

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



ANNUAL REPORT

2020-2021

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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<https://www.uthsc.edu/pharmacy/dcpts/cpet.php>

Center for Pediatric Experimental Therapeutics

Mission Statement

The mission of the Center for Pediatric Experimental Therapeutics (CPET) is the integration of basic, applied, and clinical sciences towards the development of new treatments for childhood diseases.

Benchmarks for success include:

(1) the number and quality of publications, (2) the quantity and quality of competitive funding to support Center activities, (3) the training opportunities for students, residents and postdoctoral fellows, and (4) the educational offerings by Center investigators to the scientific community. Specific goals:

Education

1. To improve the quality of education by coordinating existing resources and by attracting outstanding nationally and internationally recognized faculty in pediatric experimental therapeutics.
2. To disseminate information resulting from Center research to health professionals and citizens in Tennessee, the Mid South region, and Nation through publications, presentations, participation in professional organizations, and continuing education.
3. To establish the Center as an internationally recognized resource for educational and research training in the area of pediatric experimental therapeutics attracting the very best students and postdoctoral trainees to Tennessee.

Research

1. To coordinate, integrate and enhance pediatric experimental therapeutics research programs, particularly in microbial pathogenesis and in new drug development, to yield highly focused and competitive research.
2. To integrate existing basic research programs and resources, including the Molecular Resource Center (MRC); Regional Bio-containment Laboratory (RBL); other UTHSC COREs; the Departments of Clinical Pharmacy and Translational Science, Microbiology, Immunology, and Biochemistry, and Pediatrics; and St. Jude Children's Research Hospital.
3. To establish the Center as an internationally recognized resources in pediatric experimental therapeutics.

Clinical Care

1. To coordinate pediatric experimental therapeutics research across the Health Science Center, the University, and State of Tennessee into a collaborative program functioning as one program, improving treatments for serious childhood diseases.
2. To recruit talented clinicians of national importance to the Center to broaden the specialized expertise in treating pediatric diseases, particularly infectious diseases and cancer.
3. To serve as a national and international resource for defining optimal pediatric treatment strategies.

Executive Summary

The Center for Pediatric Experimental Therapeutics (CPET) is the only state supported Center of Excellence that includes in its primary mission the health care and treatment of citizens of Tennessee. The University of Tennessee, Health Science Center, has a primary mission to improve human health through education, research, outreach and patient care. The CPET is an example of this effort. The University serves to coalesce programs in affiliated clinical institutions to form a dynamic Center focused on advancing the use of medication in children. The University brings together St. Jude Children's Research Hospital and Le Bonheur Children's Medical Center as both have clinical and laboratory faculty members who are internationally recognized as leaders in their field.

Since receiving accomplished center status in September of 1989, the CPET has not relented in its quest to remain one of the nation's premier centers for the improvement of therapeutics in children. Faculty comprising the CPET have sustained a high level of research productivity during the past year, having authored over 60 peer-reviewed articles in leading medical or scientific journals.

The CPET is dedicated to better understanding of microbial pathogenesis and antiinfectives in children. During the past year, CPET investigators have made substantial progress in their research programs related to improving antiinfective therapeutics in children, through a more complete understanding of infectious diseases and microbial pathogenesis, anti-infective pharmacotherapy, and antimicrobial resistance. Productivity is evidenced by the enclosed list of publications. These papers report the results of studies that will ultimately lead to improvements in the treatment of childhood infectious diseases. These studies are built on a substantial number of laboratory-based investigations that CPET faculty members are undertaking to define the biochemical and molecular basis for specific pediatric infectious diseases and to discover novel therapeutic targets and therapeutic agents for their treatment.

In the past academic year, CPET faculty disclosed almost \$10 million in direct costs of NIH grants. This is at a time when NIH funding has never been more competitive, and many laboratories were faced with the challenge of COVID-19 pandemic-induced closures.

Education of students, post-doctoral trainees and visiting investigators continued to be a major priority in the Center. In 2019-2020, the CPET faculty continued to direct the training of sizable numbers of graduate students and professional students in the Colleges of Pharmacy and Medicine. In particular, the Center has continued to support a select group of exceptional students designated as CPET scholars. The hallmark of CPET teaching and research programs continues to be the integration of basic and translational sciences, with the goal of enhancing pharmacotherapeutic strategies for the treatment of pediatric illnesses.

2020-2021 Annual Report

Table of Contents

Part I

“About the Center”

Leadership	7
Faculty	8-9
Emeritus Faculty	10
CPET Scholars	11-12
Faculty Research Activities	13-28

Part II

“Direction of the Center”

Goals/Future Plans	30
Annual Budget Report	31

Part III

“Year in Review”

Program Overview and Accomplishments	33-34
CPET Seminar Series Invitees	35
CPET Seed Grant Program	36-38
CPET Faculty Funding	39-47
Publications	48-54

ABOUT THE CENTER

2020-2021

Leadership



Jarrod R. Fortwendel, PhD

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



Glen E. Palmer, PhD

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



Richard E. Lee, PhD

- Scientific Advisor
- Member, Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital
- Adjunct Professor, University of Tennessee Health Sciences Center



Jeremy S. Stultz, PharmD, BCPPS

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

Faculty

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

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

James B. Dale, M.D.

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

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

- Associate Professor, Department of Clinical Pharmacy and Translational Science

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

- Assistant Professor, Department of Pharmaceutical Sciences

Camaron Hole, PhD

- Assistant Professor, Department of Clinical Pharmacy and Translational Science

Santosh Kumar, Ph.D.

- Associate Professor, Department of Pharmaceutical Sciences

Richard E. Lee, Ph.D.

- Member, Chemical Biology & Therapeutics Department, St. Jude Children's Research Hospital
- Adjunct Professor, University of Tennessee Health Science Center

Bernd Meibohm, Ph.D.

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

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

- Associate Professor, Department of Clinical Pharmacy and Translational Science

Brian M. Peters, Ph.D.

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

Joseph F. Pierre, PhD

- Assistant Professor, Department of Pediatrics-Obesity

Todd B. Reynolds, Ph.D.

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

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

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

Jason W. Rosch, PhD

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

Jeffery Rybak, PharmD, PhD

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

Jeremy Stultz, PharmD (*Fellowship Coordinator*)

- Associate Professor, Department of Clinical Pharmacy and Translation Science

Emeritus Faculty

Dennis D. Black, M.D.

- Director, Children's Foundation Research Institute, Le Bonheur Children's Hospital
- Vice-President for Research, Le Bonheur Children's Hospital
- Professor, Departments of Pediatrics and Physiology
- J.D. Buckman Endowed Professorship in Pediatrics at UTHSC

Steven C. Buckingham, M.D.

- Former Associate Professor, Department of Pediatrics, Division of Pediatric Infectious Diseases, Le Bonheur Children's Hospital
(Dr. Buckingham passed away November 24, 2015.)

Russell W. Chesney, M.D.

- Former Scientific Advisor and Past Director
- Former Professor, Department of Pediatrics, Le Bonheur Children's Hospital
Division of Pediatric Nephrology
(Dr. Chesney passed away April 2, 2015.)

William E. Evans, Pharm.D

- Member, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital
- Professor, Departments of Clinical Pharmacy and Translational Science, Pediatrics, and Pharmaceutical Sciences
- Endowed Chair in Pharmacogenomics
- Former Scientific Advisor and Inaugural Director

Richard A. Helms, Pharm.D.

- Former Scientific Advisor and Past Director
- Former Professor, Department of Clinical Pharmacy and Translational Science
- Former Professor, Department of Pediatrics

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

Sheldon B. Korones, M.D.

- Emeritus Professor, Department of Pediatrics, Division of Neonatology, Le Bonheur Children's Hospital
- Past Director, Newborn Center, The Regional Medical Center at Memphis
(Dr. Korones passed away July 3, 2013.)

John H. Rodman, Pharm.D.

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

CPET Scholars

Graduate Trainees

A major priority of the CPET is to train the next generation of scientists to tackle the ever-evolving therapeutic challenges faced by children across the state of Tennessee. 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.

