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

ANNUAL REPORT
2023-2024

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 anti-infectives and vaccines in children. The Center brings together the University of Tennessee Health Science Center, St. Jude Children's Research Hospital, the University of Memphis, Le Bonheur Children's Medical Center, Rhodes College, the University of Tennessee-Knoxville, and East Tennessee State University as each 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 46 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, 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 ultimatey 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 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 $19.5 million in NIH, NSF, DoD and private industry/foundation grants and contracts.

Education of students, post-doctoral trainees and visiting investigators continues to be a major priority in the Center. In 2023-2024, the CPET faculty continued to direct the training of sizable numbers of graduate students and professional students in the Colleges of Pharmacy and Medicine at UTHSC and Biological Sciences at UTK and Rhodes College. In particular, the Center has continued to support a select group of exceptional students designated as CPET Scholars and now includes the possibility of being granted a Travel Award to attend a scientific conference to share progress and network with other scientists. 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.

2023-2024 Annual Report

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2023-2024

Leadership

Jarrod R. Fortwendel, PhD

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

Glen E. Palmer, PhD

- Scientific Advisor
- 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

Brian M. Peters, PhD

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

Faculty

Theodore Cory, Pharm.D., Ph.D.
- Associate Professor, Department of Clinical Pharmacy and Translational Science

Jarrod R. Fortwendel, Ph.D. (*Director*)
- Professor, Department of Clinical Pharmacy and Translational Science

Kirk E. Hevener, Pharm.D., Ph.D.
- Associate 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, Sholarly 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*)
- Professor, Department of Clinical Pharmacy and Translational Science

Brian M. Peters, Ph.D.
- First Tennessee Endowed Chair of Excellence in Clinical Pharmacy
- 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, Deparmtment of Pharmaceutical Sciences

Jason W. Rosch, PhD
- Member, Infectious Diseases Department, St. Jude Children's Research Hospital

Jeffery Rybak, PharmD, PhD
- Assistant Member, Pharmacy and Pharmaceutical Science Department, St. Jude Children's Research Hospital

Qian Shen, PhD
- Assistant Professor, Department of Biology, Rhodes College

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. Cheseney. 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.)

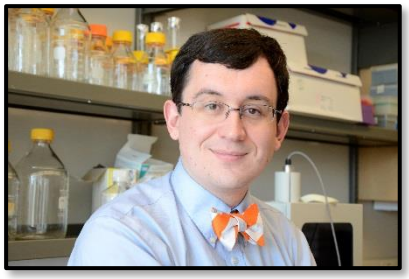
John H. Rodman, Pharm.D.
- Former Vice Chair and Member, Pharmaceutical Sciences Department, St. Jude Children's Research Hospital
- Former Professor, Department of Clinical Pharmacy
  (Dr. Rodman passed away April 29, 2006.)

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.

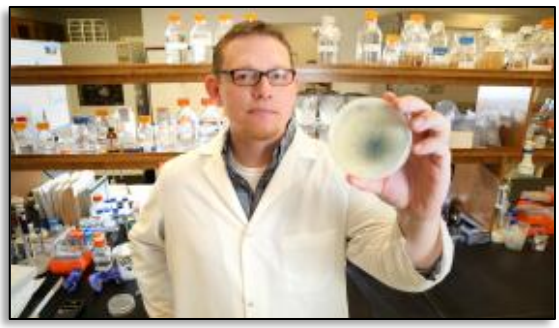


Current lab members

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 cavitary 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 cavitary 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 anitfungal resistance in *Aspergillus* species.



Current Lab Members:

Jarrod R. Fortwendel, PhD – Principal Investigator
Adela Martin-Vicente, PhD – Senior Research Scientist
Uxue Perez Cuesta, PhD – Postdoctoral Fellow
Devi Bale – Graduate Student, Pharmaceutical Sciences Program
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, Osama Alaidi
Pharmacy Students –Darcy Doran

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. The World Health Organization ranks *C. neoformans* as the #1 highest-priority fungal pathogen. Despite effective ART and antifungal drugs, the mortality rate in AIDS patients is between 10-30% in medically advanced countries and as high as 30%-50% in resource-poor areas. 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

[1] 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 *chs3*Δ at a dose previously shown to induce protection with cda*1Δ2Δ3Δ* 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.

[2] Neutrophils have a complicated role in the cryptococcal immune response. Clear data exists for both the helpful and harmful roles of neutrophils in cryptococcal infections, but why this dichotomy exists is ***unknown***. There is increasing evidence that neutrophils do more than originally thought and exist as unique, diverse subsets of heterogeneous populations with different functions. We initially sought to define the role of neutrophils in the immune

response to *C. neoformans* by first depleting neutrophils. It was previously reported that neutrophil depletion leads to increased mouse survival. To our surprise, the neutrophil-depleted mice succumbed to the infection faster than the controls. Mortality was not due to changes in fungal burden, suggesting that death was host-mediated. Cytokine/chemokine and flow cytometry analysis found that deletion of neutrophils induces a strong proinflammatory immune response, with changes in recruitment and ratios of multiple monocyte subsets, highlighting the potential immunomodulatory role of neutrophil in the immune response to *C. neoformans*.

[3] There are only three approved drugs with efficacy against cryptococcosis, and current treatments are often hindered by medication shortages, drug toxicity, the emergence of drug resistance, and the inability of the host's immune defenses to assist. Therefore, there remains an urgent need for novel treatments to combat cryptococcosis. Only a handful of antiretroviral drugs, the protease inhibitors, have been investigated for anti-cryptococcal activity. However, the effects of the current generation of antiretrovirals on cryptococcal growth have not been investigated. We found that all 5 of the HIV integrase strand transfer inhibitors (INSTI)) had anti-cryptococcal activity. We combine expression, genetic, and phenotypic data to characterize the INSTI: cryptococcal interactions.

