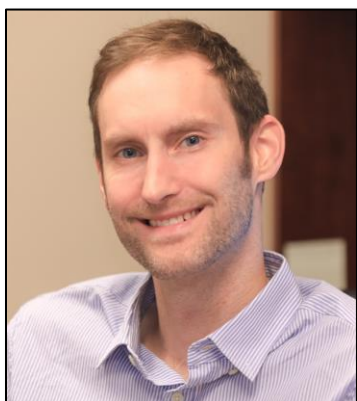
education, and translational research. The primary focus of his research program is to examine differences in catheter-related bloodstream infection (CR-BSI) in pediatric patients receiving parenteral nutrition (PN) with different intravenous fat emulsions (IFE) and investigate in vitro mechanisms for pathogens associated with varying infection rates. Through this endeavor, he published a single-center analysis of differences in CR-BSI rates in pediatric patients receiving PN with SO-IFE or MO-IFE on *Pharmacotherapy* in December 2022. In addition, preliminary results of his investigation on IFE impact on *C. albicans* biofilm formation and hyphal growth were presented as a poster at the Candida and Candidiasis meeting- hosted by the Microbiology Society. During the second year of his fellowship, he performed multi-center analyses to examine differences in *Candida* spp. distribution and

outcomes in fungal CR-BSIs based on IFE receipt. Publications from these analyses are currently pending and planned for submission at the end of Summer 2022.

His program's second focus is on acute kidney injury (AKI) prevalence in pediatric patients based on antimicrobial utilization practices. His main investigative endeavor on this focus is examining differences on AKI prevalence in pediatric patients that received vancomycin using different pharmacodynamic targets. The project combines 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 exposures. Preliminary results for this project were shared as a platform presentation at the 32nd Annual Pediatric Pharmacy Association (PPA) meeting and he received the Christensen Memorial Young Investigator Award for his efforts. On a separate note, during the second year of his fellowship, Dr. Alvira also mentored two pharmacy residency research projects at LBCH examining differences in AKI prevalence in critically ill neonates receiving nephrotoxic medications with CAKUT and characteristics associated with sedative success of critically pediatric patients with dexmedetomidine.

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. Lastly, he is an active member of PPA where he serves on the Practice-based Research Network and is developing educational materials providing pharmacy trainees and junior pharmacy investigators an introduction to common statistical analyses methods.

CPET Seminar Series



“In the search for novel antifungal targets, blind mice lead the way.”

Kevin Fuller, PhD

Assistant Professor
Department of Microbiology and Immunology
Department of Ophthalmology
Oklahoma University Health Science Center



“Cell Wars – the ultimate battle between host and pathogen”

Kirsten Nielsen, PhD

Professor
Department of Microbiology
University of Minnesota, Medical School



“Targeting the *Aspergillus fumigatus* hypoxia response for therapeutic development”

Robert A. Cramer, Jr., PhD

Professor
Department of Microbiology and Immunology
Dartmouth College, Geisel School of Medicine



“Natural variation in the *Candida albicans* biofilm regulatory network”

Aaron P. Mitchell, PhD

Professor and Chair
Department of Microbiology
University of Georgia

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 2022-2023 Seed Grant Funds includes the exciting advancements in ART-related drug interactions during HIV co-infections with the fungal pathogen *Cryptococcus neoformans*. His findings have led to a grant submission for an NIH Director’s



Pioneer award for new investigators for the 2023-2024 cycle.

CPET Capital Equipment Grant Program

The CPET is committed to supporting joint research endeavors among Center faculty, both within the UTHSC College of Pharmacy and throughout the State on TN. For the 2022-2023 cycle, this support included the purchase of a new Nikon Eclipse Ti2 inverted fluorescence microscope with a Tokai Hit live-cell stage adapter (stock photos shown below). Shipment and installation is expected for mid-September 2023. This equipment will be housed in a shared microscopy equipment space within the UTHSC College of Pharmacy where it will be directly accessible to the CoP Center faculty. This equipment purchase will support the development of *in vitro* assays for novel target-based antifungal drug screens, host-microbe and microbe-microbe interactions.