Laura Doorley



“Novel Mechanisms of Fluconazole Resistance in *Candida albicans* and *Candida parapsilosis*”

Advisor: P. David Rogers, Pharm.D., Ph.D.
UTHSC Integrated Biomedical Sciences

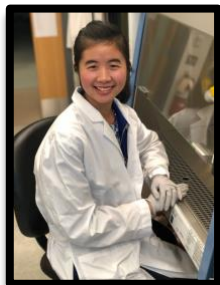
Ying Mu



“Effects of tobacco and alcohol on transporter expression and function in HIV infected macrophages”

Advisor: Ted Cory, Pharm.D., Ph.D.
UTHSC Pharmaceutical Sciences

Tina Dao



“Immune constraints of antibiotic resistance development”

Advisor: Jason Rosch, Ph.D.
UTHSC Integrated Biomedical Sciences

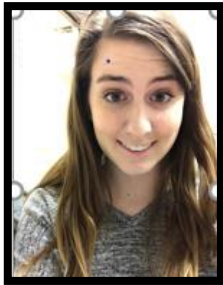
Parker Reitler



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

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

Olivia Todd



“Mechanisms of Synergistic Virulence during Polymicrobial Intra-Abdominal Infection”

Advisor: Brian M. Peters, Ph.D.
UTHSC Integrated Biomedical Sciences

Ashley Nywening



“Illuminating network biology underpinning basal intracellular drug-induced stress responses and drug resistance in *Aspergillus fumigatus*”

Advisor: Jarrod Fortwendel, Ph.D.
UTHSC Integrated Biomedical Sciences

Yue Aeric Zhao



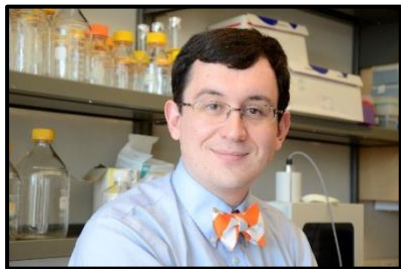
“The phosphatidylserine synthase, Cho1p, from *Candida albicans* as a novel antifungal drug target”

Advisor: Todd Reynolds, Ph.D.
UTK College of Arts and Sciences

Faculty Research Activities

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

Viral persistence is a critical barrier to the eradication of HIV-1 in infected individuals. One hypothesis is that HIV resides in cells in locations with subtherapeutic antiretroviral



concentrations, which are insufficient to fully inhibit viral replication, making elimination of the virus from these sites impossible. These sites include the brain, lymph nodes, and secondary lymphoid tissues. While CD4+ T cells are the primary target of HIV, macrophages are infected early, and remain an important infected cell population. These two host cells interact in lymph nodes and secondary lymphoid tissue. Macrophages exist in two phenotypically dissimilar

polarized subsets, the classically activated (M1) phenotype, which is pro-inflammatory and involved in the destruction of intracellular pathogens, and the alternatively activated (M2) phenotype, which is anti-inflammatory and involved in tissue repair. The role of these two subsets of macrophages in HIV is uncertain, as is the disposition of antiretrovirals in the cells. Our goal is to define the mechanisms by which intracellular antiretroviral concentrations are altered in macrophage subsets, and the effect of this on viral replication and spread, and to 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

Ying Mu, M.S. – Graduate Student (Pharmaceutical Sciences Graduate Program)

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

James B. Dale, M.D.
Gene H. Stollerman Professor of Medicine
Chief, Division of Infectious Diseases
University of Tennessee Health Science Center, Memphis

James B. Dale, MD is the Gene H. Stollerman Professor of Medicine and Chief of the Division of Infectious Diseases at the University of Tennessee Health Sciences Center in Memphis. He received his undergraduate degree from the University of Tennessee in Knoxville and his MD degree from the University of Tennessee, Memphis. He has achieved a national and international reputation for research on group A streptococcal infections. He has published over 135 original scientific articles and reviews in the area of infectious diseases. Dr. Dale has received continuous U.S. federal research funding for 36 years and has devoted his entire research career to the study of the pathogenesis of group A streptococcal infections and the design, development and clinical testing of streptococcal vaccines.



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

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



Current Lab Members:

Jarrold R. Fortwendel, PhD – Principal Investigator

Wenbo Ge – Research Associate

Adela Martin-Vicente, PhD – Postdoctoral Fellow

Xabier Guruçea Sierra, PhD – Postdoctoral Fellow

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

Harrison Thorn – Graduate Student, Pharmaceutical Sciences Program

Jinhong Xie, MS – Graduate Student, Pharmaceutical Sciences Program

Brittany Tipton – PharmD/PhD Dual Enrollment Graduate Program

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

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

Every year in the United States, nearly 3 million people are infected with drug-resistant bacteria and over 35,000 people die as a direct result of these infections. The overuse of broad-spectrum antibacterial agents has been linked to the alarming rise in drug-resistant



bacteria we are currently seeing. Further, we are continuing to understand the role of the human microbiome in health and disease and the adverse effects on human health that can result from the disruption to the microbiome caused by broad spectrum antibacterials. Therefore, there is an urgent need to validate and characterize novel antibacterial targets, particularly those that may result in a narrow-spectrum antibacterial effect against pathogenic, invasive organisms that can spare the human microbiota, and to develop therapeutic agents that affect these validated targets. The Hevener laboratory is currently investigating two such targets: the enoyl-acyl carrier protein (ACP) reductase enzyme (FabK) in *Clostridioides difficile*, *Porphyromonas*

gingivalis, & *Fusobacterium nucleatum* and the topoisomerase I enzyme in *Streptococci*. FabK is an essential enzyme in the bacterial fatty acid synthesis pathway (FAS-II) of certain pathogenic organism, such as *C. difficile* and *P. gingivalis*, which are responsible for GI and oral infections. FabK is a unique isozyme at this essential step that is distinct from the FabI isozyme found at this step in many of the non-pathogenic digestive tract organisms, which makes it an attractive target for narrow-spectrum antibacterial design. The type 1A topoisomerase found in Streptococci presents another potential narrow-spectrum antibacterial target as many non-pathogenic organisms express additional, redundant topoisomerase enzymes that pathogenic species of Streptococci do not. My laboratory is using a variety of microbiological, biochemical and structural biology approaches to validate and characterize these targets and is concurrently using structure-based design strategies to identify novel and potent inhibitors of these targets for further use as chemical probes and potential drug discovery leads.

Current lab members:

Postdoctoral Fellow – Afroza Akhtar, Ph.D.

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

Pharmacy Students – Humna Meer, Thao La

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

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



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

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

Dr. Kumar graduated from the Indian Institute of Technology (IIT)-Bombay, India. Dr. Kumar did his post-doctorate fellowship from the University of Missouri-Kansas City (UMKC) followed by joined as a junior faculty at the University of Texas Medical Branch. He then went back to UMKC as an Assistant Professor before coming to UTHSC in 2014. Dr. Kumar is trained as a biochemist and enzymologist with expertise in drug metabolism, HIV, and substance abuse. His laboratory works in the field of HIV/AIDS, neuroAIDS, and substance use/abuse, especially alcohol and smoking, and extracellular vesicles. For the past 8 years Dr. Kumar's research projects are funded by several NIH grants. In the past 11 years, Dr. Kumar's group has published substantially in this field (~75 papers), with a total of >115 papers in his career. Dr. Kumar has mentored eight graduate students and three post-doctorate fellows along with numerous other trainees. Currently, he is mentoring three graduate students and two PDFs. In addition to research, Dr. Kumar participate significantly in classroom teaching to both professional pharmacy students and graduate students.



Dr. Kumar has been actively engaged in serving the Society on Neuroimmune Pharmacology (SNIP), not only as a member, but also as Chair of "Early Career Investigator Committee, as well as Secretary and President-elect of the society. As a result of his distinguished contributions to research, teaching, mentoring, and service, Dr. Kumar has received numerous awards and honors. In the past five years

Dr. Kumar has received: 1) Mahatma Gandhi Pravasi (Non-resident Indian (NRI)) Samman (Honor) from NRI, India, 2) Teacher of the Year Award from UMKC-SOP, 3) Distinguish Service Award from the SNIP, 4) Postdoctoral Fellow Outstanding Junior Mentoring Academy Award from the Post-doctorate Association, UTHSC, 5) Phi Delta Chi (PDC) "Professor of the Year Award" from UTHSC-COP (2018 and 2019), 6) UT Alumni Association "Outstanding Teacher Award", from the University of Tennessee, 7) Inducted in Phi Lambda Sigma society, UTHSC-COP, 8) The Student Government Association Executive Council (SGAEC) "Excellence in Teaching Award", from UTHSC-GCHS, 9) Full member of PDC fraternity.