Current lab members:

Lab Manager – Rebekah Watson

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

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 UTSHC-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:

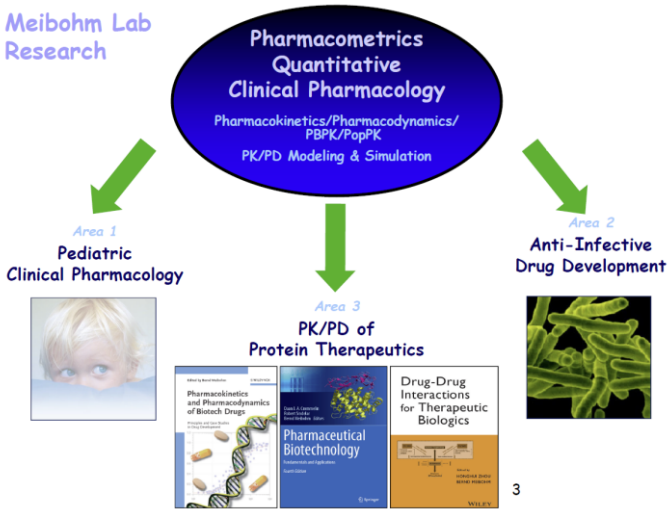
Mr. Sandip Godse, Ms. Lina Zhou, Dr. Golnoush Mirzahosseini, and Ms. Namita Sinha

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
UTHSC Distinguished Professor, Chair,
Department of Pharmaceutical Sciences
Associate Dean for Research and Graduate Programs
Harriet S. Van Fleet Endowed Professor in Pharmaceutics
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)
Haiyang Zhang, BS (PhD Student, Pharmaceutical Sciences Program)
Thorben Zurzbach, BPharm (PhD student, Pharmaceutical Sciences Program)
Christelle Mathieu, BS (PharmD/PhD student)

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

An n 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. Research in the Palmer lab focuses upon several species of *Candida* that naturally colonize the mucosal membranes of healthy individuals, but which can cause invasive fungal disease in immunosuppressed patients. 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). Fungal fatty acid biosynthesis; or 2). Coenzyme A 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 antifungal leads, with a defined mechanism of action can be identified. A second major research interest focuses upon defining how non-antifungal drugs i.e. those consumed for unrelated conditions, affect the physiology and capacity of *Candida* species to cause human infections.

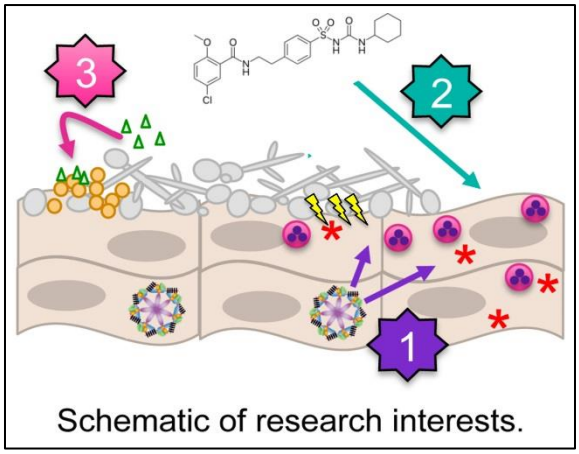
Current Lab Members:
Christian DeJarnette – Research Associate
Ravinder Kumar – Research Associate
Samar Ahmed - Graduate Student, Pharmaceutical Sciences Program
Parker Reitler – Postdoctoral Fellow

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
Scientific Adivsor, Center for Pediatric Experimental Therapeutics

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.



Schematic of research interests.

[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 sulfonylurea 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:

Amirhossein Davari, MS – Graduate Student, Pharmaceutical Sciences Program
Nasim Ahamdi – Graduate Student, Pharmaceutical Sciences Program
Jennifer Carnahan – Technician
Jian Miao, MS - Graduate Student, Pharmaceutical Sciences Program
Saikat Paul, PhD – Postdoctoral Fellow

Todd B. Reynolds, Ph.D.
Professor
Department 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 synthase PS and bears little sequence similarity to the fungal enzyme. Altogether, this indicates that inhibitors of fungal PS synthase would prevent virulence, have broad applicability to other fungi, and have low toxicity. My lab is exploring the structure of *C. albicans* PS synthase with a goal of developing small molecule inhibitors of this enzyme. 2) A second major direction of my lab is to explore the role of immunotherapy against *Candida* species. Oral and invasive infections do not occur as often in the immunocompetent, so enhancing the residual immune response in immunocompromised patients should improve health outcomes. We have found that hyperactivation of some signaling pathways in *C. albicans* leads to greater exposure of the fungus to immune cells and a reduction in virulence during infection. We are working to discover how these pathways cause this reduction in virulence with the long-term goal of exploiting this to improve immunotherapy. Altogether, these two foci in my lab complement one another as they both focus on aspects of the cell envelope that can be exploited to improve antifungal therapies.

Current Lab Members:

Graduate students – Ainsley King, Mikayla Mangrum, Adrianna Matthews, Nazanin Mohammed

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
St. Jude 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.

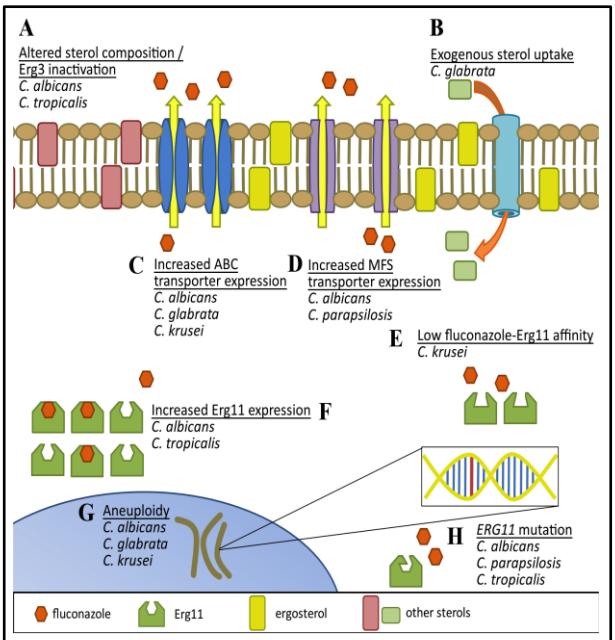


Figure 1. Comparison of documented fluconazole resistance mechanisms in *Candida* species. A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. **B)** Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production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