Extramural Funding

Extramural Funding

Federal Funding (including NIH)

Investigator: **Cory TJ** (MPI **Kumar S**, subcontract **Meibohm B**)
Title: Monocytic and plasma exosomal cytochrome P450 in smoking-mediated HIV-1 pathogenesis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01DA047178
Dates: 9/2001 to 6/2024
Total: \$1,700,000
Annual Total: \$342,000

Investigator: **Fortwendel JR** (MPI Peters BM)
Title: Genetic determinants of *Aspergillus* host-pathogen interactions
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI178048
Dates: 06/2023 to 05/2025
Total: \$431,500
Annual Total: \$231,000

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: 03/2020 to 02/2025
Total: \$3,286,625
Annual Total: \$657,325

Investigator: **Fortwendel JR**
Title: Unlocking the cidal activity of echinocandins against *Aspergillus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI158442
Dates: 03/2020 to 02/2025
Total: \$1,552,025
Annual Total: \$449,016

Investigator: **Hevener KE**
Title: Development and evaluation of inhibitors of the *C. difficile* enzyme, FabK, as microbiome-sparing antibacterials
Source: Department of Defense (DoD), PRMRP
W81XWH-20-1-0296
Dates: 7/2020 to 6/2024
Total: \$1,400,976
Annual Total: \$350,244

Investigator: **Hevener KE** (Pi Li W)

Title: Dual inhibition of MDM2 and XIAP as a therapeutic strategy in cancer
Source National Cancer Institute (NCI)
5R01CA240447
Dates: 7/2020 to 6/2025
Total: \$2,750,000
Annual Total: \$530,672

Investigator: **Hevener KE (PI Palmer GE)**
Title: Broad spectrum antifungals targeting fatty acid biosynthesis
Source National Institute of Allergy and Infectious Diseases (NIAID)
4R33AI127607
Dates: 12/2017 to 11/2023
Total: \$800,000
Annual Total: \$447,999

Investigator: **Hole CR**
Title: Cryptococcal Chitin Synthase 3 and Host Immune Responses
Source National Institute of Allergy and Infectious Diseases (NIAID)
1K22AI148724
Dates: 08/2021 to 07/2023
Total Direct: \$423,500
Annual Total: \$108,000

Investigator: **Kumar S (MPI Cory TJ, subcontract Meibohm M)**
Title: Monocytic and plasma exosomal cytochrome P450s in smoking-mediated HIV-1 pathogenesis
Source National Institute of Drug Abuse (NIDA)
R01DA047178
Dates: 9/2021 to 8/2024
Total: \$1,700,000
Annual Total: \$342,000

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: 04/2021 to 03/2023
Total: \$423,500
Annual Total: \$192,500

Investigator: **Kumar S**
Title: Extracellular vesicles in AD-like pathology in HIV and its potential therapeutics
Source National Institute of Ageing (NIA)
1R21AG081140
Dates: 03/2023 to 02/2025
Total: \$423,500

Annual Total: \$231,000

Investigator: **Meibohm B** (PI Kumar S)
Title: Extracellular vesicles-based drug delivery of antiretroviral regimen to target CNS HIV reservoirs
Source: National Institute of Mental Health (NIMH)
5R21MH125670
Dates: 09/2018 to 06/2023
Total: \$423,500
Annual Total: \$192,500

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: 7/2020 to 6/2025
Total: \$2,720,508
Annual Total: \$453,310

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: 6/2021 to 5/2026
Total: \$3,343,775
Annual Total: \$550,560

Investigator: **Meibohm B** (PI Lee RE)
Title: Spectinomycins for non-tuberculosis mycobacterial infections
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI157312
Dates: 09/2021 to 08/2025
Total: \$2,720,508
Annual Total: \$591,304

Investigator: **Meibohm B** (PI Jonsson CB)
Title: Center of Excellence for Encephalitic Alphavirus Therapeutics
Source: National Eye Institute (NEI)
1U19AI142762
Dates: 3/2019 to 2/2024
Total: \$21,104,316
Annual Total: \$2,594,183

Investigator: **Meibohm B, Jonsson CB** (PI Baric R)
Title: Rapidly Emerging Antiviral Drug Development Initiative – AviDD
Center (READDI-AC)
Source: National Institute of Allergy and Infectious Diseases (NIAID)
U19AI171292

Dates: 05/2022 to 04/2027
Total: \$53,749,784
Annual Total: \$256,308

Investigator: **Meibohm B (PI Palmer GE)**
Title: Antifungal antagonism as a cause of treatment failure for invasive mycoses
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI152067

Dates: 04/2021 to 03/2026
Total: \$3,135,467
Annual Total: \$608,395

Investigator: **Meibohm B (PI Kumar S, Cory T)**
Title: Monocytic and exosomal cytochrome P450s in smoking-mediated HIV-1 pathogenesis
Source: National Institute on Drug Abuse (NIDA) R01DA047178
Dates: 09/2018 to 06/2023
Total: \$1,710,000
Annual Total: \$192,500

Investigator: **Palmer GE (subcontracts to Hevener KE, Meibohm B)**
Title: Broad spectrum antifungals targeting fatty acid biosynthesis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
4R33AI127607
Dates: 12/2017 to 11/2023
Total: \$800,000
Annual Total: \$447,999