Research Projects

1. Alcohol, HIV, antiretroviral therapy (ART), extracellular vesicles, and cytochrome P450
2. Tobacco/nicotine, HIV, and extracellular vesicles, and cytochrome P450
3. Antiretroviral therapy (ART) and nanoformulations
4. HPV/Cervical cancer and HIV/AIDS

Current Lab Personnel:

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

Recently trained PDFs and graduated students

PDFs: Dr. PSS Rao, Dr. Narasimha Midde

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

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

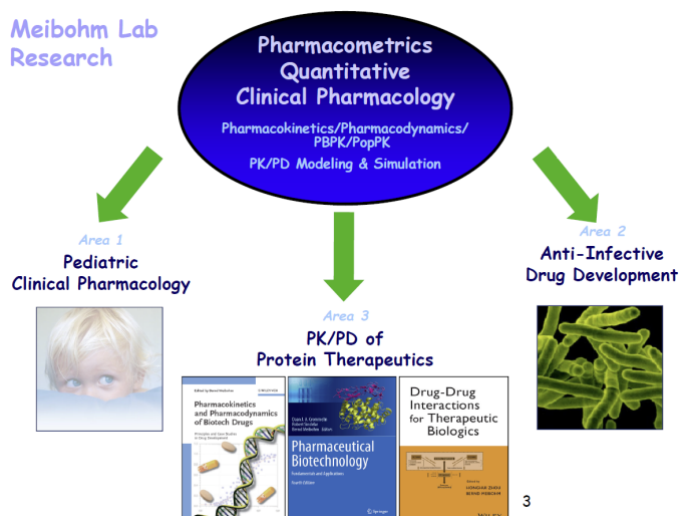
Dr. Meibohm's research is focused on the investigation of the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs with special emphasis on PK/PD-correlations.

Pharmacokinetic/pharmacodynamic (PK/PD)-modeling bridges the gap between dynamic dose-concentration relationships and static concentration-effect relationships of drugs. By combining information provided by pharmacokinetics and by pharmacodynamics, it facilitates the description and prediction of the time course of drug effects that are resulting from a certain dosing regimen. The application of these PK/PD-modeling concepts has been identified as beneficial in all phases of preclinical and clinical drug development as well as in applied clinical pharmacotherapy, where it provides a more rational basis for patient-specific dosage individualization. Thus, the ultimate goal of the research in Dr. Meibohm's lab is to contribute to the optimization of dosing regimens for increased efficacy and reduced toxicity and to modulate pharmacotherapy according to the needs of the individual patient.



Special areas of interest are:

1. Pharmacokinetics and pharmacodynamics of small molecule drugs and biologics in pediatric patients and their dependency on developmental changes.
2. Pharmacokinetics and pharmacodynamics of anti-infective drugs with specific focus on development of therapies against tuberculosis and alphavirus infections.
3. Application of pharmacometrics and quantitative pharmacology concepts in preclinical and clinical drug development, with specific focus on therapeutic proteins.



LAB PERSONNEL

- Pradeep Lukka, PhD (postdoctoral fellow)
- Ashish Srivastava, PhD (postdoctoral fellow)
- Santosh Wagh, MS (PhD student, Pharmaceutical Sciences Program)
- Keyur Parmar, MS (PhD student, Pharmaceutical Sciences Program)
- Zaid Temrikar, MS (PhD student, Pharmaceutical Sciences Program)
- Paridhi Gupta, BPharm (PhD student, Pharmaceutical Sciences Program)

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

An estimated 1.5 million people die each year from invasive fungal infections, and many millions more are afflicted by debilitating mucosal and subcutaneous mycoses. Current



antifungal therapies have serious deficiencies including poor efficacy, limited spectrum of activity, patient toxicity and the emergence of resistant fungi. Consequently, mortality rates are disturbingly high. A major obstacle to developing effective new antifungal drugs is the fundamental similarity between the cells of these eukaryotic pathogens and their mammalian host. This presents a challenge in devising therapeutic agents with pathogen selective toxicity. A major long-term goal of my research program is to identify and validate new target proteins that can provide a basis to develop efficacious new antifungal therapies. Current investigations within my lab include the discovery and development of new classes of antifungal agents that target either: 1). The integrity of a sub-cellular organelle called the fungal vacuole; 2). Fungal fatty acid biosynthesis; and 3) aromatic amino acid biosynthesis. As part of these studies we have devised several high-throughput (HTP) chemical screening assays to identify compounds that target these cellular functions. This includes a new and broadly applicable type of target based whole-cell screen (TB-WCS) that combines the benefits of both traditional target-based and cell-based chemical screens into a single HTP assay. We anticipate our TB-WCS approach to chemical screening will greatly enhance the speed and efficiency with which new pre-therapeutic leads, with a defined mechanism of action can be identified. Through these efforts, I have become increasingly excited about the enormous potential of applying yeast-based systems (which are highly amenable to HTP approaches) to the discovery of new pharmacotherapies that target human disease related proteins.

Current Lab Members:

Tracy Peters M.S - Lab Manager

Jessica Regan - Graduate Student, Pharmaceutical Sciences Program

Parker Reitler – Graduate Student, Integrated Program in Biomedical Sciences

Joseph F. Pierre, Ph.D.
Assistant Professor of Pediatrics
Assistant Professor of Microbiology, Immunology, and Biochemistry
University of Tennessee Health Science Center, Memphis

My research program focuses on underlying microbiome mediated mechanisms of metabolic and immunologically driven diseases - including in obesity, liver disease, inflammatory



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

Current Lab Members:

Qusai Al Abdallah, PhD – Lab manager

Tahliyah Mims, BS – Research Technician

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

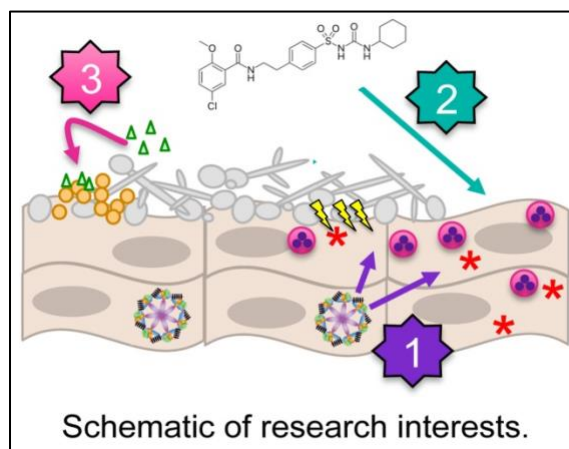
The Peters lab has two main foci of research: **1)** the host and fungal molecular mechanisms responsible for the immunopathogenesis of vulvovaginal candidiasis and **2)** quorum sensing and toxin regulation during fungal-bacterial intra-abdominal infection.

Immunopathogenesis of vulvovaginal candidiasis:

Candida albicans, an opportunistic human fungal pathogen, is the leading causative agent of vulvovaginal candidiasis (VVC) and presents major quality of life issues for women worldwide. It is estimated that nearly every woman of childbearing age will be afflicted by VVC at least once in her lifetime. Although these treatments are typically effective at reducing organism burden, static function of azole activity, fungal recalcitrance to clearance, and lack of comprehensive understanding of disease pathology necessitates further insight into the host and fungal factors that contribute to vaginitis immunopathology.



[1] We are interested in exploring virulence mechanisms utilized by *C. albicans*, including the fungal toxin candidalysin, to activate inflammasome signaling at the vaginal mucosa. Current projects seek to identify relative pathogenicity of candidalysin alleles observed amongst clinical isolates and delineating mechanisms to explain inefficient toxin activity. We are also focused on determining the downstream signaling events relevant to disease pathogenesis, including activation those that contribute to neutrophil influx at the vaginal mucosa.



[2] We are also currently interrogating the sulfonyleurea drug class as repurposed adjunctive therapeutic agents to more quickly arrest symptomatic disease. Recent work has demonstrated this class inhibits the NLRP3 inflammasome. Newer work with colleagues in the College of Pharmacy has led to the identification of inhibitors that demonstrate both antifungal and anti-inflammatory efficacy. Using a forward genetics approach, we are also interested in understanding how host genetic determinants alter symptoms of vaginal disease in the BXD recombinant inbred line. Follow-up studies to delineate molecular mechanisms are currently underway.

Polymicrobial intra-abdominal infection:

[3] Microorganisms rarely exist as single species communities but instead exist within multi-species consortia where mutually beneficial, parasitic, and antagonistic interactions may develop. However, relatively little is known about the functional consequences of these interactions as they relate to health and disease.

We aim to determine the complex inter-microbial signaling events that mediate infectious synergism observed during intra-abdominal infection with the ubiquitous bacterial pathogen *Staphylococcus aureus* and the fungus *C. albicans*. Prior studies have identified that the staphylococcal agr quorum sensing system is augmented during in vitro and in vivo growth with *C. albicans*, leading to elevated levels of cytolytic α -toxin. Both genetic and passive immunization strategies against α -toxin significantly attenuate infectious synergism in vivo. The murine model of polymicrobial intra-abdominal infection serves as an excellent system for determining microbe-microbe induced virulence gene regulation in vivo. Current studies are aimed at delineating mechanisms by which *C. albicans* activates the agr system, identifying host pathways that are substantially altered during co-infection, and devising strategies to treat downstream effects of α -toxin activity.

