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

ANNUAL REPORT
2024-2025

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, Vanderbilt University 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 42 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 $17 million in federal grants and contracts.

Education of students, post-doctoral trainees and visiting investigators is a major priority of the Center. In 2024-2025, 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 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.

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ABOUT THE CENTER

2024-2025

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

Brian M. Peters, PhD

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

P. David Rogers, PharmD, PhD, FCCP

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

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

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. (***Scientific Advisor***)
- 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

Sudeshna Roy, PhD
- Associate Professor, Department of Pharmaceutical Sciences

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

Qian Shen, PhD
- Associate 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.)

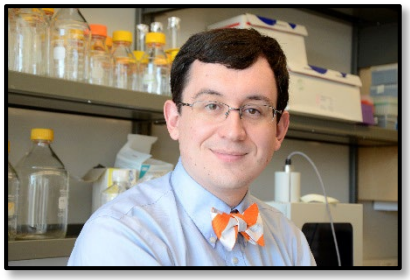
John H. Rodman, Pharm.D.
- Former Vice Chair and Member, Pharmaceutical Sciences Department, St. Jude Children's Research Hospital
- Former Professor, Department of Clinical Pharmacy
  (Dr. Rodman passed away April 29, 2006.)

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.

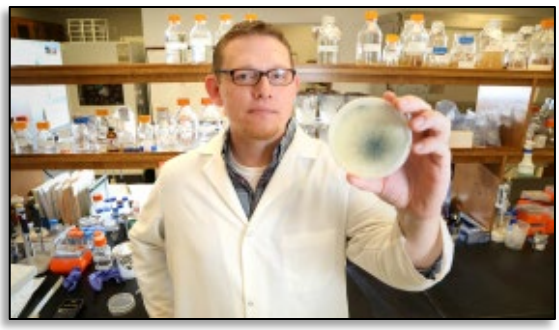


Current lab members:

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:

Adela Martin-Vicente, PhD – Senior Research Scientist
Asmita Nandi, MS – Lab Manger
Uxue Perez Cuesta, PhD – Postdoctoral Fellow
Devi Bale, MS – 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

Each year in the United States, approximately 3 million individuals contract infections caused by drug-resistant bacteria, resulting in over 35,000 direct fatalities. By 2050, antimicrobial resistance is projected to have a devastating global impact with nearly 2 million deaths annually resulting from drug-resistant infections. The widespread use of broad-spectrum antibacterial agents has significantly contributed to the concerning increase in drug-resistant bacterial strains. Additionally, ongoing research continues to elucidate the critical role of the human microbiome in health and disease, as well as the negative effects associated with its disruption due to broad-spectrum antibacterials. Consequently, there is an urgent need to validate and characterize innovative antibacterial targets, particularly those that may enable narrow-spectrum effects against pathogenic and invasive organisms while preserving the integrity of human microbiota, and to develop therapeutics aimed at these validated targets.

The Hevener laboratory is actively investigating one such target: enoyl-acyl carrier protein (ACP) reductase enzyme (FabK)—present in Clostridioides difficile, Porphyromonas gingivalis, and Fusobacterium nucleatum. FabK functions as an essential enzyme in the FAS-II bacterial fatty acid synthesis pathway in certain pathogenic organisms, including these organisms, which are associated with gastrointestinal and oral infections. Notably, FabK represents a unique isozyme at this essential step, differentiated from the FabI isozyme found in many non-pathogenic digestive tract microorganisms, thereby highlighting its potential as a target for narrow-spectrum antibacterial development. The Hevener laboratory utilizes a comprehensive array of microbiological, biochemical, and structural biology methodologies to validate and characterize these targets, while concurrently employing structure-based design strategies to identify novel, potent inhibitors. These efforts aim to facilitate the development of chemical probes and potential leads for future narrow-spectrum antimicrobial drug discovery.

Current lab members:
Postdoctoral Fellows – Dr. Manjula Ramu, Dr. Osama Alaidi
Graduate Students –Kristiana Avad (PharmD/PhD candidate, CPET Fellow)
Pharmacy Students –David Roberts (PharmD/PhD student)

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 <u>*unknown*</u>. 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

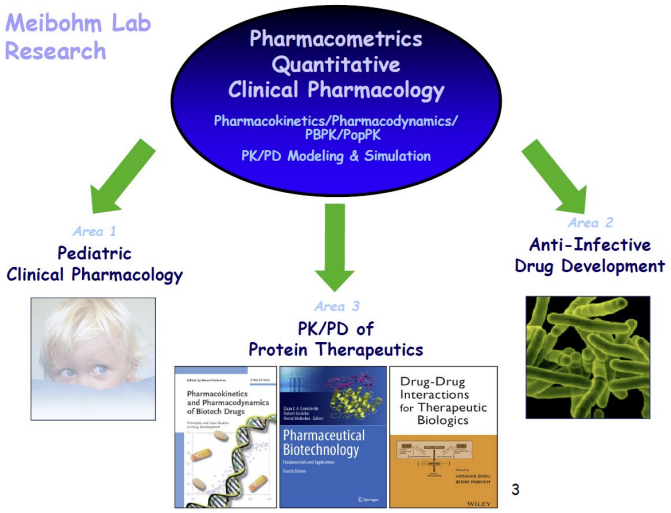
response to *C. neoformans* by first depleting neutrophils. It was previously reported that neutrophil depletion leads to increased mouse survival. To our surprise, the neutrophil-depleted mice succumbed to the infection faster than the controls. Mortality was not due to changes in fungal burden, suggesting 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

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.

Current lab members:

Ashish Srivastava, PhD (postdoctoral fellow)
Amarinder Singh, PhD (postdoctoral fellow)
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, PharmD (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.

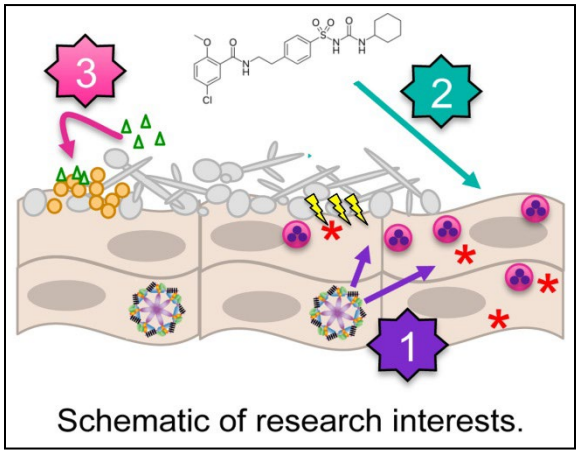
Current Lab Members:
Christian DeJarnette, PhD – Research Associate
Ravinder Kumar, PhD – Research Associate

Brian M. Peters, Ph.D.
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, metabolism, 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 also seek to identify novel therapeutic strategies to more quickly arrest symptomatic disease, including 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. Passive and active vaccination strategies against candidalysin are also being pursued.