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: 11/2020 – 10/2023
Total: \$418,000
Annual Total: \$190,000

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: 03/2021 – 02/2026
Total: \$2,059,240
Annual Total: \$608,395

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: 04/2022 to 03/2023
Total: \$418,000
Annual Total: \$190,000

Investigator: **Peters BM**
Title: Candidalysin: a key mediator of *Candida* vaginitis immunopathology
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI134796
Dates: 09/2022 to 08/2023
Total: \$1,520,000
Annual Total: \$380,000

Investigator: **Peters BM**
Title: Modeling host-fungal interactions in Hirschsprung-associated enterocolitis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI163503
Dates: 06/2022 to 05/2023
Total: \$418,000
Annual Total: \$3,000

Investigator: **Peters BM**
Title: The role of gut mycobiota in regulating host lipid absorption and obesity
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21DK129890-01A1
Dates: 04/2022 to 03/2023
Total: \$418,000
Annual Total: \$18,000

Investigator: **Peters BM** (MPI, Fortwendel JR)
Title: Genetic determinants of *Aspergillus* host-pathogen interactions
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI178048
Dates: 06/2023 to 05/2025
Total: \$431,500
Annual Total: \$231,000

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: \$1,009,308

Annual Total: Not Reported

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: \$2,533,727
 Annual Total: \$508,939

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: \$1,412,827
 Annual Total: \$318,321

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: 03/2020 to 02/2025
 Total: \$3,286,625
 Annual Total: \$657,325

Investigator: **Rogers PD** (MPI, Cuomo C)
 Title: Mapping the genomic and molecular mechanisms of antifungal resistance in the emerging fungal pathogen *Candida auris*
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 R01AI169066
 Dates: 03/2023 to 02/2028
 Total: \$6,239,395
 Annual Total: \$1,247,879

Investigator: **Rosch JW**
 Title: Consequences of Direct Viral-Bacterial Interactions
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI168214
 Dates: 01/2022 to 06/2027
 Total: \$2,978,495
 Annual Total: \$502,279

Investigator: **Rosch JW**
 Title: Evolvable Essentiality of in the pan-genome of *Streptococcus pneumoniae* and its mechanistic and evolutionary consequences
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI171038-01
 Dates: 07/2022 to 06/2027

Total: \$3,047,341
Annual Total: \$601,612

Investigator: **Rosch JW** (PI Rock)
Title: Regulation of lipid metabolism in bacteria
Source: National Institute of General Medical Sciences (NIGMS)
5R01GM034496-37
Dates: 12/1984 to 11/2023
Total: \$2,911,600
Annual Total: \$723,024

Investigator: **Rosch JW** (PI Orihuela)
Title: PspA binds necroptotic cells to cause disease and transmit
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI156898-01
Dates: 09/2020 to 08/2025
Total: Not Reported
Annual Total: \$38,886

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: 09/2022 to 06/2026
Total: Not Reported
Annual Total: \$1,624,345 (Project 1); \$363,624 (Project 2)

Investigator: **Rosch JW**
Title: Consequences of direct viral-bacterial interactions
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R56AI155614-01A1
Dates: 07/2021 to 06/2023
Total: \$531,058
Annual Total: \$531,058

Investigator: **Rosch JW**
Title: CEIRR – Center of Excellence for Influenza Research and
Response_MOD 3
Source: National Institute of Allergy and Infectious Diseases (NIAID)
FP00020507
Dates: 09/2021 to 08/2023
Total: \$669,899
Annual Total: \$669,899

Investigator: **Rybak JM**
Title: Development of M-drive: a recyclable Mucor-optimized Cas9 gene-
drive system capable of multi-target gene editing
Source: National Institute of Allergy and Infectious Diseases (NIAID)

R03AI178552
Dates: 06/2023 to 05/2025
Total: \$207,000
Annual Total: \$103,500

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: 04/2022 to 03/2023
Total: \$418,000
Annual Total: \$190,000

Foundation and Industry Funding

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: \$300,000

Investigator: **Rosch JW**
Title: Blue Water Vaccines SRA-2
Source: Blue Water Vaccines
N/A
Dates: 08/2022 to 12/2023
Total: \$75,063

Investigator: **Peters BM**
Title: Dean's Enhancement Program
Source: University of Tennessee Health Science Center College of Pharmacy
Dates: 12/2022 to 06/2023
Total: \$15,000

Investigator: **Fortwendel JR**
Title: Dean's Enhancement Program
Source: University of Tennessee Health Science Center College of Pharmacy
Dates: 12/2022 to 06/2023
Total: \$15,000

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