Lab Members:

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

Jian Miao, MS - Graduate Student, Pharmaceutical Sciences Program

Amanda Vogel - Graduate Student, Integrated Biomedical Sciences Program

Jabez Fortwendel – Undergraduate researcher, University of Tennessee Knoxville

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

Fungi cause over 1 billion infections world-wide, and the most common cause genus of fungi that causes these infections are yeast of the genus *Candida*. The most frequently isolated



Candida species from infectious sites is *C. albicans*, and it, along with other *Candida* species, are natural commensals of the human gut, vaginal, tract, and skin. However, they can become pathogenic under conditions that compromise immune protection and cause painful mucosal infections and life-threatening invasive infections. Mucosal infections can range from vaginal infections in women to oropharyngeal infections in immunocompromised patients that have AIDS, use corticosteroids, take broad spectrum antibiotics, or take certain drugs. Life threatening infections are associated with cancer and organ transplant chemotherapies as well as the use of intravascular catheters. In fact, *Candida* species are the 3rd-4th most common cause of catheter associated invasive infections in

intensive care units. A major concern with *Candida* infections is that there are only three classes of antifungals commonly used for invasive infections, and these are limited in their efficacy by a combination of drug toxicity, drug resistance, and only a few can be taken orally. My lab is exploring this through two major foci that both involve components of the cell envelope (cell wall and plasma membrane). 1) We have found that the *C. albicans* phosphatidylserine (PS) synthase enzyme has great potential as a drug target. PS is plasma membrane lipid, and the fungal PS synthase is the sole source for PS in fungi, and is required for virulence of *C. albicans* in mouse models of both oral and invasive infection. Moreover, it is essential for viability in the fungal pathogen *Cryptococcus neoformans*. In addition, PS synthase is conserved throughout fungi, and the human PS synthase uses a completely different mechanism to synthase PS and bears little sequence similarity to the fungal enzyme. Altogether, this indicates that inhibitors of fungal PS synthase would prevent virulence, have broad applicability to other fungi, and have low toxicity. My lab is exploring the structure of *C. albicans* PS synthase with a goal of developing small molecule inhibitors of this enzyme. 2) A second major direction of my lab is to explore the role of immunotherapy against *Candida* species. Oral and invasive infections do not occur as often in the immunocompetent, so enhancing the residual immune response in immunocompromised patients should improve health outcomes. We have found that hyperactivation of some signaling pathways in *C. albicans* leads to greater exposure of the fungus to immune cells and a reduction in virulence during infection. We are working to discover how these pathways cause this reduction in virulence with the long-term goal of exploiting this to improve immunotherapy. Altogether, these two foci in my lab complement one another as they both focus on aspects of the cell envelope that can be exploited to improve antifungal therapies.

Current Lab Members:

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

Research Specialist – Stephen Lumsdaine, B. S.

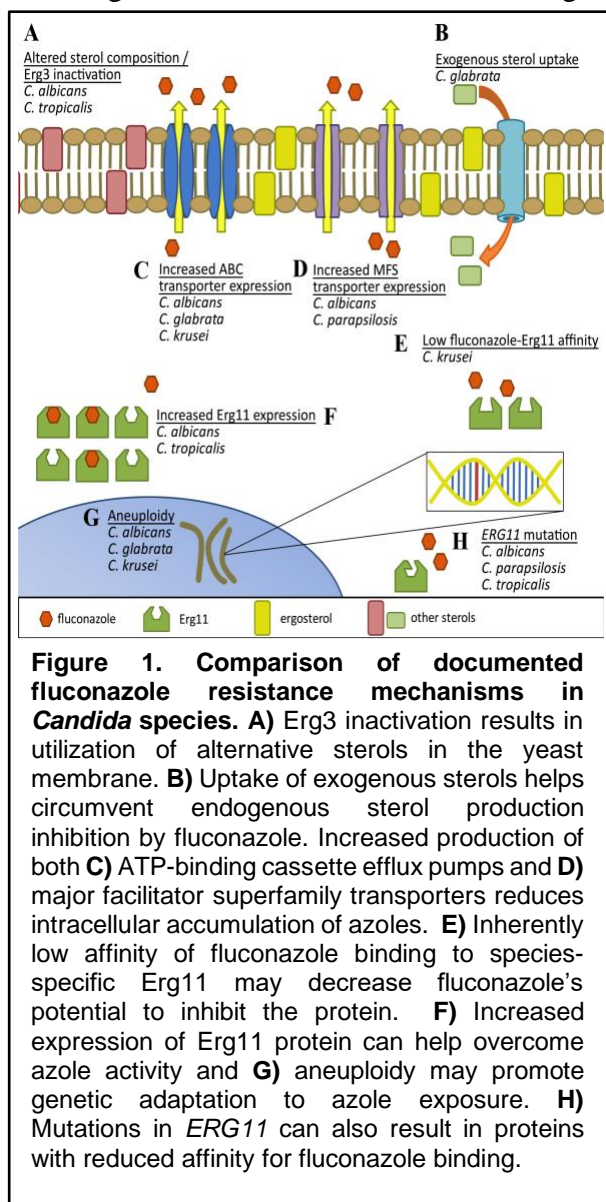
P. David Rogers, Pharm.D., Ph.D., FCCP
Member, St. Jude Faculty
Chair, Department of Pharmacy and Pharmaceutical Sciences
Endowed Chair in Pharmaceutical Sciences
Scientific Advisor, Center for Pediatric Experimental Therapeutics

The overarching long-term goal of the Rogers lab is to improve the safety and efficacy of antifungal pharmacotherapy. My interest in this area is driven by insights gained as an infectious diseases clinical pharmacist into the significant limitations that exist with regard to the treatment of serious fungal infections.



Indeed, treatment of such infections is limited to only three antifungal classes. The polyene amphotericin B is effective for many fungal infections, but its use is

hampered by significant infusion-related reactions and nephrotoxicity. It is also only available for intravenous administration. The triazole antifungals are effective and, in some cases, superior, yet much less toxic, inexpensive, and available both orally and intravenously. Unfortunately, resistance has emerged which limits the utility of this antifungal class. The echinocandins, such as caspofungin, are particularly useful for invasive candidiasis, but lack utility against other fungal pathogens and are only available for intravenous administration. Moreover, resistance to this antifungal class has begun to emerge, particularly in the fungal pathogen *Candida glabrata*. It must also be underscored that no new antifungal drug classes are on the horizon. Novel strategies are therefore urgently needed to preserve, improve, and expand the current antifungal armamentarium.



For over a decade our primary focus has been on understanding the molecular and cellular basis of resistance to the triazole class of antifungal agent in pathogenic fungi (overviewed in **Figure 1**). A long-term interest of my laboratory has been the use of genome-wide technologies to study antifungal stress responses in *Candida* species. We used microarray and proteomic analysis to identify changes in the gene expression and proteomic profiles of these organisms in response to the various classes of antifungal agents. This revealed both

general and specific responses, some of which aligned with the mechanisms of action of these agents, and gave insight into factors that influence antifungal susceptibility (such as the azole-induction of the Cdr1 transporter). We also used this approach for genome-wide analysis of azole antifungal proteomic analysis to identify changes in the gene expression and proteomic profiles of these organisms in response to the various classes of antifungal agents. This revealed both general and specific responses, some of which aligned with the mechanisms of action of these agents, and gave insight into factors that influence antifungal susceptibility (such as the azole-induction of the Cdr1 transporter). We also used this approach for genome-wide analysis of azole antifungal resistance in *Candida* species, which has provided insight into this process (1-4).

My laboratory, working in collaboration with the laboratory of Joachim Morschhauser, discovered the transcriptional regulator Mrr1 and demonstrated that activating mutations in this transcription factor gene result in up-regulation of the Mdr1 transporter and fluconazole resistance in clinical isolates of *C. albicans*. In further work we have delineated the regulon of this transcriptional regulator and identified other regulators required for its activity (5-8). Working again in collaboration with the Morschhauser laboratory, we discovered that activating mutations in the transcription factor Upc2 leads to up-regulation of the gene encoding the azole target (*ERG11*), and increased azole resistance in clinical isolates. We have shown that this is a common and important mechanism of resistance among clinical isolates, identified additional regulators required for its activity, and have found it to be essential for azole resistance in clinical isolates exhibiting the major resistance mechanisms (9-12). More recently we have delineated the contribution of the putative lipid translocase Rta3 in azole resistance in this organism (13).

Our work has also explored the problem of triazole resistance in other fungal species. Working in collaboration with the laboratory of Thomas Edlind, we discovered that activating mutations in the transcription factor Pdr1 were responsible for azole resistance in *C. glabrata*. This led to further work by our group elucidating the role of this transcription factor, as well as the transcription factor Upc2, in azole antifungal resistance in this important *Candida* species (14-17). More recently we have begun to dissect this process in other non-albicans *Candida* species as well as the important fungal pathogen *Aspergillus fumigatus* (18, 19). Currently my research program maintains three focus areas: 1) Understanding the genetic and molecular basis of triazole antifungal resistance in *Candida albicans*, 2) Dissecting the Upc2A transcriptional pathway, protein interaction partners, and genetic network to overcome fluconazole resistance in *Candida glabrata*, and 3) Delineating the genetic and molecular basis of triazole resistance in the fungal pathogen *Aspergillus fumigatus*.

