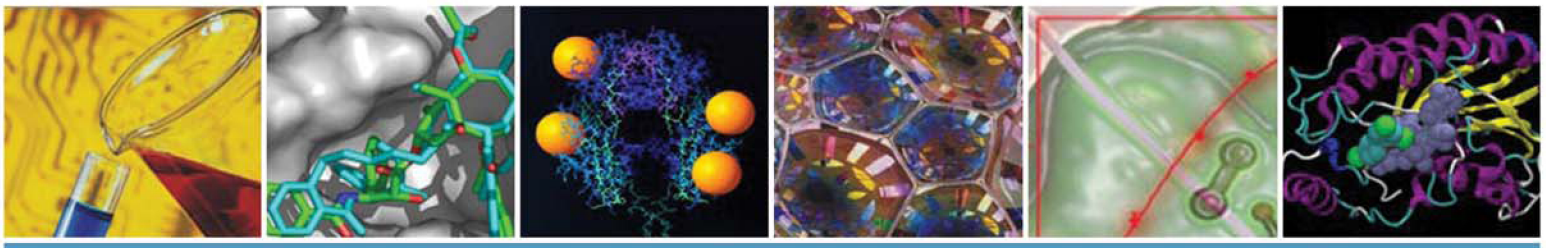
THIRTEENTH ANNUAL SYMPOSIUM

ICB&DD



Institute of Chemical Biology & Drug Discovery

"Frontiers of Infectious Disease Control"

Thursday, October 10, 2019

Charles B. Wang Center

Stony Brook University

From the Director

The primary objective of the Institute of Chemical Biology & Drug Discovery (ICB&DD) is to establish and sustain a world-class "Center of Excellence" in chemical biology and drug discovery at Stony Brook University. The rapid and impressive advancements in chemical biology during the last decade have clearly demonstrated that solutions for a vast majority of medical problems rely on the understanding of the molecular basis of diseases, therapeutic targets, drug actions, and drug resistance. ICB&DD promotes highly productive interdisciplinary and collaborative research among chemists, biologists, medicinal chemists, pharmacologists, and physicians to tackle major biomedical problems to find solutions including the discovery of novel therapeutic drugs and innovative diagnostic tools.

—Iwao Ojima, Director, Institute of Chemical Biology & Drug Discovery

Dr. Iwao Ojima received his B.S., M.S., and Ph.D. (1973) degrees from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position of Senior Research Fellow until 1983. He joined the faculty at the Department of Chemistry, State University of New York at Stony Brook first as Associate Professor (1983), was promoted to Professor (1984), Leading Professor (1991), and then to Distinguished Professor (1995). He served as the Department Chairman from 1997 to 2003. He has been serving as the founding Director for the Institute of Chemical Biology and Drug Discovery (ICB&DD) from 2003. He has a wide range of research interests in synthetic organic and medicinal chemistry as well as chemical biology, including discovery and development of anticancer agents, antimicrobials, and targeted drug delivery systems. His awards and honors include Arthur C. Cope Scholar Award (1994), E. B. Hershberg Award for Important Discoveries of Medicinally Active Substances (2001), the Medicinal Chemistry Hall of Fame (2006), ACS Award for Creative Work in Fluorine Chemistry (2013), and E. Guenther Award in the Chemistry of Natural Products (2019, named) from the American Chemical Society; the Chemical Society of Japan Award (1999); Outstanding Inventor Award (2002) from the Research Foundation of the State University of New York; Elected Fellow of J. S. Guggenheim Memorial Foundation, the American Association for the Advancement of Science, the New York Academy of Sciences, the American Chemical Society and the National Academy of Inventors.

ICB&DD's History and Mission

The ICB&DD was established in 2004 with Stony Brook University's institutional support as well as the NYSTAR Faculty Development Award. One of ICB&DD's strengths is that it has been founded by reorganizing existing exceptional talents on campus, and thus the core of the institute is a well proven entity with an excellent track record. ICB&DD is open to a wide range of collaborative research programs with pharmaceutical and biotechnology industrial firms. Members of ICB&DD are from the departments of Chemistry, Pharmacological Sciences, Medicine, Molecular Genetics and Microbiology, Biochemistry and Cellular Biology, Physiology and Biophysics, Applied Mathematics and Statistics, Oral Biology and Pathology, Cancer Center, Center for Structural Biology, Center for Infectious Diseases, and Brookhaven National Laboratory. In addition, ICB&DD has two core laboratories located in the Chemistry Building: Analytical Instrumentation Laboratory and Discovery Chemistry Laboratory.