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 and microbial metabolic pathways that are substantially altered during co-infection, and devising strategies to treat downstream effects of α-toxin activity.

Current Lab Members and Mentees:

Saikat Paul, PhD – Postdoctoral Fellow
Amirhossein Davari, MS – PhD Candidate, Pharmaceutical Sciences Program
Nasim Ahamdi – Graduate Student, Pharmaceutical Sciences Program
Md Robin Khan – Graduate Student, Pharmaceutical Sciences Program
Jennifer Carnahan – Technician
Anthony Wells – Technician
Freddy Dett – Visiting PhD Candidate, Sao Paolo State University
Abigail Cassius – Undergraduate, Summer Research Scholar from Univ. of Arizona

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 ways to address this by improving the efficacy of the echinocandin class, which is first-line therapy, and targets the cell wall of *Candida* species. The echinocandins block cell wall synthesis by inhibiting the Fks1 protein, which manufactures the essential cell wall polysaccharide ß-1,3-glucan (**Figure 1**). Unfortunately, the drug only has a 60% cure rate, but it in animal models it works better when the immune system is engaged. Studies have shown that the drug sometimes does not reach high enough levels in infected sites in some tissues in animal models to kill the fungus. However, we have found that even at very low concentrations, the drug can cause exposure of ß-1,3-glucan to the immune system, which may be why it is more effective in animals when the immune function is stronger. We are exploring how the drug may be acting through the immune function. There are at least 3 main immune receptors for ß-1,3-glucan, but this cell wall polymer is typically covered (masked) beneath a layer of glycosylated cell wall proteins (**Figure 1A**). Treatment with echinocandins like caspofungin cause exposure of the ß-1,3-glucan to the immune receptors by disrupting the outer mannosylated protein layer (**Figure 1B**). The mechanism by which the exposure occurs is not well understood, but we have discovered that there are at least 3 fungal stress signaling pathways that when activated drive unmasking in response to caspofungin. Moreover,

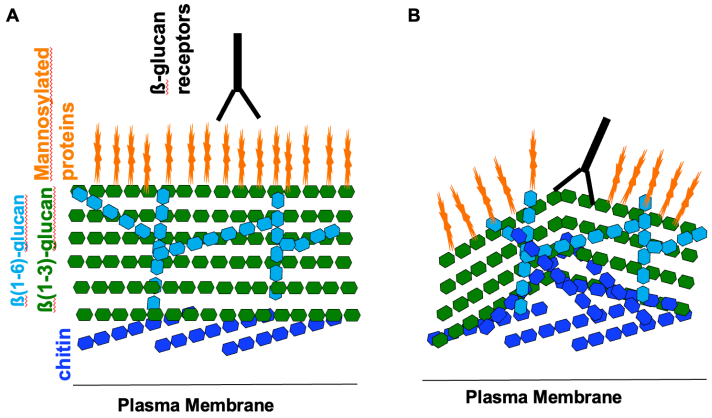


Figure 1. A. Cell wall mannosylated proteins of *C. albicans* protects ß-glucan from binding by immune ß-glucan receptors. **B.** Treatment with echinocandins increases stress responses, and this causes exposure of ß-glucan to the immune receptors.

hyperactivation of at least of these signaling pathways causes greater exposure of the fungus to immune cells and a reduction in virulence during infection. We are now identifying on cell wall effector proteins downstream of these signaling pathways that are involved in this process of "unmasking". We are also identifying host immune pathways that are responsible for responding to the exposed ß1,3-glucan in order to improve overall responses. Altogether, our research is aimed at making the echinocandin class more effective and raise the cure rate of the drug.

Current Lab Members:

Graduate students – Ainsley King, Mikayla Mangrum, Nazanin Mohammed, Millen Tesfamarian, Kaley Taylor, Katya Faber-Quimby

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.

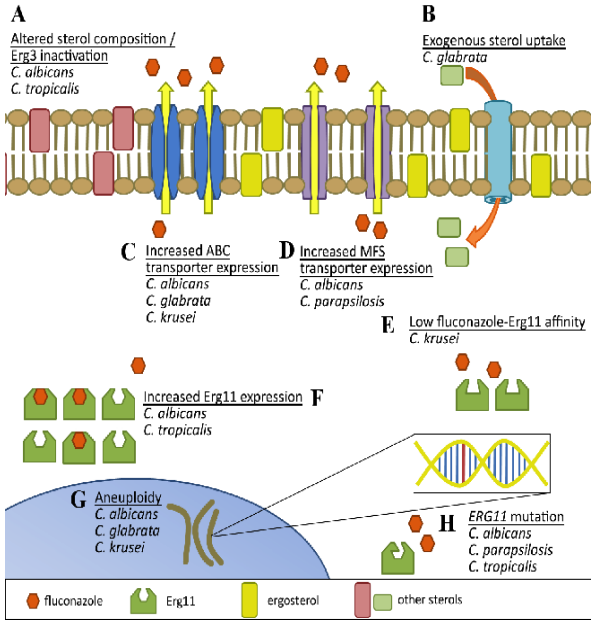


Figure 1. Comparison of documented fluconazole resistance mechanisms in *Candida* species. A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. **B)** Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production 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 interactions 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:
Jemma Clary, Graduate Student
Christine Dunn, Graduate student
Haley Echlin, PhD, Staff scientist
Amy Iverson, Lab manager
Cydney Johnson, PhD, Postdoctoral Fellow
Ilmur Jonsdottir, PhD, Postdoctoral Fellow
Yuri Lagune Terai, Research technician
Ashton McKinnon, Graduate student

Abigail McKnight, Research technician
Brenden Morrow, Graduate student
Nadia Olivero, Postdoctoral Fellow
Trevor Penix, Graduate student
Shyra Wilde, PhD, Postdoctoral Fellow

Sudeshna Roy, PhD
Associate Professor of Pharmaceutical Sciences
University of Tennessee Health Science Center, Memphis

At the Roy Laboratory, we see ourselves as *molecular architects*—designing and refining the medicines of tomorrow by studying drugs at the molecular level. We explore their chemical and biological properties, then apply these insights to develop therapies for some of the world's most pressing diseases.

Fighting Tuberculosis and Transforming Patient Outcomes

Since its inception, our lab has focused on one of humanity's oldest and deadliest foes—tuberculosis (TB). In 2023 alone, TB affected over 10.8 million people, with the greatest toll in developing nations. Our mission is to outsmart the bacterium *Mycobacterium tuberculosis* (*Mtb*) by designing selective growth inhibitors with a unique mode of action—drugs that can evade resistance mechanisms and remain effective over time.