Lab Members:

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

Kathy Barker, Ph.D. – Senior Scientist

Qing Zhang – Laboratory Manager

Ana Camila Oliveira Souza – Staff Scientist

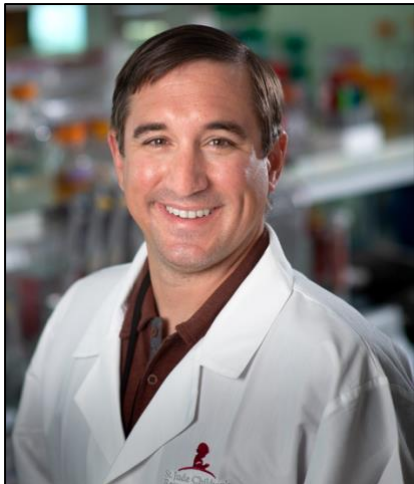
Christian DeJarnette – Postdoctoral Fellow

Lillian Pereira Silva – Postdoctoral Fellow

Laura Doorley – Graduate Student, Integrated Program in Biomedical Sciences

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

The overall goals of my research program are gain a greater understanding for the novel strategies to target invasive bacterial infections, particularly bacterial pneumonia and sepsis.



My specific interest is gaining an understanding of infections and the development of antibiotic resistance in the context of high-risk hosts. Our lab has extensive experience with the genetic manipulation and characterization of Gram-positive pathogens including modeling bacterial pathogenesis and host response in the context of various murine models of infection including colonization, transmission, pneumonia, bacteremia, meningitis, and acute otitis media. This background in bacterial genetics and pathogenesis modeling has allows us to achieve mechanistic insights into host-pathogen interactions.

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

Current Lab Members:

Lab manager – Amy Iverson, B.S.

Research Associate – Haley Echlin, PhD.

Graduate Student – Tina Dao, B.S

Postdoctoral Fellow – Andy Nishimoto, PhD, PharmD.

Animal Research Technician – Aaron Poole

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

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



Lab Members:

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

DIRECTION OF THE CENTER

2020-2021

Goals and Future Plans

In the coming year, the CPET will continue its focus on the overarching themes of Pediatric Infectious Diseases and Antiinfective Pharmacotherapy. We will continue to expand our work specifically in the areas of fungal pathogens, HIV/AIDS, and anti-infective drug discovery and development. For 2020-2021, the CPET was instrumental in expanding our expertise with the recruitment of new external faculty focused on host responses to pulmonary fungal infection. With this addition, the Center membership is now looking to add additional core faculty focused on childhood asthma, lung co-infections, and research-active clinical faculty focused on cystic fibrosis through interactions with the Le Bonheur Children's Hospital Cystic Fibrosis Center.

The newly established "CPET Seed Grant Program" was implemented for the 2020-2021 cycle and successfully supported multiple forth-coming grant and manuscript submissions. Through this program, CPET investigators receive seed monies for projects deemed competitive for extramural funding (e.g., NIH, DoD, etc.). For the coming 2021-2022 cycle, this Program is aiming to fund collaborative work between UTHSC Center faculty and clinical research at Lee Bonheur and St. Jude Children's to facilitate truly translational discoveries and to support the generation and dissemination of new knowledge regarding the treatment of childhood diseases throughout UTHSC, the state of Tennessee, and the nation. To do this, the Center is requesting applications for seed funding that are focused on the development of NIH Program Project Grants that preferentially fund collaborative, multidisciplinary teams. Research questions in pediatric infectious disease and antiinfectives development are large in scope and significant advance is often beyond the capabilities of individual investigators. This challenging area of research truly benefits from the integrated efforts of teams of research laboratories employing complementary approaches and having multiple areas of intellectual and technical expertise. As such, the CPET looks to help provide the necessary resources to accomplish a unified scientific goal in this area.

We will continue to train elite graduate students in the biomedical and pharmaceutical sciences with the support of the CPET Scholars Program. For the 2021-2022 Scholars program, Center support will require scholars to generate at least one first-authored research publication in a peer-reviewed scientific journal and to submit for external fellowship funding by the end of their second year in the program. These expectations will ensure that training in research remains rigorous. Dissemination of our discoveries and sharing and exchange of new ideas will be facilitated through CPET support of events such as the annual Tennessee Fungal Pathogens Group Conference and the CPET Seminar Series. Finally, for the 2021-2022 year, the CPET will provide partial salary support for a Pediatric ID Clinical Pharmacy Fellow as part of an exciting NIH-funded study (R21AI153768) into determinant of candidemia in pediatric patients. In doing so, the Center is working to positively and immediately impact therapeutic advances in children.

Schedule 7

CENTERS OF EXCELLENCE ACTUAL, PROPOSED, AND REQUESTED BUDGET

Institution:

University of Tennessee Health Science Center

Center:

Pediatric Pharmacokinetics

Expenditures	FY 2020-21 Actual			FY 2021-22 Proposed			FY 2022-23 Requested		
	Matching	Appopr.	Total	Matching	Appopr.	Total	Matching	Appopr.	Total
Salaries									
Faculty	\$1,202,746	\$8,071	\$1,210,817	\$1,214,773	\$9,000	\$1,223,773	\$1,214,773	\$9,000	\$1,223,773
Other Professional	\$218,054		\$218,054	\$220,235	\$8,221	\$228,456	\$220,235	\$8,221	\$228,456
Clerical/ Supporting	\$230,671	\$0	\$230,671	\$232,978		\$232,978	\$232,978		\$232,978
Assistantships	\$167,402	\$96,443	\$263,845	\$169,076	\$126,811	\$295,887	\$169,076	\$109,644	\$278,720
Total Salaries	\$1,818,873	\$104,515	\$1,923,388	\$1,837,062	\$144,032	\$1,981,094	\$1,837,062	\$126,865	\$1,963,927
Longevity (Excluded from Salaries)	\$7,631	\$25	\$7,656	\$7,707	\$30	\$7,737	\$7,784	\$35	\$7,819
Fringe Benefits	\$434,380	\$4,827	\$439,207	\$438,723	\$5,821	\$444,544	\$438,723	\$5,821	\$444,544
Total Personnel	\$2,260,884	\$109,367	\$2,370,251	\$2,283,492	\$149,883	\$2,433,375	\$2,283,569	\$132,721	\$2,416,290
Non-Personnel									
Travel			\$0		\$5,000	\$5,000		\$5,000	\$5,000
Software		\$80	\$80			\$0			\$0
Other Supplies		\$77,956	\$77,956		\$90,500	\$90,500		\$70,500	\$70,500
Equipment		\$32,217	\$32,217		\$42,086	\$42,086		\$32,761	\$32,761
Other (Specify):									
Media Processing		\$348	\$348		\$400	\$400		\$400	\$400
Communication		\$1,146	\$1,146		\$1,200	\$1,200		\$1,500	\$1,500
Professional Services & Memberships		\$1,134	\$1,134		\$3,517	\$3,517		\$4,000	\$4,000
Insurance & Interest		\$8,055	\$8,055		\$4,000	\$4,000		\$4,000	\$4,000
Grants & Subsidies		\$959	\$959		\$1,500	\$1,500		\$1,500	\$1,500
Contractual & Special Services		\$1,500	\$1,500		\$28,000	\$28,000		\$25,000	\$25,000
Total Non-Personnel	\$0	\$123,394	\$123,394	\$0	\$176,203	\$176,203	\$0	\$144,661	\$144,661
GRAND TOTAL	\$2,260,884	\$232,761	\$2,493,645	\$2,283,492	\$326,086	\$2,609,578	\$2,283,569	\$277,382	\$2,560,951
Revenue									
New State Appropriation		\$255,443	\$255,443		\$264,173	\$264,173		\$277,382	\$277,382
Carryover State Appropriation		\$39,231	\$39,231		\$61,913	\$61,913			\$0
New Matching Funds	\$2,260,884		\$2,260,884	\$2,283,492		\$2,283,492	\$2,283,569		\$2,283,569
Carryover from Previous Matching Funds			\$0			\$0			\$0
Total Revenue	\$2,260,884	\$294,674	\$2,555,558	\$2,283,492	\$326,086	\$2,609,578	\$2,283,569	\$277,382	\$2,560,951

YEAR-IN-REVIEW

2020-2021

Program Overview and Accomplishments

The Center for Pediatric Experimental Therapeutics (CPET) has been continuously funded for over 30 years. It achieved accomplished status early and has been among the best Centers statewide when one considers return on investment. The CPET is among the smallest Centers by total annual appropriations, but consistently brings grant and contract dollars in excess of \$7 million per year to the Health Science Center (HSC), its affiliated programs, and the State of Tennessee. The Center has been multidisciplinary, interprofessional, multi-institutional, multi-college and multi-departmental from its beginning, and has had translational science at its core (from bench-top to patient and back again). It is the only state-funded Center of Excellence with improvement in children's health as its primary mission. The CPET has accomplished its mission over the years through research, education, outreach, and patient care.