ICB&DD has three major programs: Structural and Computational Biology Program, Infectious Diseases Research Program, and Cancer Research Program. In addition, ICB&DD has two strategic Research Laboratories on Cancer Stem Cell Research and Anti-inflammatory Research. ICB&DD collaborates with the Stony Brook University Cancer Center to develop a Cancer Therapeutics Program. ICB&DD integrates the existing strengths at Stony Brook University in the basic medical sciences as well as medicinal chemistry and brings in complementary expertise from outside to explore drug discovery and development. At present, ICB&DD focuses on drug discovery in therapeutics for cancer, infectious diseases, neurodegenerative diseases and inflammation.

Through ICB&DD connections, a number of collaborative research teams have been created and research proposals have successfully acquired grants from NIH and other funding agencies. (Total grant funding > 54M). Currently, there are 15 ongoing ICB&DD-designated projects (Total funding: $18.1M).

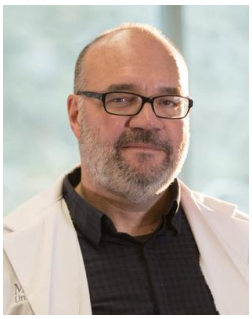
ICB&DD 13th Annual Symposium

Thursday, October 10, 2019

"Frontiers of Infectious Disease Control"

9:15 am to 9:30 am	**Opening Remarks** Dr. Maurizio Del Poeta, Professor of Microbiology and Immunology. Chair, Symposium Organizing Committee Dr. Nicole Sampson, Distinguished Professor and Interim Dean, College of Arts and Sciences Dr. Iwao Ojima, Distinguished Professor and Director, Institute of Chemical Biology and Drug Discovery, Stony Brook University
9:30 am to 10:15 am	*Moderator*: Dr. Jessica Seeliger **Dr. Gerry Wright**, Professor, Biochemistry and Biomedical Sciences, McMaster University. Director, Michael G. DeGroote Institute for Infectious Disease Research. Canada Research Chair in Antimicrobial Biochemistry ***"Back to the Future: Revisiting Natural Products in Antibiotic Discovery"***
10:15 am to 11:00 am	*Moderator*: Dr. Isaac Carrico **Dr. Peter Tonge,** Professor and Chairman, Department of Chemistry, Stony Brook University ***"Translating Slow-Binding Enzyme Inhibition Into Prolonged Antibacterial Activity"***
11:00 am to 11:45 am	*Moderator*: Dr. Elizabeth Boon **Dr. Alita Miller**, Head of Bioscience, Entasis Therapeutics ***"A Novel Class of Gram-Negative PBP Inhibitors Discovered using Rational Design of Both Biochemical Potency and Bacterial Permeation"***
11:45 am to 1:00 pm	**Lunch and Poster Session** Chapel *(invited faculty only)* Zodiac Gallery *(students)*
1:00 pm to 1:45 pm	*Moderator*: Dr. Eszter Boros **Dr. Marvin Miller,** Professor Emeritus, Department of Chemistry and Biochemistry, University of Notre Dame ***"Design, Syntheses and Studies of Antibiotics to Circumvent Bacterial Resistance"***
1:45 pm to 2:30 pm	*Moderator*: Dr. Maurizio Del Poeta **Dr. John Perfect** James B. Duke Professor of Medicine. Chief, Division of Infectious Diseases, Duke University School of Medicine ***"New Antifungal Agents and Strategies"***
2:30 pm to 3:30 pm	**Coffee Break and Student Poster Session** Theatre Lobby and Zodiac Gallery
3:30 pm to 4:15 pm	*Moderator*: Michael Airola **Dr. Michal Olszewski** Associate Professor, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine University of Michigan Medical School ***"Cryptococcal Interactions with Pulmonary and CNS Host-Defenses: Implications for Immunotherapy"***
4:15pm to 5:00pm	*Moderator*: Dr. Adam Rosebrock **Dr. Peter Smith**, Scientist, Department of Infectious Diseases, Genentech ***"Optimized Arylomycins are a New Class of Gram-Negative Antibiotic"***
5:00 pm to 5:05pm	**Closing Remarks:** Dr. Adam Rosebrock
5:05 pm to 6:00pm	**Reception and Poster Session *(three poster awards)*** Theatre Lobby and Zodiac Gallery
6:00 pm to 6:15 pm	**Announcement of Poster Awards:** Dr. Eszter Boros Theatre Lobby
6:15 pm	**DINNER,** Chapel *(by invitation only)*