This work is a collaborative effort with Dr. Christina Stallings at Washington University in St. Louis. Beyond drug design, we explore innovative strategies to disarm bacterial defenses, including unconventional targeting of bacterial proteins and the use of artificial intelligence to accelerate discovery.

Exploring Fluorination Technologies in Drug Discovery

The introduction of fluorine into organic molecules and pharmaceuticals offers several advantages because of its unique properties. Despite the advancements in the area that led to the surge of fluoro-pharmaceuticals, some aspects remain understudied.

Our lab is advancing the **functionalization of fluorinated alkenes** and investigating their chemical reactivity to enable regioselective synthesis of **fluorinated heterocycles**—molecular scaffolds with vast potential for next-generation medicines.

Amino Acid-Based Therapeutics to Treat Cryptococcosis

In partnership with Dr. Camaron Hole from the College of Pharmacy, we are tackling **cryptococcosis,** a life-threatening meningitis caused by the fungal pathogen *Cryptococcus neoformans*. Our work focuses on development of **amino acid–based therapeutics** with fungicidal activity—aiming to deliver urgently needed treatment options for this neglected disease.

Inspiring the Next Generation of Scientists

Science advances not only in the lab but also through mentorship and education. I am deeply committed to raising awareness about **drug resistance** in infectious diseases and inspiring future innovators. Through summer research programs in antibacterials and antifungals, along with networking and professional development opportunities, we empower high school and undergraduate students to envision careers in science.

By fostering curiosity, accessibility, and resilience, we aim to build a diverse and skilled generation of scientists ready to take on the challenges of global health.

Current lab members:

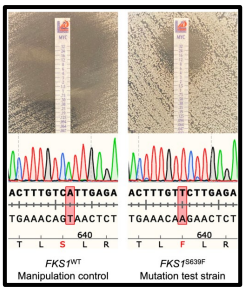
Sudeshna Roy, PhD – Principal Investigator
Mohammed Khalifa, PhD – Postdoctoral Research Scholar
Tzu-Yu Huang, MS – PhD student, Pharmaceutical Sciences Program
Destinee Manning, BS – PhD student at University of Mississippi, UTHSC Visiting Scholar
Ahmed Elsawi, MS - PhD student, Pharmaceutical Sciences Program
DaJai Ashford, BS - PhD student, Pharmaceutical Sciences Program
Mohamed Hefina, MS - PhD student, Pharmaceutical Sciences Program
Ghada Abada, MS - PhD student, Pharmaceutical Sciences Program
Alixandria Kirkendol, BS - PharmD/PhD 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

Qian Shen, Ph.D.
Associate 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

2024-2025

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, will be offered for the coming 2025-2026 year as these programs have supported new faculty in submitting for federal funding and have increased the research infrastructure in the UTHSC CoP. Early Stage Investigator, Camaron Hole, PhD, was the sole recipient of the CPET Seed Grant for the past three annual cycles as a mechanism to ensure successful startup of his laboratory. As Dr. Hole has active research projects and collaborations and is now on the cusp of his first NIH award, the CPET Seed Grant Program will now shift focus. For the coming 2025-2026 cycle, this Program is aiming to fund collaborative work between basic science laboratories at UTHSC, UTK, UofM and Rhodes and clinical research at Le Bonheur, St. Jude Childrens, and Vanderbilt. This approach seeks 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.

We will continue to train elite graduate students in the biomedical and pharmaceutical sciences with the support of the CPET Scholars Program. Building upon the success of the 2024-2025 Scholars program that resulted in one Scholar receiving an F31 award, the Center will seek to support new training opportunities in grant writing and scientific communication for selected individuals. The Program 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 experienced a drop in the number of Scholars supported for the 2024-2025 cycle to six but, with appropriate accomplishments considered, will increase this back to seven scholars for the coming year. For 2024-2025, 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 2026, 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 four speakes for the 2025-2026 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)

	FY 2024-2025 Proposed	FY 2024-2025 Actual	FY 2025-2026 Proposed
Salaries			
Faculty	$20,000	$19,160	$20,000
Other Professional		$40,927	
Clerical/ Supporting	$10,000	$11,157	$12,000
Assistantships	$130,000	$87,214	$130,000
Total Salaries (exclude Longevity)	**$160,000**	**$158,459**	**$162,000**
Longevity (Excluded from Salaries)			
Fringe Benefits	$8,000	$42,187	$20,016
Total Personnel	**$168,000**	**$200,646**	**$182,016**
Non-Personnel			
Travel	$12,000	$9,523	$12,000
Software	$500	$150	$500
Books & Journals			
Other Supplies		$20,172	$20,000
Equipment	$48,919		$70,000
Maintenance			
Scholarships	$14,000	$2,371	$10,000
Consultants			
Other (Specify):			
Printing, Duplicating, Binding			
Postage, Freight, & Telephone		$819	$1,000
Professional Serv & Memberships	$24,000	$14,400	$16,000
Computer Services			
Insurance		$4,578	$5,000
Rentals	$500	$450	$500
Grants & Subsidies			
Contractual & Special Services	$5,000	$6,799	$7,000
Other Expenditures	$5,000	$1,914	$2,000
Entertainment, Food & Housing	$16,000		
Facilities & Admin			
Direct Cost Sharing			
Total Non-Personnel	$125,919	**$61,176**	**$144,000**
GRAND TOTAL	$293,919	**$261,822**	**$326,016**
Revenue			
New State Appropriation	$293,919	$293,919	$293,919
Carryover State Appropriation			$32,097
Total Revenue	$293,919	**$293,919**	**$326,016**

YEAR-IN-REVIEW 2024-2025

Program Overview and Accomplishments

2024-2025 CPET Highlights

42 peer-reviewed scientific publications
(*including high-impact journals like Nature Microbiology, Nature Communications, Cell Chemical Biology, and Journal of Infectious Diseases*)

Over $17 million in Total Cost funding for FY25
(*including federal awards from NIH and NSF*)

CPET Scholar, Harrison Thorn, awarded an F31 Predoctoral Individual National Research Service Award from the NIH totalling $80,792
(*first in history to be housed in the UTHSC College of Pharmacy*).

Center Director, Jarrod Fortwendel, PhD, interviewed by NBC News for national story on the rise of antifungal drug resistance

CPET Scholars receive travel awards to present their work at international confeences in Dublin, Ireland and Vienna, Austria

CPET Seminar Series hosts seven internationally recognized experts in fungal and bacterial diseases

The Center for Pediatric Experimental Therapeutics (CPET) has been continuously funded for over 35 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 2024-2025 cycle, Center faculty reported over $17 million in total funding. The Center has been multidisciplinary, interprofessional, multi-institutional, multi-college and multi-departmental from its beginning, and has had translational science at its core (from bench-top to patient and back again). It is the only state-funded Center of Excellence with improvement in children's health as its primary mission. The CPET has accomplished its mission over the years through research, education, outreach, and patient care.

