Concept Title: **Integrative Analyses of Environmental Factors Impacting Animal and Human Health Through Perturbations of Microbial Communities**

Potential Faculty Team:

Clayton Caswell (Lead)
Biomedical Sciences and Pathobiology

Ansar Ahmed
Biomedical Sciences and Pathobiology

Nammalwar Sriranganathan
Biomedical Sciences and Pathobiology

Irving Allen
Biomedical Sciences and Pathobiology

Xin Luo
Biomedical Sciences and Pathobiology

Xiang-Jin Meng
Biomedical Sciences and Pathobiology

Michelle Theus
Biomedical Sciences and Pathobiology

Lijuan Yuan
Biomedical Sciences and Pathobiology

Laura Hungerford
Population Health Sciences

Bill Pierson
Population Health Sciences

Cassidy Rist
Population Health Sciences

Vision Statement

The term 'microbiome' defines the vast microscopic communities collectively composed of bacteria, viruses, fungi, and eukaryotic protozoans that inhabit myriad niches, including environmental locales, as well as the surfaces and organ systems of animals and humans. Recent empirical evidence clearly demonstrates the substantial role that microbiomes play in facilitating the homeostasis of complex biological systems, and as such, perturbation of these microbial communities can lead to dysregulation of environmental ecosystems, significant declines in animal and human health, and the emergence of detrimental conditions, such as infectious diseases, inflammatory disorders, and neurodegenerative aliments. A variety of factors are involved in shifting the composition and complexity (i.e., the functionality) of microbiomes, including the contamination of soil, water, and food sources with toxicants, pharmaceuticals, and antimicrobial compounds.

Our Faculty Team seeks to establish an interdisciplinary group aimed at addressing the multifaceted interplay between environmental contamination, microbiomes, and animal and human health (Appendix II). This group plans to utilize our cooperative expertise in environmental engineering, microbial ecology, crop and soil sciences, infectious diseases, animal science, neurobiology, and population-level analytics to systematically dissect the problems leading to the genesis of microbiome aberrations, the molecular events occurring during these inappropriate shifts in microbial communities, and the adverse outcomes of microbiome manipulation on the health of animals and humans. In addition to comprehensively characterizing the connections and mechanisms associated with microbiome dysbiosis, the overarching goal of this Team is to provide the theoretical and applied technologies that will be needed in the future to recognize potential problems areas and to intervene and correct these issues before significant environmental and/or health impacts are effected.

A number of current Virginia Tech faculty members will comprise the initial Team, and while the skill-set of this group is diverse and extremely appropriate to fulfill the vision of this Concept, new team members will need to be incorporated to ensure that we are able to meet the challenges of the complex problems we propose pursuing with this Team.

Relevance

The Global Systems Science (GSS) Destination Area (DA) has evolved into a large-scale research initiative that will undoubtedly transform interdisciplinary collaborations across the University, and our proposed Concept (Integrative Analyses of Environmental Factors Impacting Animal and Human Health Through Perturbations of Microbial Communities) will support the mission of GSS by organizing and mobilizing a diverse group of investigators to study complex issues related to environmental suitability, as well as animal and human health globally. This Concept will be an important element of GSS, and will address the large-scale issue of environmental contamination and its impact on microbiomes, which ultimately affects the health and vitality of animals and humans. The relevant broad thrust areas can be grouped as follows:

Assessment of Environmental Contamination – A variety of environmental areas are consistently bombarded with contaminants, including toxicants, pharmaceuticals, and antibiotics, and this results in significant levels of these agents in soil, water, and food sources. Nonetheless, neither the true level of pollution by these compounds nor the comprehensive identification of the agents is currently known for many habitats. The Team will focus efforts on the identification and characterization of contaminants in a wide variety of environmental locations.

Impacts on the Microbial Communities – It is not surprising that the contamination outlined in the previous section wreaks havoc on microbial communities, but it remains unclear what the exact nature of the organismal shifts and functional detriment within microbiomes as a result of environmental contamination are. Our Team will define the physiologic, metabolic, and functional dysregulation that occurs in the microbiomes found in the environment, as well as in animals and humans.