For 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
Darian Santana, Ph.D. – Post-doctoral Fellow
Luisa Gomez Londono, Ph.D. – Post-doctoral Fellow
Garrett Weeks – Graduate Student, Microbiology, Immunology, and Biochemistry Graduate Program

Jason W. Rosch, Ph.D.
Member, Department of Host-Microbe Interactions
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:

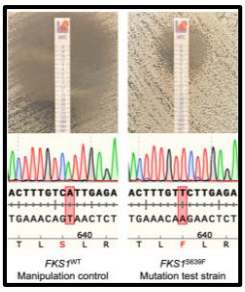
Christine Dunn, Graduate student
Haley Echlin, PhD, Staff scientist
Amy Iverson, Lab manager
Cydney Johnson, PhD, Postdoctoral FellowYuri Lagune Terai, Research technician
Ashton McKinnon, Graduate student
Abigail McKnight, Research technician
Brenden Morrow, Graduate student
Andy Nishimoto, PhD, PharmD, Postdoctoral Fellow
Trevor Penix, Graduate student

Jeffrey M. Rybak, Pharm.D., Ph.D.
Assistant Member, St. Jude Faculty
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
Laura Doorley, PhD – Postdoctoral Fellow
Vanessa Meza Perez – Graduate Student, St Jude Childrens Research Hospital

Qian Shen, Ph.D.
Assistant Professor
Department of Biology
Rhodes College

Histoplasma capsulatum is a primary fungal pathogen that causes respiratory tract infections (i.e., histoplasmosis) in both immune-competent and immune-compromised individuals. Among immune-compromised individuals (e.g., AIDS patients), infections can progress into disseminated histoplasmosis, resulting in life-threatening situations. The mortality rate among HIV patients infected by *Histoplasma* is 30% in Latin America. Spores produced by *Histoplasma* reside in the soil. When the spore-containing soil is disturbed, the aerosolized spores can be inhaled and reach the lower respiratory tract. In the lung environment, *Histoplasma* spores germinate into pathogenic yeasts under the elevated temperature (i.e., 37°C).

Unlike the opportunistic fungal pathogens such as *Candida* and *Aspergillus*, *Histoplasma* yeasts cannot be readily eliminated by macrophages which normally control microbial infections. Instead, they survive and proliferate within the phagosomal compartment of macrophages which is a nutrient-depleted environment. My research program seeks to understand the molecular mechanisms employed by *Histoplasma* yeasts to acquire sufficient nutrients (e.g., carbon, nitrogen, and sulfur) to proliferate within macrophages.

Histoplasma must adapt to the mammalian host environment to successfully establish infections. The habitat of *Histoplasma* in the soil is vastly different from the host environment during infection. Differences such as temperature, nutrient availability, and level of carbon dioxide (CO_2) can significantly impact the physiology and potentially the virulence of *Histoplasma*. Our work also focuses on understanding how *Histoplasma* senses and responds to elevated CO_2 within the mammalian host.

DIRECTION OF THE CENTER

2023-2024

Goals and Future Plans

In the coming year, the CPET will continue its focus on the overarching themes of infectious diseases affecting children and anti-infective drug discovery and development.

The CPET Seed and Equipment Grant Program, originally implemented originally for the 2020-2021 cycle, is planned to be offered again for the coming 2024-2025 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 2024-2025 cycle, this Program is again aiming to fund collaborative work between UTHSC Center faculty and research at Le Bonheur and St. Jude Childrens to facilitate truly translational discoveries and to support the generation and disseminatation of new knowledge regarding the treatment of childhood diseases throughout UTHSC, the state of Tennesse, and the nation. The Seed Grant Program will also invest for its final year in our newest recruited faculty, Dr. Camaron Hole, to focus 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 2024-2025 Scholars program, Center support will again require scholars to generate at least one first-authored research publication in a peer-revewed scientific journal (submitted), to attend at least one national or international conference and present research findings in either oral or poster format, and to encourage submission 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 increased the number of Scholars supported for the 2023-2024 cycle to seven and, accomplishments considered, will maintain this level for the coming year. For 2023-2024, the Center also provided competitive travel awards to Scholars to attend regional, national, and international confrerences to disseminate findings and assist in the development of young scientists. The Center will again offer Travel Awards given the success of the past cycle. The CPET Scholars trainees will again be further supported through the CPET support of the Tennessee Fungal Pathogens Group Conference and Retreat to be held in June/July of 2025, 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 five speakes for the 2024-2025 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.

Centers of Excellence Actual and Proposed Budget

Institution: University of Tennessee Health Science Center

Center: Center for Pediatric Experimental Therapeutics (R079700142)