Extramural funding and research publications from faculty supported by the Center are outlined in the following pages. In addition to this grant support and research productivity, the Center 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 supported five Scholar, one of which successfully competed for an NIH F31 predoctoral fellowship (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 2024-2025 invovled speakers focused on genetic determinants of invasive fungal and bacterial 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 instrumental in supporting the annual Tennessee Fungal Pathogens Group Conference and Retreat that took place in June of 2025.

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. 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 - In the News

Center Director, Dr. Jarrod Fortwendel, was interviewed by NBC News Health correspondent, Kaitlin Sullivan, regarding the rise in antifungal drug resistance noted among pathogenic *Aspergillus* species. The news piece was published on July 9, 2025, and can be found at the following website. The full excerpt is also provided below.

Fungal Infections as Getting Hader to Treat
https://www.nbcnews.com/health/health-news/fungal-infections-are-getting-harder-treat-rcna217831.

July 9, 2025, 5:30 PM CDT

By Kaitlin Sullivan

Fungal infections are getting harder to treat as they grow more resistant to available drugs, according to research published Wednesday in The Lancet Microbe.

The study focused on infections caused by Aspergillus fumigatus, a fungus that is ubiquitous in soil and decaying matter around the world. Aspergillus spores are inhaled all the time, usually without causing any problems. But in people who are immunocompromised or who have underlying lung conditions, Aspergillus can be dangerous.

The study focused on infections caused by Aspergillus fumigatus, a fungus that is ubiquitous in soil and decaying matter around the world. Aspergillus spores are inhaled all the time, usually without causing any problems. But in people who are immunocompromised or who have underlying lung conditions, Aspergillus can be dangerous.

The fungus is one of the World Health Organization's top concerns on its list of priority fungi, which notes that death rates for people with drug-resistant Aspergillus infections range from 47%-88%.

The new study found that the fungus' drug resistance is increasing. On top of that, patients are typically infected with multiple strains of the fungus, sometimes with different resistance genes.

"This presents treatment issues," said the study's co-author, Jochem Buil, a microbiologist at Radboud University Medical Centre in the Netherlands.

Buil and his team analyzed more than 12,600 samples of Aspergillus fumigatus taken from the lungs of patients in Dutch hospitals over the last 30 years. Of them, about 2,000 harbored mutations associated with resistance to azoles, the class of antifungals used to treat the infections. Most of them had one of two well-known mutations, but 17% had variations of the mutations.

Nearly 60 people had invasive infections – meaning the fungi spread from the lungs to other parts of the body – 13 of which were azole-resistant. In those people, nearly 86% were infected with multiple strains of the fungi, making treatment even more complicated.

"It is an increasingly complicated story and physicians may have trouble identifying whether or not they are dealing with a drug-resistant fungal infection," said Dr. Arturo Casadevall, chair of

molecular microbiology and immunology at the Johns Hopkins Bloomberg School of Public Health, who wasn't involved with the research.

Before treating an Aspergillus fungal infection, doctors look for resistance genes that can give them clues about which drugs will work best. If someone is infected with multiple strains of the same type of fungus, this becomes much less clear-cut. Oftentimes, different strains will respond to different drugs.

"Azoles are the first line of treatment for azole-susceptible strains, but they do not work when a strain is resistant. For those, we need to use different drugs that don't work as well and have worse side effects," Buil said, adding that some people will require treatment with multiple antifungal drugs at the same time.

The findings illustrate a larger trend of growing pressure on the few drugs available to treat fungal infections – there are only three major classes of antifungal drugs, including azoles, that treat invasive infections, compared with several dozen classes of antibiotics.

Resistance to such drugs is growing, and new ones are uniquely difficult to develop.

Humans and fungi share about half of their DNA, meaning we're much more closely related to fungi than we are to bacteria and viruses. Many of the proteins that are essential for fungi to survive are also essential for human cells, leaving fewer safe targets for antifungal drugs to attack.

"The big problem for all of these fungal species is that we don't have a lot of antifungals," said Jarrod Fortwendel, a professor of clinical pharmacy at the University of Tennessee Health Science Center, who was not involved with the research. "Typically the genetic mutations that cause resistance don't cause resistance to one of the drugs, it's all of them, so you lose the entire class of drugs."

fungicides. The fungicides typically have the same molecular targets as antifungal drugs. Farmers spray them on crops, including wheat and barley in the U.S., to prevent or treat fungal disease. (The first instance of azole resistance was documented in the Netherlands, where antifungals are widely used on tulips.) Aspergillus fungi aren't the target, but exposure to the fungicides gives them a head start developing genes that are resistant to the targets, sometimes before an antifungal drug with the same target even hits the market.

This was the source of the vast majority of the drug resistance analyzed in the study.

Fortwendel noted that fungal resistance is increasingly found around the world. "Basically everywhere we look for drug-resistant isotopes, we find them," he said. "We are seeing this azole drug-resistance happening throughout the U.S. Those rates will likely climb."

Any individual person's risk of having an azole-resistant Aspergillus fumigatus is low, Casadevall said. Infections typically affect people who are immunocompromised and amount to around a few thousand cases per year in the U.S., Casadevall said. While relatively uncommon, the bigger risk is the broader trend of drug-resistant fungal infections.

"The organisms that cause disease are getting more resistant to drugs," he said. "Even though it's not like Covid, we don't wake up to a fungal pandemic, this is a problem that is worse today than it was five, 10 or 20 years ago."

Kaitlin Sullivan

Kaitlin Sullivan is a contributor for NBCNews.com who has worked with NBC News Investigations. She reports on health, science and the environment and is a graduate of the Craig Newmark Graduate School of Journalism at City University of New York.

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 and 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 conference and retreat 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 2024-2025 conference and retreat was attended by over 40 individuals and was again held at Evins Mill Retreat Center, where trainees provided updates on research progress. The keynote lecture was provided by Dr. Zachary Lewis, PhD, Professor from the University of Georgia College of Arts and Science in the Department of Microbiology. A fungal geneticist by training, Dr. Lewis delivered an insightful lecture on epigentic control of antifungal drug responses in addition to highlighting his recent work aimed at improving the efficacy of clinically approved antifungal drugs through the generation of "smart bombs".

CPET Scholars Program

Harrison Thorn is a 5th-year graduate student in the Fortwendel lab.

