

**BIOMEDICAL & VETERINARY SCIENCES
GRADUATE PROGRAM**



ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Ashwin Kumar Ramesh

“Study of enteric virus infection and parenteral vaccines in the gnotobiotic pig model”

Thursday, December 5th, 2019

9:00 am

Integrated Life Sciences Building – Room 1040

Bio



Ashwin was born in Chennai, India. He grew up in Singapore and Sunderland, United Kingdom. He graduated from University of Westminster with a BSc in Biotechnology (Honours) in 2011. He completed his MSc in Medical Parasitology at London School of Hygiene and Tropical Medicine in 2012. In 2013, he started his PhD in the BMVS program. His current research focuses on evaluating the immunogenicity and protective efficacy of intramuscular vaccines against enteric viruses in gnotobiotic pigs.

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Anhui Zhifei Longcom Biopharmaceutical Co. Ltd., China

VMCVM Office of Research and Graduate Studies

Lay Language Abstract

People of all age groups are susceptible to acute gastroenteritis (AGE), a condition characterized by sudden onset of diarrhea, nausea and abdominal cramps. The two most important viral pathogens responsible for causing AGE are rotavirus (RV) and norovirus (NoV). Gnotobiotic (Gn) pigs have been valuable in helping us understand the mechanism of infection, pathogenesis, immunity and have played a key role in the expediting development of novel vaccines and therapeutics against both of these viruses. Live oral RV vaccines are available but they are not very effective in low income countries where the vaccines are needed the most. Next generation parenteral vaccines are proposed to improve the RV vaccine efficacy. Our first study showed that a nanoparticle-based intramuscular (IM) RV vaccine effectively reduced the duration and severity of human RV infection and diarrhea in Gn pigs. Secondly, we examined in detail the infectivity of Human NoV (HuNoV) and identified accurately using different mathematical models on how much virus would be required to infect and cause diarrhea in naïve Gn pigs. This knowledge would greatly help in the accurate assessment of the efficacy of NoV vaccines. Third, we evaluated the immunogenicity and protective efficacy of a quadrivalent IM NoV vaccine in Gn pigs. Although the vaccine was highly immunogenic, it did not confer any protection against infection and diarrhea upon challenge with the NoV at different doses. NoVs are so diverse that one year we might be infected with one strain and a few years later, we might be infected again with another strain, even though they belong to the same genotype, and experience the same symptoms. This is because, changes brought about due to mutation in the virus capsid protein allow the viruses to hide from neutralizing antibodies induced by previous infection or

vaccination as we have revealed in this study. NoV diversity and lack of cross protection need to be taken into consideration during vaccine development. This thesis shows how Gn pigs have been used to study these components in order to further maximize our ability to understand and combat enteric viral diseases.

Publications

Peer-reviewed Publications

- Ramesh A**, Mao J, Giri-Rachman E, Lei S, Twitchell E, Yuan L. Parenterally-administered quadrivalent VLP vaccine evaluated in Gn pig model of GII.4 human norovirus infection and diarrhea. (manuscript in preparation)
- Ramesh A**, Parreño V, Lei S, Zhong W, Jiang X, Yuan L. Evaluation of different dose response models for the calculation of 50% infectious dose of human norovirus in gnotobiotic pigs. (manuscript in preparation).
- Ramesh A**, Mao J, Lei S, Twitchell E, Jiang X, Tan M, Shiraz A, Huang E, Yuan L. 2019. Parenterally administered P24-VP8* nanoparticle vaccine conferred strong protection against rotavirus diarrhea and virus shedding in gnotobiotic pigs. *Vaccines* 2019 7(4), 177; <https://doi.org/10.3390/vaccines7040177>.
- Lei S, Twitchell E, **Ramesh A**, Bui T, Majette E, Tin C, Avery R, Arango-Argoty G, Zhang L, Becker-Dreps S, Azcarate-Peril M, Jiang X, Yuan L. 2019. Enhanced GII.4 human norovirus infection in human gut microbiota transplanted gnotobiotic pigs. *Journal of General Virology*. doi: 10.1099/jgv.0.001336.
- Bui T, Li G, Kim I, Wen K, Twitchell E, Hualei S, **Ramesh A** Weiss M, Yang X, Clark-Deener S, Choy R, Yuan L. 2017. Effects of Racecadotril on Weight Loss and Diarrhea Due to Human Rotavirus in Neonatal Gnotobiotic Pigs (*Sus scrofa domesticus*). *Comparative Medicine*, 67(2), 157–164.