Speakers



Dr. Gerry Wright is the Director of the Michael G. DeGroote Institute for Infectious Disease Research and the David Braley Centre for Antibiotic Discovery. He is a Professor in the Department of Biochemistry and Biomedical Sciences at McMaster University and holds the Michael G. DeGroote Chair in Infection and Anti-Infective Research and a Tier 1 Canada Research Chair in Antibiotic Biochemistry. From 2001-2007 Dr. Wright served as Chair of the Department of Biochemistry and Biomedical Sciences at McMaster. He was elected as a Fellow of the Royal Society of Canada (2012) and a fellow of the American Academy of Microbiology (2013). He is the recipient of a Killam Research Fellowship (2011-1012), R.G.E. Murray Award for Career Achievement of the Canadian Society of Microbiologists (2013) and the NRC Research Press Senior Investigator Award from the Canadian Society for Molecular Biosciences (2016), Premier's Research Excellence (1999) and the Polanyi Prize (1993). He is the co-founder of the Canadian Anti-Infective Innovation Network (www.cain-amr.ca). He has trained over 70 graduate students and postdocs and is the author of over 260 manuscripts and is a member of the editorial boards of several peer-reviewed journals. Gerry is the co-founder of Symbal Therapeutics. In 2016 he was named a McMaster Distinguished University Professor, the highest academic honor at the university. Dr. Gerry Wright received his BSc in Biochemistry (1986) and his PhD in Chemistry (1990) from the University of Waterloo working in the area of antifungal drugs under Dr John Honek. He followed this up with 2 years of postdoctoral research in Chris Walsh's lab at Harvard Medical School in Boston where he worked on the molecular mechanism of resistance to the antibiotic vancomycin in enterococci. He joined the Department of Biochemistry at McMaster in 1993. His research interests are in the origins and mechanisms of antibiotic resistance and the discovery of new anti-infective strategies, in particular focusing on the application of microbial natural products and synthetic biology towards this goal.

"Back to the Future: Revisiting Natural products in Antibiotic Discovery"

The selection for multidrug resistant infectious pathogens and their global distribution is fueling the need for new antibiotics and their alternatives. Natural products from bacteria and fungi are the traditional sources for our antibiotics used in human and animal health, however, the antibiotic discovery and development sector have largely pivoted away from these molecules towards synthetic compounds over the past three decades with poor results. The move away from natural products in antibiotic discovery was prompted, among other things, by the frequent rediscovery of known scaffolds with a resulting lack of new chemical diversity, the chemical complexity and low yields of many natural products that is incompatible with modern high throughput discovery, the challenges of identifying new biological sources of compounds, and a focus on single agent broad spectrum candidates. The 21st Century genomic era offers creative solutions to many of these drawbacks. In this presentation, I will cover our efforts to build a library of producers of natural products and the use of modern genomic technologies to identify new and rare compound scaffolds and the repurposing of known ones for new uses.

Dr. Peter Tonge is a Distinguished Professor of Chemistry and of Radiology (by courtesy) at Stony Brook University, where he is the Chair of the Department of Chemistry, Director of the Center for Advanced Study of Drug Action (CASDA) and the co-Director of the NIH-funded T32 Chemical Biology Training Program. He is also an Associate Editor for ACS Infectious Diseases. Dr. Tonge earned his B.Sc. and Ph.D. degrees in Biochemistry from Birmingham University, UK, and was a SERC/NATO post-doctoral fellow in the Division of Biological Sciences at the National Research Council of Canada (NRCC). After positions as a Research Associate and Research Officer at NRCC, he was a Staff Investigator at the Picower Medical Research Institute before joining Stony Brook University. His awards include an Alfred P. Sloan Research Fellowship in 2000 and a Fellowship from the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation in 2017 which funded a sabbatical at Genentech. He has over 200 publications and patents and has graduated 58 students. His research program combines kinetic, structural, synthetic, computational and biophysical approaches including ultrafast spectroscopy to develop inhibitors of enzyme drug targets, and understand the mechanism of photoreceptors and optogenetic devices. A primary interest of his program, which provides the foundation for CASDA, is to develop drugs that have extended target engagement, which should enable dosing frequency and exposure to be reduced, resulting in decreased side effects and increased compliance. This is aided by the use of quantitative pharmacology to design pharmacokinetic/pharmacodynamic models that integrate drug-target kinetics into the prediction of drug activity in humans, and the use of positron emission tomography to non-invasively image drug bio distribution. His interests in translational research also led him to co-found the START-UP NY company Chronus Pharmaceuticals Inc. to provide a mechanism for the commercialization of novel therapeutics and diagnostics.