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 has recently focused on SidB, the final kinase in the SIN pathway, and its coactivator MobA. Harrison has found that mechanisms of SidB regulation are conserved in *A.* fumigatus: SidB requires MobA binding and phosphorylation at two conserved binding sites for full function. Harrison has adapted the TurboID system to identify protein-protein interactions in *A. fumigatus*. To utilize this system, Harrison has generated strains of *A. fumigatus* that encode TurboID tags attached to SidB and MobA. The TurboID tag biotinylates nearby interactors of SidB and MobA while they perform their normal functions in the cell. Biotinylated proteins are then extracted and sequenced to identify which proteins interact with the SidB/MobA complex in septation. Harrison is currently performing downstream work to characterize potential interaction partners identified using this method. Harrison used preliminary data from the TurboID project to submit an application for a Ruth R. Ruth L. Kirschstein National Research Service Award (NRSA) Individual Fellowship from the NIH, which scored an impact factor of 17 (6th percentile) and was funded in April 2025.

Awards:

- NIH/NIAID: F31AI191701-01 – ($80,792)
- UTHSC College of Graduate Health Sciences: Graduate Student of the Year in Pharmaceutical Sciences
- College of Graduate Health Sciences Travel Award for ECFG 2025 ($500)
- CPET Travel Award for ECFG 2025

Publications:

- Martin-Vicente A, Nywening A, Xie J, **Thorn HI**, Guruceaga X, Fortwendel JR. Genetic analysis of common triazole resistance mechanisms in a collection of Aspergillus lentulus clinical isolates from the United States. AAC, accepted for publication (2025).
- Nywening AV, **Thorn HI**, Xie J, Martin-Vicente A, Guruceaga X, Ge W, Gibbons JG, Fortwendel JR. Loss of the Aspergillus fumigatus spindle assembly checkpoint components, SldA or SldB, generates triazole heteroresistant conidial populations. Microbiol Spectr 0:e00536-25 (2025).
- Martin-Vicente A., Souza A.C.O., Guruceaga X, **Thorn HI**, Xie J, Nywening AV, Ge W, Fortwendel JR. A conserved fungal morphogenetic kinase regulates

pathogenic growth in response to carbon source diversity. Nat Commun 15, 8945 (2024).

Presentations:

- **Thorn HI**, Martin-Vicente A, Perez Cuesta U, Xie J, Bale D, Nandi A, Fortwendel JR. "Identification of novel *Aspergillus fumigatus* Septation Initiation Network (SIN) interactors through near-neighbor analysis." UTHSC CGHS Graduate Research Day 2025. Memphis, TN. Poster. May 2025.
- **Thorn HI**, Martin-Vicente A, Perez Cuesta U, Xie J, Bale D, Nandi A, Fortwendel JR. "Identification of novel *Aspergillus fumigatus* Septation Initiation Network (SIN) interactors through near-neighbor analysis." Pharm Forum. Memphis, TN. Poster. May 9, 2025.
- **Thorn HI**, Martin-Vicente A, Perez Cuesta U, Xie J, Bale D, Nandi A, Fortwendel JR. "Identification of novel *Aspergillus fumigatus* Septation Initiation Network (SIN) interactors through near-neighbor analysis." UM AAPS PharmAdvance. Oxford, MS. Poster. April 2025
- **Thorn HI**, Martin-Vicente A, Perez Cuesta U, Xie J, Bale D, Nandi A, Fortwendel JR. "Identification of novel *Aspergillus fumigatus* Septation Initiation Network (SIN) interactors through near-neighbor analysis." 17th European Conference on Fungal Genetics. Dublin, Ireland. Oral. March 5, 2025.
- **Thorn HI**, Martin-Vicente A, Perez Cuesta U, Xie J, Bale D, Nandi A, Fortwendel JR. "Identification of novel *Aspergillus fumigatus* Septation Initiation Network (SIN) interactors through near-neighbor analysis." Asperfest 21. Dublin, Ireland. Poster. March 1, 2025.

Amir H Davari is a 3rd-year Ph.D. candidate in the Peters lab.

Project description:

Amir's research focuses on the structure–function relationship of candidalysin (CL), a peptide toxin from *Candida albicans* that drives epithelial damage and inflammation during vulvovaginal candidiasis (VVC). Using CRISPR/Cas9-mediated alanine scanning, he has identified non-toxic CL variants with reduced pathogenicity that are being evaluated as toxoid vaccine candidates. He is also assessing natural CL sequence variations from clinical isolates to determine their impact on pathogenicity. These studies aim to define conserved functional regions of CL and inform strategies to mitigate VVC immunopathology. This year, Amir successfully passed his qualifying exam.

Honors/Awards:

- John Autian Student Enrichment Fund Awardee. College of Graduate Health Sciences, UTHSC. Dec 2024.

- South Central Medical Mycology Meeting Travel Award. Nov 2024.

Oral presentations:
"Delineating the structure–function of candidalysin to reveal new therapeutic approaches for the management of vulvovaginal candidiasis."

- 21st South Central Medical Mycology Meeting, New Orleans, LA, Nov 22, 2024.
- 8th Annual Tennessee Fungal Pathogens Group (TFPG) Research Conference, Evins Mill, TN, June 25, 2025.

Posters and Abstracts:

- IL-1R signaling orchestrates antifungal immunity and immunopathology during vulvovaginal candidiasis. Amir H Davari, Amanda K Vogel, Jian Miao, Brian M Peters (2025). Gordon Research Conference (GRC) and Gordon Research Seminar (GRS) on Immunology of Fungal Infections. Ventura, CA.

Disclosure:

- Disclosure submitted to the University of Tennessee Research Foundation (UTRF), Invention Report No. 0578302-24-0002, for the project "Delineating the structure–function of candidalysin to reveal new therapeutic approaches for the management of vulvovaginal candidiasis." Contributors: Brian Peters and Amir Davari.

Ainsley King is a 6th year Ph.D. student in the Reynolds lab.

Project Description:
Ainsley's current research focuses on understanding the role of the putative cell wall protein Fgr41 in modulating cell wall β(1,3)-glucan exposure and immune recognition in *C. albicans.* Exposed β(1,3)-glucan in the cell wall triggers a robust pro-inflammatory response, but an outer layer of mannosylated proteins covers, or masks, this β-glucan layer, hindering recognition by innate immune cells. Previous work in the Reynolds lab demonstrated that loss of Fgr41 causes β(1,3)-glucan exposure and an immune system-dependent attenuation in virulence. This year, Ainsley has found that the *fgr41*Δ/Δ mutant induces murine macrophages to release much higher levels of the proinflammatory cytokine TNF-α than wild type. Antibody neutralization of dectin-1, the primary macrophage receptor responsible for β(1,3)-glucan recognition, had no significant impact on the levels of TNF-α stimulated by the *fgr41*Δ/Δ mutant. However, *fgr41*Δ/Δ-induced stimulation was significantly reduced by pretreatment with laminarin, an inhibitory soluble β-glucan. This data suggests that another β(1,3)-glucan receptor may be responsible for macrophage recognition of the *fgr41*Δ/Δ mutant. Ongoing work is exploring macrophage signaling pathways triggered by the *fgr41*ΔΔ mutant to discover through what receptor(s) it drives TNF-α signaling.