- 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. 2016. High Protective Efficacy of Probiotics and Rice Bran against Human Norovirus Infection and Diarrhea in Gnotobiotic Pigs. *Sci Rep.*6, 25017. doi: 10.1038/srep25017.
- 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. 2016. Increased and prolonged human norovirus infection in RAG2/IL2RG deficient gnotobiotic pigs with severe combined immunodeficiency. *Sci. Rep.* 6, 25222; doi:10.1038/srep25222. PMC4846862.
- Lei S, Samuel H, Twitchell E, Bui T, **Ramesh A**, Wen K, Weiss M, Li G, Yang X, Jiang X, Yuan L. 2016. Enterobacter cloacae inhibits human norovirus infectivity in gnotobiotic pigs. *Sci. Rep.* 6, 25017; doi:10.1038/srep25017. PMC4845002.
- 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. *Gut Pathog.* 2016 Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs 8;8:51. eCollection 2016. doi: 10.1186/s13099-016-0136-y.
- Yang X, Twitchell E, Li G, Wen K, Weiss M, Kocher J, Lei S, **Ramesh A**, Ryan EP, Yuan L. 2015. High protective efficacy of rice bran against human rotavirus diarrhea via enhancing probiotic growth, gut barrier function, and innate immunity. *Sci Rep* 5, 15004. doi:10.1038/srep15004. PMC4602212.

Book chapters

- Yuan L, Hendricks A, **Ramesh A**. 2019. Chapter 22. Molecular Mechanisms of Host Immune Responses to Rotavirus. In *Molecular Food Microbiology*, Edited by Donyou Liu. CRC Press/Taylor & Francis Group (in press).

Yuan L, Bui T, **Ramesh A**. 2019. Chapter 11. Rotavirus. In Handbook of Foodborne Diseases, Food Microbiology Series, Edited by Donyou Liu. CRC Press/Taylor & Francis Group. p121-136.

Published Abstracts

Ramesh A, Parreño V, Lei S, Zhong W, Jiang X, Yuan L, Determination of median infectious dose (ID₅₀) and diarrhea dose (DD₅₀) of human norovirus GII.4/2003 Cin-1 variant in gnotobiotic pigs with different dose response mathematical models. Abstract #S9.5. 7th International Calicivirus Conference, October 13-17, 2019. Sydney, Australia. (oral presentation).

Yuan L, Lei S, **Ramesh A**, Twitchell E, Allen I, Lee J, Li S, G Arango-Argoty, L Zhang. Interactions of human gut microbiota and human norovirus in gnotobiotic pigs. Abstract #209. 7th International Calicivirus Conference, October 13-17, 2019. Sydney, Australia.

Yuan L, Twitchell E, **Ramesh A**, Lei S, Shiraz A. Using gnotobiotic pig model for preclinical evaluation of candidate rotavirus vaccines at 13th international dsRNA symposium September 26, 2018. Vayamundo Houffalize, Houffalize, Belgium.

Ramesh A, Hendricks A, Lei S, Twitchell E, Bui T, Majette E, Yuan L. Quadrivalent human norovirus-like particle (VLP) vaccine induces VLP-specific IFN- γ producing T cell responses in systemic lymphoid tissues of gnotobiotic pigs at 29th Annual Research Symposium. March 15, 2018. Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA.