"Translating Slow-Binding Enzyme Inhibition into Prolonged Antibacterial Activity"

Time-dependent enzyme inhibitors are of particular interest in drug discovery programs since the rate of complex dissociation (k_{off}) can be slower than the time scale of *in vivo* drug elimination, leading to sustained target occupancy at low drug concentration, enabling dosing frequency and exposure to be reduced and thus improving the therapeutic window. However, the translation of sustained occupancy to prolonged drug activity depends on factors such as target vulnerability and the rate of target turnover which in turn impact the potential benefits of kinetic selectivity. To provide direct insight into target vulnerability we are developing time-dependent inhibitors of antibacterial targets and determining the factors that modulate the translation of slow, tight-binding enzyme inhibition to antibacterial activity at the whole cell and whole organism level. A mechanistic PK/PD model that incorporates drug-target kinetics provides a framework to model and test hypotheses of time-dependent changes in antibacterial activity following compound washout.

Speakers

Dr. Alita Miller is a Senior Director and Head of Bioscience at Entasis Therapeutics, a small biotech outside of Boston dedicated to the discovery and development of novel antibacterial agents to treat serious infections by resistant Gram-negative bacteria. At Entasis, Dr. Miller oversees both preclinical biology and clinical microbiology research. As a member of the senior leadership team, she is also involved in the strategic planning and execution of the company's long-term research objectives. Alita has over 15 years of experience in antibacterial research, first at Pfizer where she led both large and small molecule discovery projects and then at AstraZeneca, where she was Head of Microbial Genetics and Genomics. Alita serves on several government review panels for proposals related to the field, is on the target selection board for NIAID Structure Genomics Centers of Infectious Diseases and is a member of the ASM Microbe program committee. She obtained a BA in Chemistry from Kalamazoo College and a PhD in Biochemistry and Molecular Biology from the University of Chicago. Her postdoctoral training was in the DiRita lab at the University of Michigan characterizing the molecular drivers of pathogenesis in *Streptococcus pyogenes*. Alita's current research interests include novel approaches to antibacterial discovery, including new ways of characterizing small molecule permeation and accumulation in bacterial pathogens.

"A Novel Class of Gram-Negative PBP inhibitors Discovered Using Rational Design of Both Biochemical Potency and Bacterial Permeation"

The emergence of antibiotic resistance, especially in Gram-negative bacteria, is an urgent threat to public health. The discovery of novel antibacterial agents against these pathogens has been impeded by a fundamental lack of understanding of the molecular drivers governing cellular permeation. An innovative, two-prong rational design approach was used to discover a novel class of non-β-lactam PBP inhibitors with Gram-negative antibacterial activity, including *Pseudomonas aeruginosa*. Using structure-based drug design, we selectively shifted target inhibition from PBP2 to PBP3/PBP1a which translated into robust *in vivo* activity in murine infection models. This new compound class maintains activity in the presence of all four classes of β-lactamases. Uptake and efflux were identified as features to increase potency against recent MDR *P. aeruginosa* clinical isolates. Overall, these results represent a new path towards a promising IV monotherapy to treat multi-drug resistant Gram-negative infections.