Publications:

- 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.

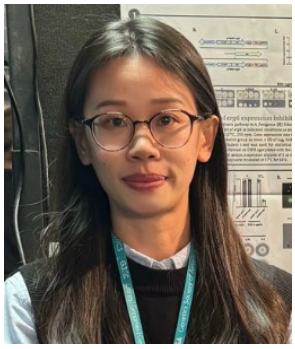
Presentations:

- **King, AE.** "Investigating the Impact of Putative Cell Wall Protein Fgr41 on β(1,3)-glucan Exposure and Immune Recognition in *C. albicans*." Oral presentation. 21st Annual South Central Medical Mycology Meeting. New Orleans, LA. November 22nd, 2024.
- **King, AE.** "Loss of Putative Cell Wall Protein Fgr41 in *C. albicans* Increases Proinflammatory Immune Response and Attenuates Virulence in a Dectin-1 Independent but β(1,3)-glucan dependent Manner." Oral presentation. 8th Annual Tennessee Fungal Pathogens Group Research Conference and Retreat. Evins Mill, Smithville, TN. June 25th, 2025.
- **King, AE.** "Loss of Putative Cell Wall Protein Fgr41 in *Candida albicans* Increases Proinflammatory Immune Response and Attenuates Virulence in a Dectin-1 Independent but β(1,3)-glucan-dependent Manner." Invitation for oral presentation. Candida and Candidiasis 2025. Berlin, Germany. October 8th, 2025.

Jinhong Xie is a fifth-year graduate student in the Fortwendel lab.

Project Description:

Her research focuses on the mechanism by which the Hmg1 mutations alter voriconazole's antifungal action, leading to resistance in *Aspergillus fumigatus*. The growing incidence of triazole resistance poses a significant threat to clinical treatment. Recent studies have frequently reported mutations in the HMG-CoA reductase-encoding gene *hmg1*, particularly in the sterol-sensing domain (SSD), as potential determinants of triazole resistance in *A. fumigatus*. This year, Jinhong has been studying *hmg1*'s accelerated protein degradation in *A. fumigatus*, a process mediated by the ubiquitin-proteasome system. Her findings reveal that *hmg1* SSD mutations impede accelerated protein degradation, thereby contributing to voriconazole resistance. Additionally, Jinhong successfully passed her PhD candidacy examination and further investigates her research on the role of *hmg1* mutations in triazole resistance.



Awards:

Outstanding Graduate Student in the UTHSC Pharmaceutical Sciences Program. 2024

Publications:

1. Adela Martin-Vicente, Ana Camila Oliveira Souza, Xabier Guruceaga, Harrison I Thorn, **Jinhong Xie**, Ashley V Nywening, Wenbo Ge, Jarrod R Fortwendel. A conserved fungal morphogenetic kinase regulates pathogenic growth in response to carbon source diversity. Nature Communications **15**, 8945 (2024).
2. Ashley Nywening, Harrison Thorn, **Jinhong Xie**, Adela Martin-Vicente, Xabier Guruceaga, Wenbo Ge, John Gibbons, Jarrod Fortwendel. Loss of the *Aspergillus fumigatus* spindle assembly checkpoint components, SldA or SldB, generates triazole heteroresistant conidial populations. Microbiol Spectr. (2025).

3. Adela Martin-Vicente, Ashley Nywening, **Jinhong Xie**, Harrison Thorn, Xabier Guruceaga-Sierra, and Jarrod Fortwendel. Genetic analysis of common triazole resistance mechanisms in a collection of Aspergillus lentulus clinical isolates from the United States. Antimicrobial Agents and Chemotherapy. 2025

Presentations:

1. **Oral Presentation.** Annual South Central Medical Mycology Meeting (New Orleans, LA, 2024)
2. **Oral Presentation.** Annual Tennessee Fungal Pathogens Group Research Conference. (Smithville, TN, 2025)
3. **Poster Presentation.** UTHSC Graduate Research Day. (Memphis, TN, 2025)
4. **Poster Presentation.** Pharm Forum Conference. (Memphis, TN, 2025)

Kristiana Avad is a 4th 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 periodontal disease. Recent studies have shown that broad spectrum antibacterials may be efficacious in the treatment of *Fusobacterium*-associated diseases, 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:

1. NIH Diversity Supplement award. National institute of Allergy and Infectious Disease. Jan 2025
2. NIH Loan Repayment Program (LRP) award. National institute of Allergy and Infectious Disease. July 2025
3. ESCMID Study Group for Clostridioides difficile (ESGCD) Travel grant

Publications:

1. Kristiana Avad Osama Alaidi, Destiny Okpomo, Darcy Doran, Madeline Matheson, Dianqing Sun, Julian Hurdle, Kirk E Hevener. Structural and biochemical characterization of *F. nucleatum* enoyl-ACP reductase (FabK) reveals the basis for bacterial species-specific inhibition. (*preparing for submission*)

2. Alaidi, O., **Avad, K**., Hevener, K. 9PL0. The structure of the Fusobacterium nucleatum Enoyl-Acyl Carrier Protein Reductase (FabK) bound to an inhibitor. PDB. July 2025.

Presentations:

1. **Avad KA,** Alaidi,O., Daran D., Hurdle JG, Sun D, Hevener KE. Structural determinants of inhibitor selectivity towards Enoyl ACP Reductase, FabK. European Society of Clinical Microbiology and Infectious Diseases. Poster. Vienna, Austria. April 2025
2. **Avad KA,** Alaidi,O., Daran D., Hurdle JG, Sun D, Hevener KE. Structural determinants of inhibitor selectivity towards Enoyl ACP Reductase, FabK. Graduate Research Day. UTHSC. April 2025.

