BIOMEDICAL & VETERINARY SCIENCES

GRADUATE PROGRAM

ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Marigold E. Ernst

“Characterization, toxicity, and biological activities of organometallic compounds and peptide nucleic acids for potential use as antimicrobials”

Thursday, March 28, 2019
10:00 am
Virginia-Maryland College of Veterinary Medicine Classroom 100 (Phase III)

Bio

Marigold grew up in Hempstead, NY and graduated from Rochester Institute of Technology with a BS in Biology. She received her DVM from the Purdue University College of Veterinary Medicine in 2010 and worked in small animal general and emergency practice for several years. In 2013 she began a combined veterinary clinical pathology residency and Biomedical and Veterinary Sciences PhD program at the Virginia-Maryland College of Veterinary Medicine. She achieved board certification in veterinary clinical pathology from the American College of Veterinary Pathologists in 2016. She is currently employed as a veterinary clinical pathologist with IDEXX Laboratories in Glen Burnie, MD.

Funded by

VMCVM Office of Research and Graduate Studies

Stamps Family Charitable Foundation, Inc.

VCOM-VMCVM Center for One Health Research seed grant

Virginia Tech Center for Drug Discovery small grant

Lay Language Abstract

Antibiotic-resistant bacteria are increasingly recognized as a threat to global health, and new antibacterial drugs are urgently needed. Before a chemical compound can advance far in the journey to becoming a new drug it must be tested for toxicity against mammalian cells. A portion of this dissertation research involved testing the toxicity of several organometallic compounds (OMCs) previously shown to have antibacterial potential. Mouse-derived mammalian cells were treated with several of the OMCs, and initial results indicated that one of the OMCs is non-toxic and is likely a safe option for additional analysis. This OMC was further tested to see if it could inhibit mycobacterial growth inside of the mammalian cells. It did not effectively clear bacteria from inside of the mammalian cells, likely because of poor penetration of the cell membrane. Further research with this compound should focus on ways to effectively transport the OMC inside infected mammalian cells so that it can reach the bacteria it is meant to target. A second portion of this research involved using a peptide nucleic acid (PNA) to try and reverse tetracycline antibiotic resistance in the bacterial strain Salmonella enterica ssp enterica serovar Typhimurium DT104 (DT104). Peptide nucleic acids are short linear molecules that can bind strongly to complementary DNA and RNA sequences and thus be used to interfere with expression of specific genes. A PNA was designed to inhibit expression of the bacterial tetA gene that codes for a protein called the TetA tetracycline efflux pump, which imparts resistances to tetracycline. Treating the bacteria with the PNA resulted in a lower dose of tetracycline needed to inhibit

bacterial growth, indicating a successful increase in tetracycline susceptibility. By using a molecular analysis technique called reverse-transriptase quantitative polymerase chain reaction (RT-qPCR), it was possible to measure the amount of tetA messenger RNA (mRNA) in cultures of DT104 treated only with tetracycline or with a combination of tetracycline and the PNA. As expected, bacteria treated with both the antibiotic and the PNA had less tetA mRNA than the cultures treated only with tetracycline, supporting the hypothesis that the PNA prevents the bacteria from effectively expressing the tetA gene. The PNA was next used in conjuction with tetracycline as an experimental treatment for mice infected with DT104. The PNA did not provide the expected protective effect under these circumstances. The overall conclusion for this part of the research is that PNAs offer an exciting potential avenue for counteracting antibiotic resistance, but additional exploration is needed, especially into more effective ways to get the PNAs inside the bacteria and into how the PNAs behave in live animals. Several other PNAs targeting different genes involved in antibiotic resistance or essential bacterial functions were also tested against DT104 with variable success.

Publications

M. Ernst, N. Weinstein, K. M. Boes, K. E. Wilson, and W. F. Gilsenan. Pathology in Practice. J Am Vet Med Assoc. 2016. 249(1):59-62

Manuscripts to be submitted:

Eukaryotic cell cytotoxicity and cellular penetration of novel organometallic compounds with inhibitory activity against nontuberculous mycobacteria. Marigold E. Ernst and Joseph S. Merola. Journal Organometallic compounds.

Peptide nucleic acids targeting expression of tetracycline resistance genes increase tetracycline susceptibility in multidrug-resistant *Salmonella enterica* ssp*. enterica* serovar Typhimurium DT104. Marigold E. Ernst and Nammalwar Sriranganathan. Journal of bacteriology or Journal of Veterinary Microbiology.

Development of a clinically relevant mouse model of *Salmonella enterica* ssp*. enterica* serovar Typhimurium oral infection. Marigold E. Ernst and Nammalwar Sriranganathan

Presentations

M. Ernst, N. Sriranganathan, S. M. Boyle, and M. R. Prater. Peptide nucleic acid-mediated suppression of the tetracycline efflux pump as a method to increase tetracycline susceptibility of multidrug-resistant Salmonella enterica ssp. enterica serovar Typhimurium DT104. Poster presentation at the 29th Annual Biomedical and Veterinary Sciences (BMVS) Graduate Student Research Symposium, VMCVM, Blacksburg, VA, March 2018

M. Ernst, N. Sriranganathan, S. M. Boyle, and M. R. Prater. Reversing drug resistance in Salmonella Typhimurium DT104. Poster presentation at the 2017 Summit of the Virginia Academy of Science, Engineering, and Medicine: Emerging Infections and Preparedness, Washington, D. C., October 2017

M. Ernst, S. M. Boyle, M. R. Prater, and N. Sriranganathan. Peptide nucleic acid-mediated suppression of the tetracycline efflux pump to increase tetracycline susceptibility of multi-drug resistant Salmonella enterica Typhimurium DT104. Poster presentation at the ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, Boston, MA, September 2017