Dr. Marvin Miller Is the George and Winifred Clark Professor Emeritus of Chemistry and Biochemistry at University of Notre Dame. Professor Miller received his B.S. in chemistry from North Dakota State University in 1971, his Ph.D. from Cornell University in 1976 and postdoctoral studies as a National Institutes of Health fellow in the Department of Chemistry at the University of California at Berkeley (1975-77). He joined the chemistry faculty at Notre Dame in 1977 and is now emeritus. He is a co-founder of Hsiri Therapeutics. The primary interests in Professor Miller's laboratory are in synthetic, bioorganic and medicinal chemistry. The Miller group has benefitted from dedicated efforts of more than 150 graduate students, postdocs and research associates as well as numerous visiting scholars, undergraduates and collaborators throughout the world. Most attention has been directed toward the development of new methodology and its incorporation into the syntheses and study of biologically important compounds. Special emphasis is given to asymmetric syntheses and studies of hydroxamic acid containing microbial iron transport agents (siderophores), amino acids, peptides, β-lactam antibiotics and carbocyclic analogs of antifungal and anticancer nucleosides. Recent efforts have been directed toward the syntheses and study of anti-TB agents and siderophore-antibiotic conjugates for iron transport-mediated drug delivery. Professor Miller has a wonderful supportive family. He and his wife, Patty (who also is a research collaborator and coworker) have four grown children and eleven grandchildren.

"Design, Syntheses and Studies of Antibiotics to Circumvent Bacterial Resistance"

New or repurposed antibiotics are desperately needed since bacterial resistance has risen to essentially all of our current antibiotics and few new antibiotics have been developed over the last several decades. A primary cause of drug resistance is the overuse of antibiotics that can result in alteration of microbial permeability, alteration of drug target binding sites, induction of enzymes that destroy antibiotics (ie., beta-lactamases) and even induction of efflux mechanisms. A combination of chemical syntheses, microbiological and biochemical studies demonstrate that the known critical dependence of iron assimilation by microbes for growth and virulence can be exploited for the development of new approaches to antibiotic therapy. Iron recognition and active transport relies on the biosynthesis and use of microbe-selective iron chelating compounds called siderophores. Our studies, and those of others, demonstrate that siderophores and analogs can be used for iron transport-mediated drug delivery ("Trojan Horse" antibiotics or sideromycins) and induction of iron limitation/starvation (development of new agents to block iron assimilation). Several examples will illustrate that, aided by chemical syntheses, this approach can generate microbe selective antibiotics. The scope and limitations of this approach, especially related to "microbe adaptability" and development of resistance, siderophore based molecular recognition requirements, appropriate linker and drug choices will be described.

Speakers

Dr. John Perfect is the James B. Duke Professor of Medicine, Professor of Molecular Genetics and Microbiology and Chief of Infectious Diseases at Duke University School of Medicine. He received his M.D from University of Toledo (1974) and did an internship at Riverside Methodist Hospital (1974-1975). He was a medical resident at University of Michigan at Ann Arbor (1975-1977) and a fellow in Infectious Diseases at Duke University School of Medicine (1977-1980) and study under the mentorship of Dr. David Durack. In his fellowship, he studied various aspects of treatment and pathogenesis for bacterial and fungal meningitis and endocarditis. He started on the faculty at Duke University Medical Center in 1980 and focused on animal models and pathogenesis of fungal infections. He was elected a member of the Association of American Physicians (AAP) in 2001, and was elected a fellow of the American Academy of Microbiology (AAM) in 2004 and a fellow of the American Association for the Advancement of Science (AAAS) in 2007. Dr. Perfect's general research focus for four decades has been on cryptococcosis: pathogenesis and management. He also investigates other fungal infections through translational and clinical trials. He interacts as a consultant for many pharmaceutical companies in the antifungal space. Along with his basic science research portfolio, he also attends to patients at the beside. He is President of the Mycoses Study Group (MSG) based in USA and President-elect of the international Society of Human and Animal Mycology (ISHAM).

"New Antifungal Agents and Strategies"

Invasive Fungal Infection (IFIs) continues to be major complications for the enlarging immunocompromised host populations. IFIs produce substantial morbidity and mortality. At present, the clinicians have only three classes of antifungal agents (polyenes, azoles and echinocandins) available to manage these IFIs. For improvement in IFI outcome we need better diagnostic strategies and new effective fungicidal drugs. In this presentation, I will review the new antifungal agents and molecules in development. There is a rich portfolio of potential drugs or inhibitor discoverers with new targets and impressive potential fungicidal activity. The challenge of management of IFIs remain but the research and development in this pace is occurring at several levels and this is encouraging. The delivery of new antifungal drugs will not be easy but the platform of discovery and strategies of use are well developed and well placed. The need of new antifungal agents is great and in multiple reports industry/academia partnerships are "all in" to find new agents to meet the clinical demand.