External Course Attended:

1. CCP4/APS School in Macromolecular Crystallography. Argonne National Laboratory. Lemont, IL. October 2024.

Ivy Antwi is a 5th-year PhD candidate in the Cory lab

Project Description

Ivy's research focuses on understanding how drugs influence macrophage responses to infectious pathogens, aiming to identify new host-directed strategies to improve treatment for fungal and viral diseases. Her work has concentrated on azithromycin (AZM), a macrolide antibiotic known for its immunomodulatory effects, and its role in the macrophage response to *Aspergillus fumigatus* (AF). Using an in vitro model with the murine J774 macrophage cell line, Ivy demonstrated that AZM treatment shifted macrophages toward an anti-inflammatory-like phenotype while enhancing fungal killing compared to classical M1 and alternative M2 subsets. This phenotype was characterized by reduced IL-6 production, increased arginase activity, and no significant change in ROS generation. Importantly, the increase in AF clearance was linked to AZM's immunomodulatory effects on macrophages rather than direct antifungal activity, suggesting that AZM enhances host–pathogen interactions by recalibrating immune function. Building on this theme of drug-mediated modulation of macrophages, Ivy's work is also aimed at exploring how antiretrovirals influence macrophage reservoirs of HIV-1 infection. Macrophages are heterogeneous and exist across a spectrum of activation states, from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, and these differences influence their role as viral reservoirs. Preliminary findings revealed that drug efflux transporters such as MRP1, BCRP, and P-glycoprotein are differentially expressed in M1 and M2 macrophages, altering

intracellular antiretroviral concentrations and impacting HIV-1 replication. Blocking these transporters changes drug disposition in a phenotype-specific manner, ultimately influencing viral persistence in macrophage reservoirs. Together, this work underscores the critical role of macrophages in shaping infection outcomes and highlights how drugs like azithromycin and antiretrovirals can reprogram macrophage function. By defining phenotype-specific drug responses in both fungal and viral contexts, Ivy's research aims to inform host-directed therapeutic strategies that target macrophages not only as effectors of immunity but also as key reservoirs of infection.

Awards:

- Center for Pediatric Experimental Therapeutics - Travel award ($2000)

Publications:

- **Ivy Antwi**, Jarrod R. Fortwendel, Theodore J. Cory. "Azithromycin Improves Macrophage Response to Aspergillus fumigatus" *Immunology Letters*. June 2025 **(Submitted)**
- **Ivy Antwi**, Theodore J. Cory. "Beyond Antibacterial: Azithromycin as a Host-Directed Therapy in Non-Bacterial Infections" *Journal of Biomedical Science.* August 2025 **(Submitted)**

Presentations:

- **Ivy Antwi**, Jarrod R. Fortwendel, Theodore J. Cory. "Azithromycin Improves Macrophage Response to Aspergillus fumigatus" UTHSC Graduate Research Day 2025. Memphis, TN. **Poster**. April 25, 2025
- **Ivy Antwi**, Jarrod R. Fortwendel, Theodore J. Cory. "Azithromycin Improves Macrophage Response to Aspergillus fumigatus" Autumn Immunology Conference, Chicago, Illinois. **Poster**. November 24, 2024
- **Ivy Antwi**, Jarrod R. Fortwendel, Theodore J. Cory. "Azithromycin Improves Macrophage Response to Aspergillus fumigatus" Autumn Immunology Conference, Chicago, Illinois. **Oral**. November 24, 2024

CPET Scholar Receives NIH F31 Fellowship

Federal Grant Fuels Graduate Student Research to Fight Deadly Fungal Infection

Written by Lee Ferguson | April 30, 2025

Harrison Thorn, a graduate student in the **Pharmaceutical Sciences** PhD program at the University of Tennessee Health Science Center, has been awarded an $80,792 grant from the National Institute of Allergy and Infectious Diseases for his work to develop new treatment strategies for a dangerous and often deadly fungal infection.

Harrison Thorn

Conducted under the mentorship of Jarrod Fortwendel, PhD, professor and director of the Center for Pediatric Experimental Therapeutics in the **Department of Clinical Pharmacy and Translational Science**, Thorn's research focuses on invasive pulmonary aspergillosis, a life-threatening lung infection caused by the fungus *Aspergillus fumigatus*, which impacts highly immunocompromised populations.

This infection can be lethal even when properly treated, with death rates reaching as high as 90%. Current antifungal treatments are often ineffective, and resistance to these drugs is growing, making the need for new therapeutic strategies urgent.

Echinocandins, a class of antifungal drugs, are commonly used to treat invasive fungal infections but have limitations against *A. fumigatus*. While they are generally safe, they fail to fully kill this fungus, especially at high doses where they may paradoxically encourage fungal growth. Thorn's research aims to make these drugs more effective by targeting the fungus's internal machinery for cell division, which involves the construction of cross-walls called septa.

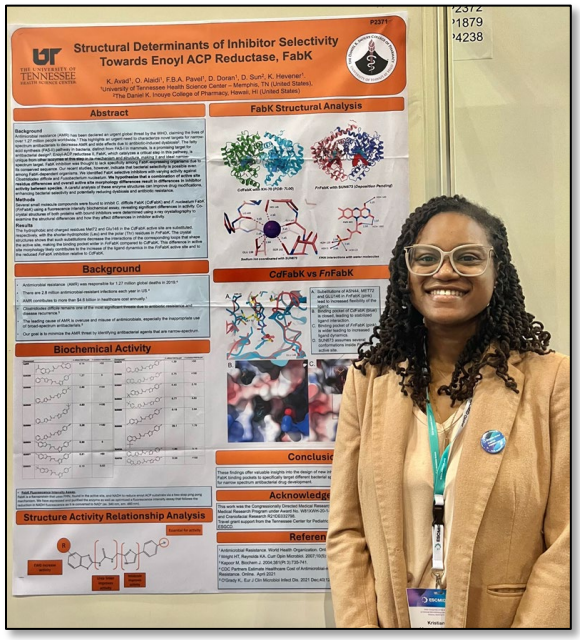
"By understanding how *A. fumigatus* builds and maintains septa during infection, we hope to find ways to make existing antifungal drugs hit harder and work better," Thorn said.

Dr. Fortwendel's lab discovered that certain fungal proteins—part of a system called the Septation Initiation Network—are essential for the formation of septa. Disabling one of these key proteins, known as SidB, or its partner MobA, not only weakened the fungus in animal experiments but also made it much more vulnerable to echinocandin treatment.

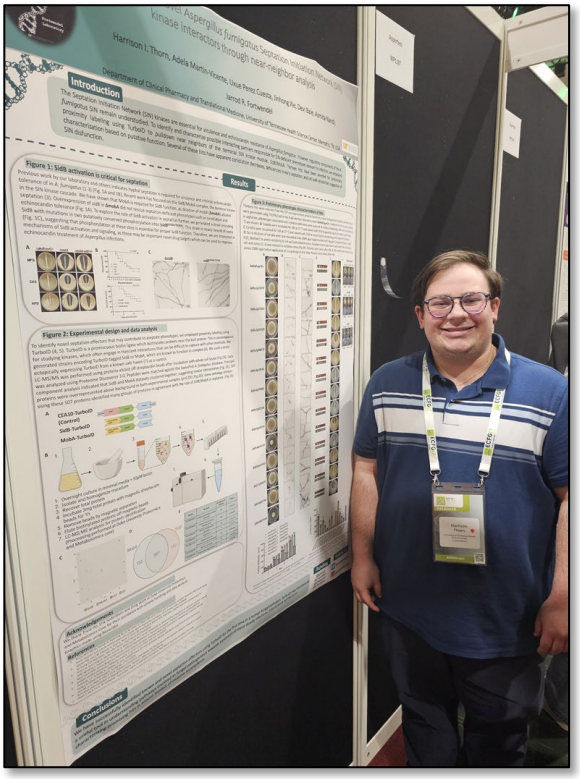
"This opens a new door for antifungal drug development," Thorn explained. "If we can block these proteins or their interactions, we might boost the effectiveness of drugs we already have."