	FY2023-2024 Proposed	FY2023-2024 Actual	FY2024-2025 Proposed
PERSONNEL			
Faculty	$ 9,000.00	$ 9,034.86	$ 20,000.00
Other Professional			
Clerical/ Supporting	$ 10,000.00	$ 7,192.44	$ 10,000.00
Assistantships	$ 97,500.00	$ 128,408.89	$ 130,000.00
Total Salaries (exclude Longevity):	**$ 116,500.00**	**$ 144,636.19**	**$ 160,000.00**
Longevity (Excluded from Salaries)	$ 40.00		
Fringe Benefits	$ 10,000.00	$ 7,046.00	$ 8,000.00
Total Personnel:	**$ 126,540.00**	**$ 151,682.19**	**$ 168,000.00**
NON-PERSONNEL			
Travel	$ 18,000.00	$ 10,489.08	$ 12,000.00
Software	$ 8,500.00	$ 449.87	$ 500.00
Books & Journals	$ -		
Other Supplies	$ 56,418.00	$ 42,272.97	
Equipment	$ 75,000.00	$ 93,938.55	$ 48,919.18
Maintenance			
Scholarships	$ 14,000.00		$ 14,000.00
Consultants			
Other (Specify):			
Printing, Duplicating, Binding	$ 500.00		
Postage, Freight, & Telephone		$ 98.07	
Professional Serv & Memberships	$ 20,000.00	$ 43,980.95	$ 24,000.00
Computer Services			
Rentals		$ 450.00	$ 500.00
Grants & Subsidies			
Contractual & Special Services	$ 5,000.00	$ 4,396.74	$ 5,000.00
Other Expenditures	$ 8,000.00	$ 1,985.77	$ 5,000.00
Entertainment, Food & Housing	$ 16,000.00		$ 16,000.00
Facilities & Admin			
Direct Cost Sharing			
Total Non-Personnel:	**$ 221,418.00**	**$ 198,062.00**	**$ 125,919.18**
GRAND TOTAL:	**$ 347,958.00**	**$ 349,744.19**	**$ 293,919.18**
REVENUE			
New State Appropriation	$ 280,951.00	$ 280,951.00	**$ 287,007.00**
Carryover State Appropriation	$ 67,007.00	$ 67,007.00	**$ 6,912.18**
Total Revenue:	**$ 347,958.00**	**$ 347,958.00**	**$ 293,919.18**

YEAR-IN-REVIEW 2023-2024

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 2023-2024 cycle, Center faculty reported over $47 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 2023-2024 cylce, 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. This year, the Center supported seven 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 2023-2024 invovled speakers focused on genetic determinants of invasive fungal disease, covering both systemic and localized 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 and Retreat that took place in June of 2024.

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 steam 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 Tennesse Fungal Pathogens Group (TFPG) Annual Conference and Retreat, the CPET Scholars Program, the CPET Travel Award Program, and the CPET Seminar Series

CPET TFPG Annual Coneference Retreat

Beginning the 2020-2021 cylce, 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 disesase 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 inital state-wide conference served to solidify the nascent "Tennessee Fungal Pathogens Group" into one of the the stongest and most influential medical mycology centers in the world. This initial conference was, therefore, deemed an outstanding success and has now bcome 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 2023-2024 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. Marc Swidergall, PhD, Assistant Professor from the UCLA David Geffen School of Medicine and an Investigator at the Lundquist Institute in the Division of Infectious Diseases at Harbor-UCLA Medical Center. An immunologist by training, Swidergall delivered an insightful lecture on immunometabolism and the regulation of host response during oral candidiasis in adults and neonates. This year, the success of the Conference and of the

research activities of the group were the focus of promotional activities through the University of Tennessee Health Science Center Communications and Marketing department (https://news.uthsc.edu/ut-health-science-center-college-of-pharmacy-spearheads-battle-against-fungal-pathogens-at-annual-conference/) as well as the Daily Memphian, a local news publisher in Memphis (https://dailymemphian.com/subscriber/article/45343/memphis-uthsc-team-researches-dangerous-fungi).

CPET Scholars Program

Harrison Thorn is a 4th-year graduate student in the Fortwendel lab

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Project description:

Harrison's work has focused on regulatory mechanisms of septation in *A. fumigatus*, with an overarching goal of identifying novel antifungal targets to improve echinocandin efficacy in treatment of invasive aspergillosis. He has focused on activating mechanisms of the three SIN kinases, SepH, SepL and SidB, mutants of which are aseptate, rendering them hypersusceptible to the echinocandins and avirulent in mouse models of disease. Therefore, blocking septation may be significant towards improving patient outcomes during invasive fungal infections, which maintain high mortality rates despite effective treatment options. Harrison previously identified that gene deletion of the conserved GTPase SpgA and its two-component GAP of ByrA and BubA did not significantly impact septation or drug resistance. Deletion of SepM and MobA, two conserved kinase activators, resulted in loss of septation and echinocandin resistance, and displayed reduced virulence in a mouse model of invasive aspergillosis. This year, Harrison has been studying suppressor mutants isolated by passaging the *sepM* deletion mutant over a low concentration of caspofungin, a clinically used echinocandin. Harrison applied for and received an Independent Project grant from the CGHS to pursue this project. The mutants he isolated were resistant to the echinocandins and displayed rescued septation. Suppressor mutants displayed significant growth defects with hyperbranched hyphae and excess sporulation. Upon whole-genome sequencing, he found that all isolated mutants had sustained an insertion in *nsdd*, likely causing a frame shift and disrupting function. Deletion of *nsdd* in Δ*sepM* and its parent strain caused increased septation at earlier timepoints but not echinocandin resistance. This year, Harrison successfully passed his admission to PhD candidacy exam and has begun work focusing on molecular mechanisms of SidB function and activation.

Awards:

- UTHSC College of Graduate Health Science – Independent Project Grant ($5000)

Publications:

- Xie J, Rybak JM, Martin-Vicente A, Guruceaga X, **Thorn HI**, Nywening AV, Ge W, Parker JE, Kelly SL, Rogers PD, Fortwendel JR. "The sterol C-24 methyltransferase encoding gene, erg6, is essential for viability of Aspergillus species." Nat Commun. 2024 May 20;15(1):4261.
- Rybak JM, Xie J, Martin-Vicente A, Guruceaga X, **Thorn HI**, Nywening AV, Ge W, Souza ACO, Shetty AC, McCracken C, Bruno VM, Parker JE, Kelly SL, Snell HM, Cuomo CA, Rogers PD, Fortwendel JR. "A secondary mechanism of action for triazole antifungals in Aspergillus fumigatus mediated by hmg1." Nat Commun. 2024 Apr 29;15(1):3642. doi: 10.1038/s41467-024-48029-2.
- **Thorn HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "MOB-mediated regulation of septation initiation network (SIN) signaling is required for echinocandin-induced hyperseptation in *Aspergillus fumigatus*." mSphere. 2024 Mar 26;9(3).

- Guruceaga X, Perez-Cuesta U, Martin-Vicente A, Pelegri-Martinez E, **Thorn HI**, Cendon-Sanchez S, Xie J, Nywening AV, Ramirez-Garcia A, Fortwendel JR, Rementeria A. "The *Aspergillus fumigatus maiA* gene contributes to cell wall homeostasis and fungal virulence." Front Cell Infect Microbiol. 2024 Jan 26;14:1327299.