Extramural funding and research publications from faculty supported by the Center are outlined in the following pages. In addition to this grant support and research productivity, the Center supports graduate education through the CPET Scholars Program. Exceptional students enrolled in graduate education at UTHSC under the direction of Center faculty have been selected for partial support from the center through either stipend relief or support for attendance to scientific meetings and publication of research findings in peer-reviewed journals (See CPET Scholar section).

In a year that was still significantly impacted by the Covid-19 pandemic, the CPET maintained high productivity. This year, in addition to the CPET Scholars Program, the Center supported three external speakers as part of the CPET Seminar Series. These speakers are invited by Center faculty and represent leading experts in the fields of pediatrics, clinical pharmacy, and infectious diseases. The CPET Seminar Series serves to promote research conducted by Center faculty and to engage leading experts for future research collaborations, as well as for networking opportunities for trainees in the CPET Scholars Program. The seminar series for 2020-2021 involved speakers focused on HIV comorbidities in children, genetic determinants of invasive fungal disease, and the rapidly developing problem of SARS-CoV-2 and pulmonary fungal co-infections. In support of the world-class medical mycology unit that comprises a major component of the membership, the CPET was also again instrumental in supporting the annual Tennessee Fungal Pathogens Group Conference that took place in September of 2021. The program focuses on research presentations from graduate students and post-doctoral fellows from each Center laboratory as well as basic science keynote lectures. This year, invited keynote speakers were junior Center members, Camaron Hole, PhD from UTHSC and Jeffery Rybak, PharmD, PhD from St. Jude Children's Hospital. Dr. Hole was newly recruited to UTHSC through CPET efforts to complement the strong medical mycology units at UTHSC, St. Jude and UTK. As a testament to the long-term positive impacts of the CPET, Dr. Rybak was a CPET-supported graduate student and postdoctoral fellow at UTHSC before beginning his independent research position at St. Jude Children's Hospital in 2020.

As a new initiative for the 2020-2021 year, the CPET established a CPET Seed Grant Program that awarded \$20,000 research seed grants to select Center members. The goal of the program for this year was to support the submission of new NIH grant applications by providing funds for the acquisition of new preliminary data. Below is a summary of the Seed Grants awarded to three Center faculty and a

description of the impact for each award. This program has already been successful in supporting new lines of research on future therapeutic advances.

In the coming year the CPET will continue to direct its efforts to focus on pediatric infectious diseases and finding ways to overcome them. Infectious diseases are a leading cause of death in the pediatric population world-wide. This has been complicated by increases in resistance to existing antimicrobial agents. New therapeutic strategies are desperately needed. The CPET has evolved to include leading investigators focused on the bacteria, fungi, and viruses that cause many of the most significant infectious diseases including tuberculosis, pneumonia, blood stream infections, HIV/AIDS, and fungal infections. We expect the years to come to be filled with novel and important research, thus invigorating CPET faculty, transforming the care of patients, and building new connections with the communities we touch. The CPET serves as a unifying force for scientists within these domains and connects the resources and efforts of our faculty through pivotal relationships with Le Bonheur Children's Medical Center and St. Jude Children's Research Hospital. In addition to our efforts in the laboratory, CPET scientists, clinicians, and educators have developed professional curriculum course materials, innovative interprofessional educational programs, scientific seminars and conferences, and train the next generation of pediatric biomedical scientists through our graduate and postdoctoral training programs.

The important work, both papers and funded projects, of CPET member faculty who shape our continuing story of innovative science, education, and patient care, are outlined in the following pages. Combined with our established investigators, the CPET is a potent force in improving the health of children in Tennessee, the country, and the world.

CPET Seminar Series



“HIV Comorbidities and Progress Towards a Cure”

Tricia H. Burdo, PhD

Associate Professor
Department of Neuroscience
Lewis Katz School of Medicine (LKSOM)
Temple University



“Genetic Approaches for Understanding Fungal Pathogenesis”

Teresa R. O'Meara, PhD

Assistant Professor
Department of Microbiology and Immunology
University of Michigan



“Systems Biology of Invasive Fungal Infections”

Vincent Bruno, PhD

Associate Professor
Department of Microbiology and Immunology
Institute for Genome Sciences, University of Maryland
School of Medicine

CPET Seed Grant Program



Awardee: Dr Kirk E. Hevener, PharmD, PhD

Project Title: The FabK enzyme from *Fusobacterium nucleatum* as a microbiome-sparing chemotherapeutic target

Project Description: Nearly 150,000 people will be diagnosed with colorectal cancer (CRC) in the U.S. and 53,000 will die from it in 2021. It is the third most diagnosed cancer and the second leading cause of cancer-related death. Recent reports indicate an association between pathogenic bacteria in the digestive system and the occurrence of colorectal cancer. One such organism is *Fusobacterium nucleatum*, an oral pathogen that is now well known to promote growth of CRC tumors. Colonization of the large bowel by *F. nucleatum* worsens CRC, by generating a tumor-promoting microenvironment, while inhibiting the anti-tumor activities of natural killer cells and tumor infiltrating T cells. Thus, there is a need for strategies to selectively eradicate *F. nucleatum*, to enhance the treatment outcomes for CRC patients. It was shown that the antibiotic metronidazole decreased *F. nucleatum* mediated tumor growth, supporting the view that elimination of *F. nucleatum* would decrease CRC tumor burden. Unfortunately, metronidazole is a broad-spectrum antibiotic and its use for *Fusobacterium*-associated CRC could adversely disrupt the microbiota of CRC patients, resulting in dysbiosis-related effects, including development of other colonic diseases. An ideal strategy would be to use a narrow-spectrum antibacterial with activity limited to *F. nucleatum*, to minimize disruption of the gut microbiota. However, no such drug is currently on the market. Therefore, there is a need for the discovery and validation of narrow-spectrum antibacterial drug targets with focused activity against the *F. nucleatum* pathogen.

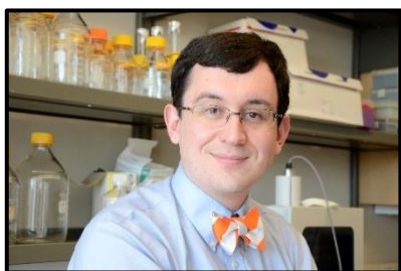
Hypothesis. One promising drug target is the FabK enzyme, an enoyl-acyl carrier protein (ACP) reductase protein involved in the fusobacterial fatty acid synthesis pathway (FAS-II). The FAS-II pathway provides fatty acid precursors for bacterial membrane phospholipids and is essential for bacteria. Importantly, mammalian cells adopt the FAS-I pathway that is distinct from FAS-II. The rate-limiting enoyl-ACP reductase step is essential for bacteria and represents a promising antibacterial drug target. Interestingly, there are four known enoyl-ACP reductase isozymes (FabI, FabK, FabL, FabV) that are differentially expressed in bacterial species and are structurally and mechanistically different to each other. *F. nucleatum* only expresses the FabK enzyme, while most other gut bacteria do not. Thus, fusobacterial FabK is an exciting target for the discovery and development of narrow spectrum antibacterials. These facts form the basis for our Central Hypothesis - that *F. nucleatum FabK (FnFabK) inhibitors will show selective antibacterial activity, cause minimal disruption to the gut microbiota, and result in decreased cancer-associated activity.*

Objective. The overarching objective of this project is to provide proof of concept that *F. nucleatum* targeted antibacterials will decrease CRC cell proliferation, thus signifying that antimicrobial strategies are a viable therapeutic approach to enhance treatment outcomes for CRC. A secondary objective is to demonstrate that inhibitors designed and optimized for *FnFabK* will have a minimal disruption to the human microbiome.

Project Status. Preliminary data generated under this CPET seed grant includes molecular cloning and optimization of the expression and purification of the target protein, development of a low-volume biochemical assay, screening and identification of small-molecule target inhibitors, demonstration of whole-cell activity in MIC studies, and preliminary work to obtain co-crystal structures (*in progress*).

Submitted Grant Proposals: A grant was submitted to the Department of Defense Congressionally Directed Medical Research Program (Peer-Reviewed Cancer Research Program) under the Idea Award mechanism (3-year, \$500K direct costs) on September 8, 2021.