M. Ernst. Cytology of inflammation and infectious agents. Lecture at the VMCVM Clinical Pathology Course for Anatomic Pathologists. VMCVM, Blacksburg, Virginia, July 2017

M. Ernst. Hemostasis. Lecture at the VMCVM Clinical Pathology Course for Anatomic Pathologists. VMCVM, Blacksburg, Virginia, July 2017

M. Ernst, N. Sriranganathan, S. M. Boyle, and M. R. Prater. Peptide nucleic acid-mediated suppression of the tetracycline efflux pump as a method to increase tetracycline susceptibility of multidrug-resistant Salmonella enterica ssp. enterica serovar Typhimurium DT104. Poster presentation at the 29th Annual Biomedical and Veterinary Sciences (BMVS) Graduate Student Research Symposium, VMCVM, Blacksburg, VA, March 2018

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M. Ernst, S. M. Boyle, M. R. Prater, and N. Sriranganathan. Peptide nucleic acid-mediated suppression of the tetracycline efflux pump to increase tetracycline susceptibility of multi-drug resistant Salmonella enterica Typhimurium DT104. Poster presentation at the ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance, Boston, MA, September 2017

M. Ernst. Cytology of inflammation and infectious agents. Lecture at the VMCVM Clinical Pathology Course for Anatomic Pathologists. VMCVM, Blacksburg, Virginia, July 2017

M. Ernst. Hemostasis. Lecture at the VMCVM Clinical Pathology Course for Anatomic Pathologists. VMCVM, Blacksburg, Virginia, July 2017

M. Ernst, S. M. Boyle, M. R. Prater, and N. Sriranganathan. Peptide nucleic acids targeting expression of the tetracycline efflux pump and an antibiotic regulatory region cause decreased tetracycline resistance in Salmonella Typhimurium DT104. Poster presentation at the 28th Annual BMVS Graduate Student Research Symposium, VMCVM, Blacksburg, VA, March 2017

M. Ernst, K. M. Boes, and G. K. Saunders. A diagnostically challenging splenic mass in a dog. Oral case presentation at the ACVP/ASVCP Annual Meeting, Mystery Slide Session, New Orleans, LA, December 2016

M. Ernst, C. Duchane, J. Merola, N. Sriranganathan, S. M. Boyle, S. Elswaifi, and M. R. Prater. Strategies to combat antimicrobial-resistant intracellular bacteria. Poster presentation at the 27th Annual BMVS Graduate Student Research Symposium, VMCVM, Blacksburg, VA, March 2016

M. Ernst and S. G. Waldrop. Control of intracellular bacterial infections: Research into novel vaccine and antibiotic strategies. Oral presentation at the Research in Progress Seminar, Virginia-Maryland College of Veterinary Medicine, Blacksburg, Virginia, February 2016.

M. E. Putnam, **M. E. Ernst,** and K. M. Boes. Canine T-zone lymphoma: Are findings from hematology, cytology, flow cytometry, and PARR enough? Poster presentation at the ACVP/ASVCP Annual Meeting, Veterinary Student Poster Session, Minneapolis, MN, October 2015

M. Ernst. Hemostasis. Lecture at the VMCVM Clinical Pathology Course for Anatomic Pathologists. Virginia-Maryland College of Veterinary Medicine, Blacksburg, Virginia, August 2015

M. Ernst, N. Weinstein, and T. LeRoith. Concurrent seminoma and Sertoli cell tumor in a German Shepherd Dog. Oral case presentation at the 43rd Annual SouthEastern Veterinary Pathology Conference, Tifton, Georgia, May 2015.

M. Ernst, K. M. Boes, and T. LeRoith. Chronic myelomonocytic leukemia in a dog. Oral case presentation at the 42nd Annual SouthEastern Veterinary Pathology Conference, Tifton, Georgia, May 2014.

M. Ernst, G. Karpin, J. Merola, M. Ehrich, and K. Boes. Exploration into the mechanism of action of iridium, rhodium, and cobalt organometallic complexes with antibacterial activity. Poster presentation at the 26th Annual BMVS Graduate Student Research Symposium, VMCVM, Blacksburg, VA, March 2015

Awards and Academic Achievements

Charles Louis Davis, DVM Foundation Student Scholarship Award 2016

Diplomate, American College of Veterinary Pathologists (Clinical Pathology) 2016

Examination Graduate Committee

Major Advisor/Chair:

Nammalwar Sriranganathan, BVSc, MVSc, PhD, Diplomate, ACVM (Co-chair)
Professor, Bacteriology
Department of Biomedical Sciences & Pathobiology

Joseph Merola, PhD (Co-chair)
Professor, Inorganic Chemistry
Department of Chemistry

Graduate Advising Committee Members:

Katie M. Boes, DVM, MS, Diplomate, ACVP

Clinical Associate Professor, Clinical Pathology
Department of Biomedical Sciences & Pathobiology

Marion F. Ehrich, MS, RPh, PhD, Diplomate, ABT
Professor, Pharmacology, Toxicology
Department of Biomedical Sciences & Pathobiology

External Examiner

Qijing Zhang, BVsc, MS, PhD

Clarence Hartley Covault Distinguished Professor
Frank Ramsey Endowed Chair in Veterinary Medicine
Associate Dean for Research and Graduate Studies
Iowa State University College of Veterinary Medicine

Seminar title: Emergence and pathogenesis of hypervirulent Campylobacter jejuni: Impact on One Health
Friday, March 29, 2019
8-9:30 am
Fralin Auditorium

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