Presentations:

- **Thorn, HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "MOB-mediated regulation of septation initiation network (SIN) signaling is required for echinocandin-induced hyperseptation in Aspergillus fumigatus." UTHSC Graduate Research Day 2024. Memphis, TN. Poster. May 31, 2024.
- **Thorn, HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "Conserved Regulators of the Septation Initiation Network are required for *Aspergillus fumigatus* Echinocandin Resistance and Virulence." Fungal Genetics Conference 2024. Pacific Grove, CA. Poster. March 14, 2024.
- **Thorn, HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "Conserved Regulators of the Septation Initiation Network are required for *Aspergillus fumigatus* Echinocandin Resistance and Virulence." Asperfest 20. Pacific Grove, CA. Poster. March 11, 2024.
- **Thorn, HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "Conserved Regulators of the Septation Initiation Network are required for *Aspergillus fumigatus* Echinocandin Resistance and Virulence." Advances Against Aspergillosis and Mucorcycosis. Milan, ITA. Poster and Podium. January 25, 2024.
- **Thorn, HI**, Guruceaga X, Martin-Vicente A, Nywening AV, Xie J, Ge W, Fortwendel JR. "Conserved Regulators of the Septation Initiation Network are required for *Aspergillus fumigatus* Echinocandin Resistance and Virulence." 2023 South Central Medical Mycology meeting. Memphis, TN. Oral. November 2023.

Jian Miao is a 5th year student in the Peters lab.

Jian earned his master's degree working on *Staphylococcus aureus* biofilm and pathogen rapid detection technique from Dr. Zhenbo Xu's lab 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. Besides, Jian also characterized a type 1 protein phosphatase regulatory subunit that active glycogen synthase in *C. albicans*. 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:

- John Autian Student Enrichment Fund Awardee. College of Graduate Health Sciences, UTHSC. February 2024.
- Outstanding Graduate Student Award. College of Pharmacy, UTHSC. January 2024.
- Dr. Pete T. Magee Trainee Award. Medical Mycological Society of the Americas. August 2023.

Publication:

- A genome-scale screen identifies sulfated glycosaminoglycans as pivotal in epithelial cell damage by *Candida albicans*.
  Jianfeng Lin, Jian Miao, Katherine G. Schaefer, Charles M. Russell, Robert J. Pyron, Fuming Zhang, Quynh T. Phan, Norma V. Solis, Hong Liu, Masato Tashiro, Jonathan S. Dordick, Robert J. Linhardt, Michael R. Yeaman, Gavin M. King, Francisco N. Barrera, Brian M. Peters, Scott G. Filler
  Nature Microbiology. July 2024. Accepted.
- Disruption to *de novo* uridine biosynthesis alters β-1,3-glucan masking in *Candida albicans*.
  Mikayla M. Mangrum, Amanda K. Vogel, Andrew S. Wagner, Ainsley E. King, Jian Miao, Yue Zhou, Elise K. Phillips, Brian M. Peters, Todd B. Reynolds
  mSphere. August 2024. DOI: 10.1128/msphere.00287-24.

Oral presentations:

- "Interrogating a regulatory mechanism underpinning the role of glycogen synthesis in *Candida albicans* fitness and host-pathogen interactions". The 8th Annual Tennessee Fungal Pathogens Group (TFPG) Research Conference. Evins Mill, TN. June 12, 2024.

- "The cell wall glucan-glycogen complex: a novel determinant of the *C. albicans* host-pathogen interaction". The 20th South Central Medical Mycology Meeting (SCMM). Memphis, TN. November 17, 2023.

Posters and Abstracts

- Miao J, et al. "Fungal glycogen contributes to *Candida albicans* β-(1,3)-glucan masking and alters cytokine release via a Dectin-1-dependent mechanism". 32nd Fungal Genetics Conference. Pacific Grove, CA. March 15, 2024.
- Lin J, Miao J, et al. "Genome-wide CRISPR screen reveals critical players in candidalysin-induced damage". 32nd Fungal Genetics Conference. Pacific Grove, CA. March 15, 2024.
- Miao J, et al. "Fungal glycogen contributes to *Candida albicans* β-(1,3)-glucan masking and alters cytokine release via a Dectin-1-dependent mechanism". Keystone Symposia, Fungal Pathogens: Emerging Threats and Future Challenges. Alberta, Canada. February 20, 2024.

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Parker Reitler is a recent graduate of the Palmer lab.

Project Description:
Parker earned his Doctor of Philosophy from the UTHSC Integrated Program in Biomedical Sciences in June 2024. His current research focuses on characterizing how non-antifungal medications alter the physiology and pathogenicity of infectious fungi and promote tolerance to the echinocandin antifungals. Such drug-fungus interactions may explain why many patients' with potentially lethal fungal infections fail to respond to echinocandin therapy.

Approximately 30-50% of patients with *Candida albicans* bloodstream infections fail antifungal therapy – resulting in very high rates of mortality. However, only a small percentage of clinical isolates are resistant to the drugs used to treat these infections, and many treatment failures remain unexplained. Our previous work has revealed that several non-antifungal medications alter fungal physiology and/or antifungal sensitivity, and thus potentially the outcome of infection. Indeed, our previous research shows that the anti-schizophrenic medication Aripiprazole and heart-related medication Amiodarone, can alter antifungal sensitivity by activating mechanisms of resistance. Our work has also revealed that many medications can also alter the way in which the mammalian host interacts with the fungal pathogen, and in-turn may impact the outcome of infection. Future studies will determine if these drug-fungus interactions are likely to affect clinical outcomes or the efficacy of antifungal therapy in humans.

Awards/Internship:

- CPET Scholar. UHTSC. Center of Pediatric Experimental Therapeutics. Advisor: Dr. Glen E. Palmer. August 2023-August 2024.

