

**BIOMEDICAL & VETERINARY SCIENCES
GRADUATE PROGRAM**



ANNOUNCES

The Doctor of Philosophy Seminar
and Examination of

Erica Twitchell

**“Influence of Enteric Microbiota on Human Rotavirus and
Human Norovirus Infection, and Rotavirus Immunity in
Gnotobiotic Pigs”**

Thursday November 15, 2018

9:00 AM

ILSB 1040

Bio



Erica obtained her BS in Pathobiology from the University of Connecticut. She obtained her DVM and MS in Comparative Pathobiology from Purdue University. She completed a residency in anatomic pathology at Purdue University and is a diplomate of the American College of Veterinary Pathologists. In 2014 Erica joined the laboratory of Dr. Lijuan Yuan to begin work on a PhD. Erica is currently employed as a veterinary pathologist by Charles River Laboratories.

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Virginia-Maryland College of Veterinary Medicine, Department of
Biomedical Sciences and Pathobiology

Office of Research and Graduate Studies

Lay Language Abstract

Intestinal microbiota is known to influence intestinal viral disease and host response to disease. Similarly, microbiota can influence the host response to vaccination. Oral vaccine efficacy is decreased in low-middle income countries compared to higher income countries, and composition of intestinal microbiota is thought to play a role. We used gnotobiotic pigs to study the effect of human gut bacteria on human rotavirus and human norovirus infection and host response.

We used gnotobiotic pigs colonized with infant gut bacteria to demonstrate how composition of intestinal bacteria influences clinical signs of human rotavirus infection, shedding of virus, host response to oral vaccination, and vaccine efficacy. Pigs colonized with “healthy” infant gut bacteria had more rotavirus specific IFN- γ producing T cells in multiple tissues compared to pigs colonized by “unhealthy” infant gut bacteria after vaccine administration. “Healthy gut bacteria induced a stronger cell-mediated immune response than “unhealthy gut bacteria”. Significant correlations existed between specific types of bacteria and the frequencies of IFN - γ producing T cells after vaccine administration. There were significant correlations between specific genera of bacteria and CD8+ and/or CD4+ T cells in multiple tissues. Composition of gut bacteria changed after rotavirus challenge. Correlation of certain bacteria with T cell responses, along with alterations in microbiome composition after rotavirus challenge warrant further investigation into the role gut bacteria play in enteric viral infection and the response of the host to the pathogen and vaccination.

We used gnotobiotic pigs to evaluate the effect of human gut bacteria on clinical signs of norovirus (HuNoV) infection, viral shedding and tissue titers, and host transcriptome response to infection. Gnotobiotic pigs colonized by gut bacteria from a health infant and challenged with human norovirus (HGM+HuNoV) had greater shedding of virus, and shed virus longer than pigs only infected with HuNoV. HGM+HuNoV pigs had more severe diarrhea and longer duration of diarrhea compared to the HuNoV pigs on days 4-10 after infection. Viral titers in the duodenum and distal ileum were higher in HGM+HuNoV pigs compared to HuNoV pigs. There were genes consistently and highly upregulated in HGM+HuNoV pigs compared to HuNoV pigs 3 days after HuNoV infection. These genes were in the category “immune system

process". As a whole, these results demonstrated the influence of HGM on HuNoV infection, and alteration in host gene expression in the gnotobiotic pig model.

Publications

Lei S, **Twitchell E**, Yuan L. Pathogenesis, immunity and the role of microbiome/probiotics in enteric virus infections in human and animal models. In Mechanisms underlying host-microbiome interactions in pathophysiology of human diseases. Sun, J., Dudeja, P.K. edit, Springer 2018.

Bui T, Li G, Kim I, Wen K, **Twitchell EL**, Lei S, Ramesh AK, Weiss MD, Yang X, Clark-Deener SG, Choy RKM, Yuan L. Racecadotril reduces human rotavirus diarrhea and prevents weight loss in neonatal gnotobiotic pigs (*Sus scrofa domestica*). *Comp Med*. 2017.

Becker-Dreps S, Vilchez S, Bucardo F, **Twitchell E**, Choi WS, Hudgens MG, Perez J, Yuan L. The Association Between Fecal Biomarkers of Environmental Enteropathy and Rotavirus Vaccine Response in Nicaraguan Infants. *Pediatr Infect Dis J*. 2016.