Over the course of the project, Thorn will investigate how these proteins function and how they help the fungus resist treatment. The ultimate goal is to lay the groundwork for next-generation antifungal therapies that could save lives.

CPET Travel Award Recipients



Recipient: Kristiana Avad
Conference: ESCMID 2025
Location: Vienna, Austria
Dates: April 11- 15, 2025
Award Amount: $2500



Recipient: Harrison Thorn
Conferences: 17th European Conference on Fungal Genetics
-and-
21st International Aspergillus Meeting
Location: Dublin, Ireland
Dates: March 1-7, 2025
Award Amount: $2500

CPET Seminar Series

"Understanding the host-microbe interactions driving *Cryptococcus* and *Candida* infections"

Felipe Santiago-Tirado, PhD
Assistant Professor
Biological Sciences
University of Notre Dame

"Melioidsis: From pathogenesis to diagnostics"

Mary Burtnick PhD
Professor
Department of Microbiology and Immunology
University of Nevada, Reno

"Melioidosis subunit vaccines: Recent developments and future directions"

Paul Brett, PhD
Professor
Department of Microbiology and Immunology
Universioty of Nevada, Reno

"Mechanisms driving fungal neuro-invasion and the development of peptides as antifungal agents"

Angela Gelli, PhD

Professor
Department of Pharmacology
School of Medicine
University of California, Davis

"Is an Immunotherapy approach targeting virulence traits of mucormycosis attainable?"

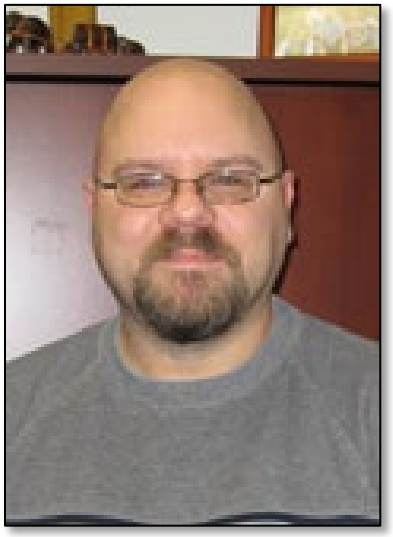
Ashraf Ibrahim, PhD

Porfessor, David Gefen School of Medicine at UCLA
Senior Investigator, The Lundquist Institute for Biomedical Innovations at Harbor-UCLA Medical Center

"Adventures with fungi: Epigenomes and antifungal smart bombs"

Zachary Lewis, PhD

Professor
Department of Microbiology
Frankilin College of Arts and Sciences
Universtiy of Georgia



“Thoughts on the cell wall of *Candida* species”

Michael Kruppa, PhD

Associate Professor
Department of Biomedical Sciences
Quillen College of Medicine
East Tennessee State University

CPET Seed Grant Program

Awardee: Dr. Camaron Hole, PhD

Project Description: Dr. Hole was awarded a CPET seed grant, renewable for four years and ended with the closeout of FY25. These renewable seed grant funds were intended as laboratory startup 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. Although Dr. Hole's primary research focus is on immunopathologies associated with *Cryptoccocus* pulmonary infections, as well as vaccine development against this deadly fugnal infection, his new collaborations within the UTHSC College of Pharmacy have broadened his research base. Data generated throught these collaborations and supported by the 2024-2025 Seed Grant Funds includes the development of novel anti-cryptoccal amino acid mimetics that have promise as future therapeutics. These studies are in collaboration with newly appointed Center member, Sudeshna Roy, PhD, and have led to the submission of a new NIH R01 grant application.

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 2024-2025 cycle, this support inlucded the purchase of a Tokai Hit live-cell stage adapter as an essential upgrade for a Nikon Eclipse Ti2 inverted fluorescence micrsopse that is housed on the 3rd floor of the College of Pharmacy. The inversted microscope was originally purchased in the 2022-2023 program cyle as a shared resource for CPET and CoP faculty. This additional upgrade equipment will now support the development of *in vitro* assays for novel target-based antifungal drug screens, host-microbe and microbe-microbe interactations that require live-cell fluorescence microscopy.

Nikon Inverted Microscope, purchased in 2023

Live cell stage adapter, purchased in 2025

Extramural Funding

Extramural Funding

Federal Funding (including NIH, NSF and DoD)

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 05/2026
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 02/2026
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:	03/2021 to 02/2026
Total:	$1,552,025
Annual Total:	$449,016

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:	**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:	$627,834

Investigator:	**Meibohm B** (PI Gonzaolez-Juarrero)
Title:	Inhalational therapy with spectinamides within new regimens of TB therapy
Source	National Institute of Allergy and Infectious Diseases (NIAID) R01AI178885
Dates:	07/2024 to 06/2029
Total:	$4,087,025
Annual Total:	$817,405

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, 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:	**Palmer GE** (co-I **Meibohm B**)
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:	$611,435

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:	$441,284

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:	$18,680

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:	$686,064

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:	$518,119

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:	$329,616

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:	$1,206,879

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:	$607,872

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:	$2,049,161
Annual Total:	$411,647

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:	$220,675

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:	**Rosch JW**
Title:	Collateral consequences of enabler genotypes in antibiotic treatment failure.
Source	National Institute of Allergy and Infectious Diseases (NIAID) 7U19AI158076
Dates:	09/2022 to 06/2026
Total:	Not Reported
Annual Total:	$1,774,417

Investigator:	**Rosch JW**
Title:	[18F]fluoromannitol: a novel imaging agent to delineate osteomyelitis in sickle cell disease
Source	National Institute of Allergy and Infectious Diseases (NIAID)
Dates:	02/2025 to 01/2029
Total:	$3,578,940
Annual Total:	$894,735

Investigator:	**Roy S** (MPI)
Title:	Development of 1,2,4-Triazolyl Compounds and their derivatives as a New Treatment for Tuberculosis
Source	National Institute of Allergy and Infectious Diseases (NIAID) R01AI181316
Dates:	08/01/2024–07/31/2029
Total:	$3,935,855
Annual Total:	$787,171

Investigator:	**Roy S**
Title:	Expanding the small molecule toolbox through novel applications of fluorinated alkenes (Maximizing Investigators' Research Award)
Source	National Institute of General Medical Sciences (NIGMS) R35GM150768
Dates:	09/01/2023–06/30/2028
Total:	$1,210,846
Annual Total:	$231,000

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 05/2026
Total:	$207,000
Annual Total:	$83,000

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

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