Publications:

- **Reitler Parker**, Regan Jessica, DeJarnette Christian, Srivastava Ashish, Carnahan Je nnifer, Tucker M. Katie, Meibohm Bernd, Peters M. Brian, Palmer E. Glen (2024). The atypical antipsychotic aripiprazole alters the outcome of disseminated *Candida albicans* infections. Infect Immun 0:e00072-24.https://doi.org/10.1128/iai.00072-24

Presentations:

- **Reitler PR.** Exploring how Non-Antifungal Medications Modulate Host-*Candida albicans* Interaction. South Central Medical Mycology Conference. Oral. Memphis, TN. November 2023.

- **Reitler PR**. Exploring how medications modulate host-*Candida* interaction. Fungal Pathogen Group Summer Conference. Oral. Smithsville, TN. July 2023

Yue "Aeric" Zhou successfully defended his dissertaition in the Reynolds lab in December 2023 and is now a postdoctoral associate in the MacKinnon lab at the Rockefeller University.

Project Description:

During the past year, I have finished the drug screening project for identifying inhibitors against *Candida albicans* phosphatidylserine synthase (PS synthase). Using the purified protein, I screened 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. One molecule, CBR-5884, is particularly interesting because it inhibits PS synthase both *in vitro* and *in vivo*, and it is shown to be a reversible competitive inhibitor to PS synthase.

I defended my Ph.D. on December 2023, and worked as a short-term postdoc in the Reynolds' lab till March 2024. Since April 2024, I moved to NYC and started to work in the MacKinnon lab, where I intended to discover molecules treating long QT syndrome. I really appreciate the time and experience being in the Tennessee fungal pathogen group.

Publications:

- **Zhou, Y.**, Phelps, G.A., Mangrum, M.M., McLeish, J., Phillips, E.K., Lou, J., Ancajas, C.F., Rybak, J.M., Oelkers, P.M., Best, M.D., Lee, R. and Reynolds, T.B.* (2024). The small molecule CBR-5884 inhibits the Candida albicans phosphatidylserine synthase. Mbio, 15(5), e00633-24.
- **Zhou, Y**., Reynolds, T.B. Innovations in Antifungal Drug Discovery among Cell Envelope Synthesis Enzymes through Structural Insights. J. Fungi. 10(3), p.171.3.
- Mangrum, M.M., Vogel, A.K., Wagner, A.S., King, A.E., Miao, J., **Zhou, Y.**, Phillips, E.K., Peters, B.M. and Reynolds, T.B.* (2024). Disruption to de novo uridine biosynthesis alters β-1, 3-glucan masking in Candida albicans. mSphere, pp.e00287-24.
- Cannon, J. A., **Zhou, Y.**, Qualey, L. T., and Reynolds, T.B.* (2024). Surface associated residues in subtilisin's contribute to poly-L-lactic acid depolymerization via enzyme adsorption. Microbial Biotechnology, 17(6), e14473.

- Lou, J., Ancajas, C.F., **Zhou, Y.**, Lane, N.S., Reynolds, T.B. and Best, M.D. * (2024). Probing Glycerolipid Metabolism using a Caged Clickable Glycerol-3-Phosphate Probe. ChemBioChem, p.e202300853.

Ivy Antwi is a 4th year student in the Cory lab.

Project description:

Ivy Antwi is a fourth-year student in the Cory lab, where she has been contributing since 2021. Her current research focuses on assessing the role of azithromycin in the macrophage response to *Aspergillus fumigatus*.

Pulmonary aspergillosis, an infection commonly observed in immunocompromised individuals, is caused by the opportunistic pathogen *Aspergillus fumigatus*, particularly prevalent in patients with cystic fibrosis. Alveolar macrophages are among the first cells to respond to pulmonary infections with *A. fumigatus*, playing a critical role in preventing acute infective flares through phagocytosis and antigen presentation. Patients with cystic fibrosis are often treated with azithromycin, a macrolide antibiotic known for its immunomodulatory and anti-inflammatory properties, to reduce pulmonary exacerbations and improve lung function. However, there are growing concerns about the potential association between azithromycin use and an increased risk of *A. fumigatus* isolation. Recent studies have presented contradictory data regarding its impact on cystic fibrosis patients.

In response to these concerns, Ivy's research over the past year has focused on exploring azithromycin's influence on the immune response to *A. fumigatus*. Using J774 macrophage cells, she has successfully characterized the inflammatory cytokines associated with azithromycin-induced macrophage polarization and determined azithromycin's role in the phagocytosis and killing of *A. fumigatus* in these cells.

Publication:

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

Presentation:

- **Seminar -** Assessing the role of azithromycin in macrophages response to Aspergillus fumigatus **– UTHSC, 2023**
- **Journal Club - 2023**

Kristiana Avad is a 3rd year student in the Hevener lab.

Project Description:

Kristiana earned his Doctor of Pharmacy from the UTHSC from the College of Pharmacy in May of 2022 before matriculating into the Pharmaceutical Science PhD program. Her current research focuses on characterization of the novel antibacterial target, enoyl-ACP reductase FabK, that result in narrow-spectrum antibacterial effect against *Fusobacterium nucleatum*.

The impact of broad-spectrum antibacterial use on the disruption of the human microbiome and increasing antibacterial drug resistance has led to an increased interest in the characterization and validation of narrow-spectrum antibacterial targets. One pathogen of particular interest for narrow-spectrum antibacterial discovery is *Fusobacterium nucleatum*, which has been associated with gastrointestinal cancers, including colorectal cancer (CRC). Recent studies have shown that broad spectrum antibacterials may be efficacious in the treatment of *Fusobacterium*-associated CRC, though there is concern this could lead to dysbiosis-related digestive system diseases. We present the biophysical and biochemical characterization of a novel and potentially narrow-spectrum antibacterial target in *F. nucleatum*, the enoyl-ACP reductase II (FabK) enzyme. FabK is an essential, rate-limiting enzyme in the bacterial fatty acid synthesis, FAS-II, pathway. It is one of four known isozymes that are structurally and mechanistically distinct, and unlike the major gut commensals, is the sole isozyme expressed by *F. nucleatum*. Based on this, we hypothesized that F. *nucleatum* FabK (*Fn*FabK) inhibitors would show selective antibacterial activity and minimal disruption of the gut flora.