Lei S, Ryu J, Wen K, Twitchell EL, 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. Abstract# W33-4. 35th American Society for Virology Annual Meeting. June 18-22, 2016. Virginia Polytechnic Institute and State University, Blacksburg, VA.

Bui T, Li G, Kim I, Wen K, Twitchell EL, Lei S, **Ramesh A**, Weiss M, Yang X, Clark-Deener S, Choy R, Yuan L. Racecadotril ameliorates rotavirus diarrhea in a neonatal gnotobiotic pig model
Abstract# P35-01. 35th American Society for Virology Annual Meeting. June 18-22, 2016. Virginia Polytechnic Institute and State University, Blacksburg, VA.

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. Abstract# P35-10. 35th American Society for Virology Annual Meeting. June 18-22, 2016. Virginia Polytechnic Institute and State University, Blacksburg, VA.

Ramesh A, Lei S, Twitchell E, Bui T, Wen K, Weiss M, Kocher J, Jiang X, Ryan E, Yuan L. Rice bran and probiotics stimulate strong intestinal IFN- γ producing T-cell responses and reduce norovirus infection in gnotobiotic pigs at 27th Annual Research Symposium. March 17, 2016. Virginia-Maryland College of Veterinary Medicine. Blacksburg, Virginia.

Twitchell E, 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, Shultz-Cherry S, Yuan L. Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs at 27th Annual Research Symposium. March 17, 2016. Virginia-Maryland College of Veterinary Medicine. Blacksburg, Virginia.

Yuan L, Yang X, Twitchell E, Wen K, Li G, Kocher J, Weiss M, Lei S, **Ramesh A**, Ryan E. Dietary rice bran protects against viral gastroenteritis through preserving intestine homeostasis and promoting growth of diarrhea-reducing probiotic bacteria in gnotobiotic pigs. Abstract. The 8th International Conference on Vaccines for Enteric Diseases. July 8-10, 2015. The Royal College of Physicians of Edinburgh, Edinburgh, UK.

Ramesh A, Weiss M, Twitchell E, Wen K, Yang X, Lei S, Li G, Ryan E, Yuan L, Identifying the effects of dietary rice bran on the growth of

IPEC-J2 cells and rotaviruses in vitro at 26th Annual Research Symposium.

Presentations

Ramesh A, Parreño V, Lei S, Zhong W, Jiang X, Yuan L, Determination of median infectious dose (ID₅₀) and diarrhea dose (DD₅₀) of human norovirus GII.4/2003 Cin-1 variant in gnotobiotic pigs with different dose response mathematical models. Abstract #S9.5. 7th International Calicivirus Conference, October 13-17, 2019. Sydney, Australia (oral presentation).

Awards and Academic Achievements

Outstanding Ph.D. Poster Award for my presentation “Quadrivalent human norovirus-like particle (VLP) vaccine induces VLP-specific IFN- γ producing T cell responses in systemic lymphoid tissues of gnotobiotic pigs” at the 29th Annual Research Symposium, Virginia-Maryland College of Veterinary Medicine. Blacksburg, Virginia. March 15, 2018.

Society for Leukocyte Biology Trainee Award for my presentation “Quadrivalent human norovirus-like particle (VLP) vaccine induces VLP-specific IFN- γ producing T cell responses in systemic lymphoid tissues of gnotobiotic pigs” at the 29th Annual Research Symposium, Virginia-Maryland College of Veterinary Medicine. Blacksburg, Virginia. March 15, 2018.

Outstanding Ph.D. Student Poster Award for my presentation “Rice bran and probiotics stimulate strong intestinal IFN- γ producing T-cell responses and reduce norovirus infection in gnotobiotic pigs” at 27th Annual Research Symposium, Virginia-Maryland College of Veterinary Medicine. Blacksburg, Virginia. March 17, 2016.

Examination Graduate Committee

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