Future Grants & Manuscripts Planned: We anticipate submission of an NIH R21 on this project in the first cycle of 2022. We plan to submit our first manuscript on this project after we successfully solve a high-resolution co-structure of the target protein with inhibitor bound.



Awardee: Theodore Cory, Pharm.D., Ph.D.

Title: Assessing the role of Azithromycin in macrophage responses to *Aspergillus*

Project Description: The overall goal of our work is to define factors that promote increased fungal burden in the lungs of patients at-risk for invasive fungal infections. The objective of this study is to delineate the impact of macrolide therapy on the rate of fungal clearance in the lung. *Aspergillus fumigatus* is a ubiquitous mold pathogen that causes both invasive and chronic disease. The health burden of chronic aspergilloses world-wide is of increasing concern as the case rates are increasing and the underlying causes are understudied. Although all at-risk patients come into contact with *Aspergillus* spores in their environment, only some will develop chronic infections. Therefore, there are likely patient- and fungal strain-specific factors at play. Patients at risk for both chronic and invasive pulmonary disease caused by the *Aspergilli*, and other environmental fungi, are typically in an immune suppressed state and are, therefore, often at-risk for many other infectious bacterial and viral diseases. To protect against these unwanted infections, patients are typically on antibacterial or antiviral medications for the life of their immune suppressed status. Recently, the macrolide antibiotics have been found to have off-target effects causing immune modulation that can alter host-pathogen interactions. Azithromycin (AZM), Calrithromycin (CAM) and Erythromycin (ERM) are commonly used at high doses and, in some cases, for extended periods to treat or protect against bacterial infections in children suffering from cystic fibrosis or adults with underlying COPD. These all represent patients at-risk for invasive pulmonary fungal infections. We have found, using published mouse models of immune modulation by macrolide therapy, that azithromycin treatment results in delayed clearance of *Aspergillus* conidia from the lungs. This delayed clearance is accompanied by alterations in inflammatory host responses *in vivo*. We therefore have hypothesized that, although beneficial for protection against bacterial infections, macrolide therapy may place patients at further risk for developing both chronic and/or invasive infections when underlying immune status is further altered. Our work is designed to understand how AZM alters the immune response to *Aspergillus* challenge and to assess any additional risk posed to pediatric patients on long-term macrolide therapy.

Project Status: We were able to extensively focus on this project over the summer, when the laboratory had a rotating student. The summer student was able to fully optimize the *in vitro* model with fixed *Aspergillus* spores and generate data showing that azithromycin and fixed fungi similarly influence inflammatory cytokine production and markers of macrophage polarization. My new graduate student is performing experiments to assess the mechanism for this response, which will be accomplished in the Fall 2021. We will then assess the response with live fungus, as well as assess fungal response to azithromycin-treated macrophages.

Future Grants & Manuscripts Planned: To date, the summer student presented our preliminary data at the 2021 Clinical Laboratory Science Research Seminar, and has prepared the first third of a manuscript. We anticipate that a paper describing the research results will be submitted before the end of the calendar year (2021), and an NIH R21 proposal will be submitted for the February 16th NIH deadline.



Awardee: Joseph F. Pierre, PhD

Title: Effects of Parenteral Nutrition on growth and development of organs and associated pathophysiology

Project Description: Parenteral nutrition (PN) is a lifesaving clinical feeding strategy used to prevent malnutrition when enteral feeding is not possible. However, complications associated with PN include digestive organ atrophy and metabolic disturbances including liver injury, especially in premature infants, warranting a deeper understanding of the mechanistic underpinnings of disease development and interventions to reduce co-morbidity risk and improve outcomes. The purpose of our study was to 1) develop and optimize and 2) characterize a novel neonatal parenteral (PN) model and study the growth, development, and functionality of critical organs including GI, liver, and brain compared with enteral fed sham controls. Additionally, administration of antibiotics (penicillin and clindamycin) prior to PN is being conducted to study gut-hepatic signaling in this model.

Future Grants and Manuscripts Planned: The graduate trainee focused on this work will be presenting our data at the IEBC Conference (Oct 8-10, 2021). Funds provided by the CPET have also already supported the submission and/or preparation of two scholarly works. These include a book chapter titled “Parenteral Nutrition Modeling in the Mouse” that will be published in the forthcoming “Animal Models in Medicine”. This chapter is currently under peer review. A manuscript titled “Hepatic immune and metabolic response to total parenteral nutrition in pediatric mice” is currently under preparation for submission in Fall 2021. An NIH R01 application, involving clinical collaborators at Le Bonheur Children’s Hospital, is planned for submission for the February or June 2022 cycles, depending on successful model development.

Extramural Funding

Extramural Funding

Federal Funding (including NIH)

Investigator: **Cory TJ (MPI Kumar S, subcontract Meibohm B)**
Title: Monocytic and Exosomal Cytochrome P450 in Smoking-Mediated HIV-1 Pathogenesis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01DA047178
Dates: 9/30/18 to 6/30/23
Total Direct: \$960,000
Annual Direct: \$225,000

Investigator: **Dale JB**
Title: Structure-Based Design of a Broadly Protective Group A Streptococcal Vaccine
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI132117
Dates: 6/8/17 to 6/30/22
Total Direct: \$2,768,850
Annual Direct: \$528,426

Investigator: **Fortwendel JR**
Title: Control of Antifungal Drug Tolerance through the *Aspergillus fumigatus* Kinome
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R21AI142509
Dates: 11/13/18 to 10/31/21
Total Direct: \$418,000
Annual Direct: \$125,000

Investigator: **Fortwendel JR**
Title: Systematic Functional Analysis of the *Aspergillus fumigatus* Kinome
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R21AI139388
Dates: 7/1/18 to 6/30/21
Total Direct: \$418,000
Annual Direct: \$125,000

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

Annual Direct: \$492,444

Investigator: **Fortwendel JR**
 Title: Unlocking the cidal activity of echinocandins against *Aspergillus*
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 R01AI143197
 Dates: 3/1/20 to 2/28/25
 Total Direct: \$1,552,025
 Annual Direct: \$310,405

Investigator: **Hevener KE**
 Title: Development and Evaluation of Inhibitors of the *C. difficile* Enzyme, FabK, as Microbiome-Sparing Antibacterials
 Source: Department of Defense (DoD), CDMRP
 PR191438
 Dates: 7/21/09 to 6/2023
 Total Direct: \$1,200,000
 Annual Direct: Not Provided

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

Investigator: **Kumar S (MPI Cory TJ, subcontract Lee R)**
 Title: Monocytic and plasma exosomal cytochrome P450s in smoking-mediated HIV-1 pathogenesis
 Source: National Institute of Drug Abuse (NIDA)
 R01DA047178
 Dates: 9/01/18 to 8/31/23
 Total Direct: \$1,700,000
 Annual Direct: \$227,000

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

Investigator: **Kumar S**
 Title: Targeted Nano-Chemosensitization of Breast Cancers
 Source: National Cancer Institute (NCI)
 1R15CA213232-01

Dates: 9/1/17 to 8/31/21
Total Direct: \$289,354
Annual Direct: \$289,354

Investigator: **Lee RE** (subcontract **Meibohm B**)
Title: Development of Novel Proteins Synthesis Inhibitors for MDR Tuberculosis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
2R01AI090810-06

Dates: 7/6/10 to 2/28/23
Total Direct: \$3,997,590
Annual Direct: \$625,254

Investigator: **Lee RE** (PI Bulitta JB)
Title: Combating resistant superbugs by understanding the molecular determinants of target site penetration and binding
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI136803

Dates: 3/1/18 to 2/28/23
Total Direct: \$875,183
Annual Direct: Not Provided

Investigator: **Lee RE** (PI Haecker H)
Title: Discovery of small molecules inhibiting Toll-like receptor-mediated inflammation
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI139014

Dates: 6/14/18 to 5/31/22
Total Direct: \$515,751
Annual Direct: No Provided

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

Dates: 9/17/20 to 8/31/25
Total Direct: \$4,200,00
Annual Direct: \$595,421

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

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

Investigator: **Meibohm B**, Braunstein MS, Gonzalez-Juarrero M, Hickey AJ

Title: Inhaled tigecycline therapy for pulmonary *M abscessus* infections
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 5R01AI155922
 Dates: 6/24/21 to 5/30/2026
 Total Direct: \$3,343,775
 Annual Direct: \$668,755

Investigator: **Meibohm B**, Braunstein MS, Gonzalez-Juarrero M, Hickey AJ
 Title: Aerosol spectinamide-1599 therapy against tuberculosis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 5R01AI120670
 Dates: 6/16/16 to 5/31/21
 Total Direct: \$3,570,230
 Annual Direct: \$714,046