Awards/Internship:

- NIH Loan Repayment Program awardee. National institute of Allergy and Infectious Disease. September 2023

- Graduate Student Intern. St Jude Children's Research Hospital. Chemical Biology and Therapeutics. Advisor: Dr. Richard Lee. November 2023- February 2024.

Publications:

- Rutherford JT, **Avad K**, Dureja C, Norseeda K, Gc B, Wu C, Sun D, Hevener KE, Hurdle JG. Evaluation of *Fusobacterium nucleatum* Enoyl-ACP Reductase (FabK) as a Narrow-Spectrum Drug Target. ACS Infect Dis. 2024 May 10;10(5):1612-1623. doi: 10.1021/acsinfecdis.3c00710. Epub 2024 Apr 10. PMID: 38597503; PMCID: PMC11091888.

Presentation:

- **Avad KA,** Rutherford JT, Okpomo D, Hurdle JG, Sun D, Hevener KE. Characterization of F. nucleatum FabK as a narrow spectrum target for Antibacterial Chemotherapy. European Society of Clinical Microbiology and Infectious Diseases. Poster. Barcelona, Spain. April 2024

- **Avad KA**. Characterization of F. nucleatum FabK as a narrow spectrum target for Antibacterial Chemotherapy. Drug Discovery & Development Colloquium/MALTO 2024. Oral. Little Rock, AR. June 2024.

- **Avad KA**. Characterization of F. nucleatum FabK as a narrow spectrum target for Antibacterial Chemotherapy. UTHSC Quarterly Scientific Meet (QSM). Memphis, TN. August 2024.

Jinhong Xie is a 4th-year graduate student in Fortwendel lab.

Jinhong's current research focuses on understanding the mechanisms by which triazole therapy induces negative feedback regulation of HMG-CoA reductase in *Aspergillus fumigatus*. The growing incidence of triazole resistance poses a significant threat to clinical therapy. Recent studies have frequently reported mutations in HMG-CoA reductase encoding gene, *hmg1*, particularly in the sterol-sensing domain (SSD), as potential determinants of triazole resistance in *A. fumigatus*. Our preliminary data suggest that Hmg1-mediated triazole resistance may be associated by Insulin Induced Gene (INSIG) ortholog *insA*. This research aims to delineate the InsA-Hmg1 interaction for sterol-induced negative feedback regulation of Hmg1. By elucidating these mechanisms, this research seeks to identify new therapeutic targets to combat triazole resistance, thus improving the efficacy of antifungal treatments against *A. fumigatus*.

Awards:

- Independent Research Award ($5000). UTHSC College of Graduate Health Sciences. May 2024

- Travel Award ($2500). CPET. May 2024

Publications:

- **Xie, J.,** Rybak, J.M., Martin-Vicente, A. *et al.* The sterol C-24 methyltransferase encoding gene, *erg6*, is essential for viability of *Aspergillus* species. ***Nat Commun*** 15, 4261 (2024).

- Rybak, J.M., **Xie, J**., Martin-Vicente, A. *et al.* A secondary mechanism of action for triazole antifungals in *Aspergillus fumigatus* mediated by *hmg1*. ***Nat Commun*** 15, 3642 (2024).

- Thorn HI, Guruceaga X, Martin-Vicente A, Nywening AV, **Xie J**, Ge W, Fortwendel JR. 2024. MOB-mediated regulation of septation initiation network (SIN) signaling is required for echinocandin-induced hyperseptation in *Aspergillus fumigatus*. **mSphere** 9:e00695-23.

- Guruceaga X, Perez-Cuesta U, Martin-Vicente A, Pelegri-Martinez E, Thorn HI, Cendon-Sanchez S, **Xie J**, Nywening AV, Ramirez-Garcia A, Fortwendel JR and Rementeria A (2024) The *Aspergillus fumigatus maiA* gene contributes to cell wall homeostasis and fungal virulence. **Front. Cell. Infect. Microbiol.** 14:1327299.

Presentations:

- The sterol C-24 methyltransferase encoding gene, *erg6*, is essential for viability of *Aspergillus* species. Poster. **32nd Fungal Genetics Conference and 20th International *Aspergillus* Meeting**. Pacific grove, CA. March 2024

- The sterol C-24 methyltransferase encoding gene, *erg6*, is essential for viability of *Aspergillus* species. Poster. **CGHS Graduate Research Day**. Memphis, TN. May 2024

CPET Travel Award Recipients

Recipient: Kristiana Avad
Conference: ECCMID 2024
Location: Barcelona, Spain
Dates: April 27- 30, 2024
Award Amount: $2500

Recipient: Harrison Thorn
Conference: 32nd Annual Fungal Genetics Conference
Location: Asilomar Conference Grounds, Pacific Grove, CA
Dates: March 11-17, 2024
Award Amount: $2500

Recipient: Jinhong Xie
Conference: 32nd Annual Fungal Genetics Conference
Location: Asilomar Conference Grounds, Pacific Grove, CA
Dates: March 11-17, 2024
Award Amount: $2500

CPET Seminar Series

"Stress-Responsive Translatome Reprogramming in *Cryptococcus neoformans* – multiple paths to a stress adaptive state."