Twitchell EL, Tin C, Wen K, Zhang H, Becker-Dreps S, Azcarate-Peril MA, Vilchez S, Li G, Ramesh A, Weiss M, Lei S, Bui T, Yang X, Schultz-Cherry S, Yuan L. Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs. *Gut Pathog*. 2016;8:51.

Lei S, Ramesh A, **Twitchell E**, Wen K, Bui T, Weiss M, Yang X, Kocher J, Li G, Giri-Rachman E, Trang NV, Jiang X, Ryan EP, Yuan L. High Protective Efficacy of Probiotics and Rice Bran against Human Norovirus Infection and Diarrhea in Gnotobiotic Pigs. *Front Microbiol*. 2016;7:1699.

Lei S, Ryu J, Wen K, **Twitchell E**, Bui T, Ramesh A, Weiss M, Li G, Samuel

H, Clark-Deener S, Jiang X, Lee K, Yuan L. Increased and prolonged human norovirus infection in RAG2/IL2RG deficient gnotobiotic pigs with severe combined immunodeficiency. *Sci Rep.* 2016;6:25222.

Lei S, Samuel H, **Twitchell E**, Bui T, Ramesh A, Wen K, Weiss M, Li G, Yang X, Jiang X, Yuan L. Enterobacter cloacae inhibits human norovirus infectivity in gnotobiotic pigs. *Sci Rep.* 2016;6:25017.

Yang X, **Twitchell E**, Li G, Wen K, Weiss M, Kocher J, Lei S, Ramesh A, Ryan EP, Yuan L. High protective efficacy of rice bran against human rotavirus diarrhea via enhancing probiotic growth, gut barrier function, and innate immunity. *Sci Rep.* 2015;5:15004.

Twitchell EL, Hartman RA, Waxman SJ, Lescun TB, Miller MA. Pathology in practice. Coronary band dystrophy with proliferative pododermatitis. *J Am Vet Med Assoc.* 2014;245(4):385-7.

Twitchell EL, Lenz SD, Lin TL. Pathology in practice. Necrotizing fasciitis, osteomyelitis, and streptococcal septicemia in a dog. *J Am Vet Med Assoc.* 2014;244(12):1389-91.

Weber ES, 3rd, Waltzek TB, Young DA, **Twitchell EL**, Gates AE, Vagelli A, Risatti GR, Hedrick RP, Frasca S, Jr. Systemic iridovirus infection in the Banggai cardinalfish (*Pterapogon kauderni* Koumans 1933). *J Vet Diagn Invest.* 2009;21(3):306-20.

Presentations

Twitchell EL, Tin C, Wen K, Li G, Ramesh A, Weiss M, Lei S, Bui T, Yang X, Shultz-Cherry S, Zhang H, Vilchez S, Azcarate-Peril MA, Becker-Dreps S, Yuan, L. Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs. American College of Veterinary Pathologists Annual Meeting. New Orleans, LA. 2016. (poster)

Twitchell EL, Tin C, Wen K, Li G, Ramesh A, Weiss M, Lei S, Bui T, Yang X, Shultz-Cherry S, Zhang H, Vilchez S, Azcarate-Peril MA, Becker-Dreps S, Yuan, L. A gnotobiotic pig model of dysbiosis and rotavirus immunity. 35th Annual Meeting American Society for Virology. Blacksburg, VA. 2016. (poster)

Twitchell EL, Tin C, Wen K, Li G, Ramesh A, Weiss M, Lei S, Bui T, Yang X, Shultz-Cherry S, Zhang H, Vilchez S, Azcarate-Peril MA, Becker-Dreps S, Yuan, L. A gnotobiotic pig model of dysbiosis and rotavirus immunity. 32nd Graduate Student Assembly Research Symposium. Blacksburg, VA. 2016. (poster)

Twitchell EL, Tin C, Wen K, Li G, Ramesh A, Weiss M, Lei S, Bui T, Yang X, Shultz-Cherry S, Zhang H, Vilchez S, Azcarate-Peril MA, Becker-Dreps S, Yuan, L. Modulating human enteric dysbiosis and rotavirus. 27th Annual BMVS Research Symposium. Blacksburg, VA. 2016. (poster)

Awards and Academic Achievements

- 2016 Outstanding PhD Poster, "Modulating human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs" 27th Annual BMVS Research Symposium
- 2010 Phi Zeta Veterinary Medicine Honor Society
- 2009 William W. Carlton Award for Aptitude in Veterinary Pathology
- 2003 Gamma Sigma Delta Agriculture Honor Society
- 2003 New England Scholar

Examination Graduate Committee

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