Michal Olszewski is an Associate Professor of the Division of Pulmonary and Critical Care Medicine Department of Internal Medicine at University of Michigan Medical School. He earned his D.V.M. degree in 1988 from Warsaw University of Life Sciences and completed his Ph.D. in 1997 at the College of Veterinary Medicine at Michigan State University, studying the pathogenesis of inflammatory airway diseases. After completing a postdoctoral fellowship with the Division of Pulmonary and Critical Care Medicine at the University of Michigan and Career Development Training at the Department of Veteran's Affairs Ann Arbor Medical Center, he was appointed as a Faculty Member at both of these institutions. At present, he holds the rank of Associate Professor at the University of Michigan and is appointed as Research Career Scientist at the Department of Veterans' Affair. He serves as a Section Editor for the *Journal of Immunology* and on Editorial Boards of *Infection and Immunity*, Frontiers in *Microbiology* and *PLOSOne*. Dr. Olszewski is recognized for his studies on *C. neoformans* with the host's immune system. He defined the immunomodulatory effects of several cryptococcal virulence genes and studied the role of cellular and molecular components of host defense, including myeloid cell subsets, T-cells, and specific cytokines, chemokines and pattern recognition receptors. The common theme of this work is determining how specific microbial factors aid the organism in immune evasion and how they could be targeted for therapeutic purposes, as well as how immunomodulation can aid immune protection and/or immunopathology.

"Cryptococcal Interactions with Pulmonary and CNS Host-Defenses: Implications for Immunotherapy"

In this presentation, we will address a number of studies focused on immunomodulation and comment on the translational values of these findings in reference to immunotherapy. As a result of immunotherapy (cytokine neutralization, receptor blockades, targeted suppression of cell subsets), patients become highly susceptible to fungal infections. On the other hand, immune reconstitution or immune boost therapies may lead to exuberant responses which become more lethal to the host than the infecting microbe. In this context, mechanisms of immune disruption post-anti-tumor necrosis factor-alpha (TNF-α) therapy with consequences on anti-fungal immunity will be presented in the first part of the talk. The development of ultra-Th1 response in the *Cryptococcus*-infected CNS and the mechanisms of resultant immunopathology will be presented in the second part of the talk. Our findings on how cryptococcal interactions with pulmonary and CNS host-defenses determine *C. neoformans* pathogenesis under immunosuppressive or immune-boosting immunotherapies will be highlighted. The translational implications of our studies for immunosuppressive and immune-boosting immunotherapies will be discussed.

Speakers

Peter Smith is a Scientist and group leader in the Infectious Diseases department at Genentech. Dr. Smith's laboratory group is interested in the basic biology of Gram-negative cell envelope biogenesis and in identifying molecular targets and processes that have the genetic and physicochemical properties suitable for antibacterial discovery and development. Prior to joining Genentech in 2014, Dr. Smith was a scientific co-founder and lead biologist at RQx Pharmaceuticals, a La Jolla California based biotechnology company focused on discovering novel broad-spectrum antibiotics. Dr. Smith received his BA in biology and chemistry from Purdue University and his PhD from Scripps Research in La Jolla, CA.

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Optimized Arylomycins are a New Class of Gram-Negative Antibiotic"

Multidrug-resistant bacteria are spreading at alarming rates, and despite extensive efforts no new class of antibiotic with activity against Gram-negative bacteria has been approved in over fifty years. Historically, natural products and their derivatives have played a key role in combating Gram-negative pathogens. In this presentation, I will describe the optimization of the arylomycins -a class of natural products with weak activity and limited spectrum- to obtain G0775, a molecule with potent, broad-spectrum activity against Gram-negative bacteria. G0775 inhibits the essential bacterial type I signal peptidase, a new antibiotic target, through an unprecedented molecular mechanism. It circumvents existing antibiotic resistance mechanisms and retains activity against contemporary multidrug-resistant Gram-negative clinical isolates *in vitro* and in several *in vivo* infection models. Additionally, I will address several mechanisms by which spontaneous resistance to G0775 can emerge and strategies to minimize such resistance *in vivo*.

NOTES_____

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