Investigator: **Meibohm B** (PI Li W)
 Title: Selective Targeting Survivin for Cancer Therapy
 Source: National Cancer Institute (NCI)
 5R01AI120670
 Dates: 5/1/16 to 4/30/21
 Total Direct: \$1,913,635
 Annual Direct: \$582,610

Investigator: **Meibohm B** (PI Lowe TL)
 Title: Nanogels for Drug Delivery across the BRB to Treat Diabetic Retinopathy
 Source: National Eye Institute (NEI)
 5R01EY023853
 Dates: 9/01/16 to 8/30/21
 Total Direct: \$1,900,000
 Annual Direct: \$250,000

Investigator: **Meibohm B** (PI Jonsson CB)
 Title: Center of Excellence for Encephalitic Alphavirus Therapeutics
 Source: National Eye Institute (NEI)
 1U19AI142762
 Dates: 3/01/19 to 2/29/24
 Total Direct: \$21,104,316
 Annual Direct: \$2,830,169

Investigator: **Palmer GE** (subcontracts **Lee RE** and **Meibohm B**)
 Title: Broad spectrum antifungals targeting fatty acid biosynthesis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 4R33AI127607
 Dates: 12/1/17 to 11/30/21
 Total Direct: \$800,000
 Annual Direct: \$379,500

Investigator: **Palmer GE**
Title: Examining the importance of folate biosynthetic enzymes in infectious fungi
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R21AI156611
Dates: 11/25/20 – 10/31/22
Total Direct: \$275,000
Annual Direct: \$150,000

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

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

Investigator: **Peters BM**
Title: Candidalysin: a key mediator of *Candida* vaginitis immunopathology
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI134796-02
Dates: 9/1/18 to 8/31/22
Total Direct: \$1,000,000
Annual Direct: \$250,000

Investigator: **Peters BM**
Title: Sulfonyleureas as repurposed agents against vulvovaginal candidiasis
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R21AI127942-02
Dates: 1/1/18 to 12/31/20
Total Direct: \$275,000
Annual Direct: \$125,000

Investigator: **Peters BM**
Title: Host and microbial factors promoting synergistic mortality during polymicrobial intra-abdominal infections with *Candida albicans* and *Staphylococcus aureus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)

1R21AI141829-01
 Dates: 11/13/18 to 10/31/20
 Total Direct: \$275,000
 Annual Direct: \$125,000

Investigator: **Peters BM** (PI Noverr MC)
 Title: Targeted and forward genetic approaches to decipher the pathogenesis of symptomatic vulvovaginal candidiasis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R01AI116025-01
 Dates: 12/1/14 to 11/30/20
 Total Direct: \$365,000
 Annual Direct: \$90,000

Investigator: **Pierre JF** (MPI Makowski)
 Title: Role of microbial-modulated bile acid receptor signaling in breast cancer
 Source: National Cancer Institute (NCI)
 R01CA253329
 Dates: 8/1/20 – 4/30/25
 Total Direct: \$2,100,000
 Annual Direct: \$274,540

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

Investigator: **Pierre JF** (PI Gosain A)
 Title: Dysbiosis in Hirschsprung Associated Enterocolitis Pathogenesis
 Source: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
 R01DK125047
 Dates: 6/1/20 – 5/30/25
 Total Direct: \$2,700,000
 Annual Direct: \$287,987

Investigator: **Pierre JF** (MPI Gosain A)
 Title: Modeling Host-Fungal Interactions in Hirschsprung-Associated Enterocolitis
 Source: National Institute of Allergy and Infectious Diseases (NIAID)
 1R21AI163503
 Dates: 05/09/21 to 05/31/23

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

Investigator: **Reynolds TB** (PI Wilhelm S)
Title: EDGE CT: Genetic tools to study giant viruses
Source: National Science Foundation, IOS Division of Integrative Organismal Systems
IOS 1922958

Dates: 10/01/19 to 9/30/22
Total Direct: \$1,009,308
Annual Direct: Not Provided

Investigator: **Reynolds TB**
Title: Regulation of β -(1,3)-glucan exposure in *Candida albicans*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R01AI153599

Dates: 5/8/20 to 4/30/25
Total Direct: \$2,533,727
Annual Direct: \$361,932

Investigator: **Reynolds TB**
Title: Integrated Membrane Program (IMP)
Source: National Institute of General Medical Sciences (NIGMS)
1T32GM142621

Dates: 06/02/21 to 05/30/26
Total Direct: \$840,000
Annual Direct: \$139,008

Investigator: **Rogers PD**
Title: Novel Azole Resistance Mechanisms in *Candida albicans*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI058145

Dates: 6/21/17 to 5/31/22
Total Direct: \$2,122,820
Annual Direct: \$312,303

Investigator: **Rogers PD**
Title: Upc2A: A Central Regulator and 'Achilles' Heel' of Fluconazole Resistance in *Candida glabrata*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI131620

Dates: 2/07/17 to 1/31/22
Total Direct: \$2,706,949
Annual Direct: \$381,416

Investigator: **Rogers PD** (MPI Fortwendel JR)
Title: Non-Cyp51A Mutation Mediated Triazole Resistance in *Aspergillus*
Source: National Institute of Allergy and Infectious Diseases (NIAID)
R01AI143197

Dates: 3/1/20 to 2/28/25
Total Direct: \$2,472,220
Annual Direct: \$492,444

Investigator: **Rosch JW**
Title: Pneumococcal pathogenesis in sickle cell disease
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI131620

Dates: 12/1/14 to 11/31/20
Total Direct: \$1,250,000
Annual Direct: \$250,000

Investigator: **Rosch JW (PI Van Opijnen T)**
Title: Predicting the emergence of antibiotic resistance through multi-omics approaches and Immune System-surveillance
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5U01AI124302

Dates: 3/1/16 to 2/28/21
Total Direct: \$9,892,074
Annual Direct: \$291,009

Investigator: **Rosch JW**
Title: Consequences of Direct Viral-Bacteria Interactions
Source: National Institute of Allergy and Infectious Diseases (NIAID)
1R56AI155614

Dates: 07/20/21 to 06/30/22
Total Direct: \$339,210
Annual Direct: \$339,210

Investigator: **Rosch JW (PI Rock)**
Title: Regulation of lipid metabolism in bacteria
Source: National Institute of General Medical Sciences (NIGMS)
5R011GM034496

Dates: 11/19/20 to 11/30/22
Total Direct: \$1,200,000
Annual Direct: \$402,779

Investigator: **Rosch JW (PI Orihuela)**
Title: PspA binds necroptotic cells to cause disease and transmit
Source: National Institute of Allergy and Infectious Diseases (NIAID)
5R01AI156898

Dates: 12/01/20 to 11/30/25
Total Direct: \$1,409,185
Annual Direct: \$281,837

Investigator: **Stultz JS (MPI Peters BM)**
Title: Lipid emulsion composition as a determinant of fungal biofilm formation and incidence of candidemia
Source: National Institute of Allergy and Infectious Diseases (NIAID)

1R21AI153768
Dates: 04/09/21 to 03/31/2022
Total Direct: \$275,000
Annual Direct: \$150,000

Foundation and Industry Funding

Investigator: **Dale JB**
Title: Strengthening the Health System Response to Rheumatic Heart Disease: Developing Evidence-Based Strategies For Prevention
Source: AHA Strategically Focused Research Network Award
Dates: 7/1/17 to 6/30/21
Total Direct: \$1,000,000
Annual Direct: \$316,691

Investigator: **Kumar S**
Title: Exosomes in alcohol-induced HIV-1 pathogenesis and neuronal damage
Source: UTHSC Bridge Grant Program
Dates: 3/1/19 to 2/28/21
Total Direct: \$75,000
Annual Direct: \$37,500

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

Investigator: **Kumar S**
Title: Development of extracellular vesicles-based drug delivery platform for HIV-associated neuronal diseases
Source: UTHSC Plough Center award
Dates: 03/01/20 to 02/28/23
Total Direct: \$300,000
Annual Direct: \$100,000

Publications

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Kiran S, Kumar V, **Kumar S**, Price RL, Singh UP. Adipocyte, Immune Cells, and miRNA Crosstalk: A Novel Regulator of Metabolic Dysfunction and Obesity. *Cells*. 2021 Apr 24;10(5):1004

Kumar A, **Kumar S**. Inhibition of extracellular vesicles pathway using neutral sphingomyelinase inhibitors as a neuroprotective treatment for brain injury. *Neural Regeneration Research*, 2021 Dec;16(12):2349-2352.

Kumar A, Zhou L, Zhi K, Raji B, Pernel S, Tadrous E, Kodidela S, Nookala A, Kochat H, **Kumar S**. Challenges in Biomaterial-Based Drug Delivery Approach for the Treatment of Neurodegenerative Diseases: Opportunities for Extracellular Vesicles. *Int J Mol Sci*. 2020 Dec 25;22(1):138.

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