John C. Panepinto, PhD

Professor
Senior Associate Dean for Biomedical Education
Department of Microbiology and Immunology
School of Medicine and Biomedical Sciences
University at Buffalo, SUNY

"Lessons from the Desert: Updates on Vaccine Development for Coccidioidomycosis"

Bridget Barker, PhD

Associate Professor
Department of Biological Sciences
Pathogen and Microbiome Institute
Northern Arizona University

"Deciphering Mechanisms of Antibiotic Persistence Using Bacterial Single-Cell Transcriptomics"

Peijun Ma, PhD

Assistant Member
Pharmacy and Pharmaceutical Sciences Department
St. Jude Children's Research Hospital

"*Salmonella*, *Candida albicans*, and Arginine: Intricate Cross-Talk in the Gut Enhances Bacterial Virulence"

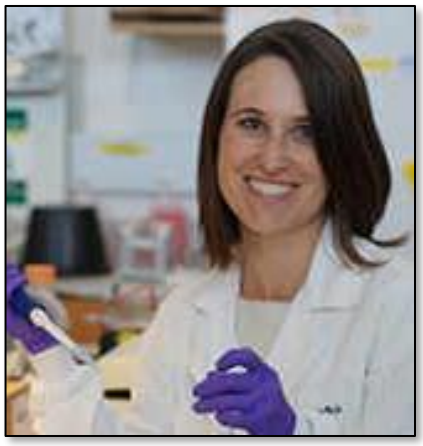
Judith Behnsen, PhD

Assistant Professor
Department of Microbiology and Immunology
University of Illinois at Chicago

"Microscale Arrays for the Characterization of Neutrophil Swarming Responses Against Fungi"

Alex Hopke, PhD

Assistant Porfessor
Department of Biomedical Sciences
Quillen College of Medicine
East Tennessee State University



"The Role of Cathelicidin in Early Host Response During Fungal Sepsis"

Alison Coady, PhD

Assistant Professor
Department of Microbiology and Immunology
The University of Texas Medical Branch

“A Multifaceted Approach to Improve Outcomes of Cerebral Aspergillosis”

Sarah R. Beattie, PhD

Assistant Professor
Stead Family Department of Pediatrics
Carver College of Medicine
University of Iowa

CPET Seed Grant Program

Awardee: Dr. Camaron Hole, PhD

Project Description: Dr. Hole has been awarded a CPET seed grant, renewable for four years (ending with FY25), 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 *Cryptoccocus* pulmonary infections, as well as vaccine development against this deadly fugnal infection. Data generated with the 2023-2024 Seed Grant Funds includes the exciting discovery that HIV integrase inhibitors display anti-cryptococcal activity setting the stage for the use of these drugs as novel dual-use therapeutics. His findings have led to NIH R21 grant submissions in the Spring of 2024.

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 2023-2024 cycle, this support inlucded the purchase and installation of a an Apricot S3 Liquid Handler. This is an automated high performance liquid handler for a flexible array of applications. The Apricot S3 facilitates the replication of chemical libraries into assay plates to screen small molecule libraries and identify novel inhibitors of potential drug targets. This expansion of screening capacity will allow efficient and rapid screening chemical libraries and facilitate the identification of lead compounds. This equipment is housed in the Palmer Laboratory on the 3rd floor of the UTHSC College of Pharmacy and is directly accessible to all CoP Center faculty.

Extramural Funding

Extramural Funding

Federal Funding (including NIH, NSF and DoD)

Investigator:	**Cory TJ** (MPI **Kumar S**, subcontract **Meibohm B**)
Title:	Monocytic and plasma exosomal cytochrome P450 in smoking-mediated HIV-1pathogenesis
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:	$195,200

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:	$656,395

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 stragtegy 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:	**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 vesicles in AD-like pathology in HIV and its potential therapeutics
Source	National Institute of Ageing (NIA) 1R21AG081140
Dates:	03/203 to 02/2025
Total:	$423,500
Annual Total:	$195,200

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 abcessus* 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: **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 biosynthetis enzymes in infectious fungi
Source National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI156611

Dates: 11/2020 – 10/2023
Total: $418,000
Annual Total: $192,500

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**
Title: Candidalysin: a key mediator of *Candida* vaginitis immunopathology
Source National Institute of Allergy and Infectious Diseases (NIAID)
R01AI134796-05A1
Dates: 02/2024 to 01/2029
Total: $1,935,675
Annual Total: $415,675

Investigator: **Peters BM**
Title: The role of gut mycobiota in regulating host lipid absorption and obesity
Source National Institute of Diabetes and Digestive and Kideny Diseases (NDDK)
1R21DK129890-01A1
Dates: 04/2022 to 03/2025
Total: $418,000
Annual Total: $141,408

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: $192,500

Investigator: **Peters BM** (MPI)
Title: Exploring the role, regulation, and antimicrobial function of Paneth cell peptides PYY and NPY in maintaining gut microbial commensalism and innate immune defense
Source National Institute of Diabetes and Digestive and Kideny Diseases (NDDK)
1R21DK113788-05A1
Dates: 04/2024 to 02/2029
Total: $3,179,168
Annual Total: $719,417

Investigator:	**Peters BM** (MPI)
Title:	Fungal-bacterial dynamics driving dysregulated host responses and lethal synergism
Source	National Institute of Allergy and Infectious Diseases (NIAID) 1R01AI177615-01A1
Dates:	07/2024 to 06/2029
Total:	$4,113,230
Annual Total:	$822,646

Investigator:	**Reynolds TB**
Title:	Regulation of ß-(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 Essenitality 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 necroptptic 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: Trivalent Live Attenuated Vaccines for Bacterial Acute Otitis Media
Source National Institute of Allergy and Infectious Diseases (NIAID) R21AI178085
Dates: 02/2024 to 12/2025
Total: $500,500
Annual Total: $273,000

Investigator: **Rosch JW**
Title: Characterization of TCS11 *Streptococcus peumoniae*
Source National Institute of Allergy and Infectious Diseases (NIAID) R21AI178084
Dates: 02/2024 to 12/2025

Total:	$500,500
Annual Total:	$273,000

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:	**Shen Q**
Title:	The molecular basis for carbon dioxide sensing and response in dimorphic fungi.
Source	National Science Foundation (BRC-BIO)
Dates:	06/2024 to 05/2027
Total:	$502,946
Annual Total:	$167,649

Foundation and Industry Funding

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

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Rutherford JT, Avad K, Dureja C, Norseeda K, Gc B, Wu C, Sun D, **Hevener KE**, Hurdle JG. Evaluation of *Fusobacterium nucleatum* Enoyl-ACP Reductase (FabK) as a Narrow-

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