Outcomes on Animal and Human Health – Ultimately, altered microbiomes in animals and humans can lead to the emergence of infectious diseases, inflammatory disorders, and neurodegenerative aliments, but the full repertoire of disease manifestations linked to the host microbiome remains to be elucidated. The Faculty Team has extensive expertise in identifying and characterizing bacterial and viral agents, inflammation-linked

mechanisms of diseases, and neurological conditions. Moreover, our Team will work to define the links between environmental contamination, microbiomes, and disease states.

Given the immense scope of this Concept, we anticipate a variety of opportunities for the Team to secure extramural funding, and of particular interest are two specific program announcements. The first is PAR-16-366 – Dual Purpose with Dual Benefit: Research in Biomedicine and Agriculture Using Agriculturally Important Domestic Animal Species. This is a program jointly funded by the NIH and USDA, and our Team will be well positioned to successfully compete for funds under this mechanism. The second is Solicitation 16-592 – Ecology and Evolution of Infectious Diseases (EEID). This is an NSF funding mechanism that seeks to support the study of ecological and evolutionary processes of transmission/virulence of infectious diseases, and here too, our Team will be highly competitive funds.

In the end, this Concept proposes the formation of a highly skilled, interdisciplinary Faculty Team that will work synergistically to address complex questions related to environmental contamination and the downstream impacts on ecosystem, animal, and human health mediated by microbiomes. Importantly, we seek not to be merely descriptive in addressing these issues, but rather, we envision developing intervention strategies to combat and remedy the global crises linked to disruption of beneficial microbiomes. To this end, it is imperative that we complement our current Faculty Team with new expertise in specialized fields, as well as train and educate students to contribute to the success of the Concept.

VMCVM has an extensive history of research and mentoring collaborations across the university. For over 10 years, the college has held two NIH funded training grants that focus on pre-doctoral (T35) and post-doctoral (T32) training in addition to a nationally recognized Merial-funded training program. Over 140 students have benefited from training funding by these grants, which would not be possible without VMCVM's well-established collaborations. Six different departments (Biological Sciences, Animal and Poultry Science, Biological and Systems Engineering, Fish and Wildlife Conservation, Biomedical Engineering and Mechanics, and Virginia Tech Carilion Research Institute) in five separate colleges are represented in the programs' mentoring teams. To further strengthening the collaborative environment cultivated at VMCVM, our faculty also contribute to funded training programs that originate from other colleges including an NIH funded R25 program administrated by the College of Agriculture and Life Sciences. Based on this past participation, we fully anticipate our ability to recruit additional faculty for this DA concept.

Curriculum Opportunities

Several existing courses at the University are highly applicable for training both undergraduate and graduate students in relation to this GSS Concept, but new courses will be required to sufficiently train students and harness the energy and unique perspectives of those students to ensure the success of the Concept. Overall, we envision a three-pronged educational approach in which students receive didactic classroom instruction, controlled hands-on training in a laboratory setting, and real world situational education where students are involved in and leading efforts outside of the boundaries of the University. Importantly, these elements will not be explored sequentially, but rather, students will be involved in all three prongs of the educational plan simultaneously. As such, students will be exposed to a full range of realistic experiences, while also assisting in answering the questions being pursued in the Concept. Specifically, new courses will be developed in the areas of:

-Microbial ecology with an emphasis on environmental and host-associated microbiomes
-Synergistic microbial communities: The viral, bacterial, fungal, and protozoan constituents of microbiomes, and their cooperative roles maintaining environmental and host homeostasis
-Laboratory techniques for the collection and analyses of environmental samples with an emphasis on both contaminant (i.e., toxicants, pharmaceuticals, and antimicrobial agents) detection and identification of microbial communities
-Advanced population dynamics computing
-Collaborative field studies where students work side-by-side with faculty members, extension agents, federal agencies, etc. to collect and catalog field samples

Description of Resource Needs

As noted previously, there will be a need to hire new faculty and expand existing research programs to fulfill the mission of this Concept, and moreover, it will be necessary to add to the University's infrastructure to ensure success of the Faculty Team. The current vision includes hiring faculty and staff, as well as advancing infrastructure, in the following areas:

Faculty and Staff

-Microbiome Specialist
-Environmental Systems Analyst (Modeler)
-Infectious Diseases Specialist (Agriculture)
-Infectious Diseases Specialist (Animal/Human)
-Environmental Toxicologist
-Systems Analyst

Infrastructure

-Advanced computing systems with state-of-the-art information technology programming capabilities
-Extremely sensitive, high throughput chemical identification technology, and advanced biological agent diagnostics
-Cutting-edge laboratory space
-Sufficient space dedicated to didactic and applied instruction, as well as for regular group meetings, journal clubs, and distinguished lecture series

Appendix I

Biosketches for members of the Faculty Team

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Clayton C. Caswell

eRA COMMONS USER NAME (credential, e.g., agency login): CASWELLC

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M University	B.S.	08/2004	Biomedical Science and Entomology
West Virginia University School of Medicine	Ph.D.	12/2008	Microbial Pathogenesis and Immunology
East Carolina University Brody School of Medicine	Postdoctoral Scholar	12/2012	Microbiology

A. Personal Statement

I am an early-career microbiologist with prior training in protein biochemistry and bacterial pathogenesis using *Streptococcus pyogenes* as a model organism. As a postdoctoral researcher, I shifted the focus of my research to gene regulation and molecular mechanisms of virulence of *Brucella abortus*. As a newly independent investigator, my laboratory is characterizing the small regulatory RNAs (sRNAs) in *Brucella*, and, more specifically, we are defining the genetic circuitry that links sRNAs to *Brucella* pathogenesis. While my immediate goals are aimed at establishing an independent research group and continuing to characterize mechanisms of *Brucella* pathogenesis, my long-term goals include studying and defining mechanisms of infection that are broadly utilized by bacterial pathogens.

As an independent investigator, I am dedicated to training the next generation of scientists, and currently, my laboratory is training four graduate students and one undergraduate student. My goal is to introduce these students to the basic laboratory principles and methodologies of molecular genetics, biochemistry, and pathogenic microbiology, and the students in my laboratory have been instrumental is developing the projects and generating the preliminary data for the present application. Recently, our work characterizing sRNA pathways linked to *Brucella* virulence led to the identification of several systems involved in more global RNA-mediated regulatory mechanisms. This new research thrust area combined with our continued work with sRNA pathways will firmly establish our laboratory as a leader in the field of *Brucella* pathogenesis, and I plan to continue mentoring and training students and research associates as we advance the characterization of mechanisms mediating *Brucella* virulence.

B. Positions and Honors

Positions

2009-12 Postdoctoral Scholar, Department of Microbiology and Immunology, East Carolina University Brody School of Medicine, Adviser: Marty Roop.

2013-Present Assistant Professor, Department of Biomedical Sciences and Pathobiology, VA-MD College of Veterinary Medicine, Virginia Tech.

Academic and Professional Honors

2008 Participant of the American Society for Microbiology Kadner Institute in Preparation for Careers in Microbiology

2013 Recipient of the Mäkelä-Cassell Travel Award for Early Career Scientists from the American Society for Microbiology and the Federation of European Microbiology Societies

2016 Teacher of the Week at Virginia Tech (Week of 29 August 2016)

2017 Scholar of the Week at Virginia Tech (Week of 30 January 2017)

Memberships in Professional Societies
American Society for Microbiology (ASM)
Entomological Society of America (ESA)

Ad Hoc Reviewer
2013 Proposal Reviewer, NIH Special Emphasis Panel in the Skeletal Biology Development and Disease Study Section
2015 Proposal Reviewer, Sigma Delta Epsilon, Graduate Women in Science
2015 Proposal Reviewer, Wellcome Trust/DBT India Alliance – Biomedical Research Fellowship Programme for India
2017 Proposal Reviewer, NSF Graduate Research Fellowship Program (GRFP)

Journals: *PLoS One, Veterinary Microbiology, FEMS Immunology & Medical Microbiology, Journal of Molecular Microbiology and Biotechnology, Metallomics, Microbiological Research, Letters in Applied Microbiology, International Journal of Microbiology, FEBS Letters, Pathogens and Disease, Molecular Microbiology, Microbiology, Journal of Applied Microbiology, Journal of Proteomics, Frontiers in Genetics, Journal of Bacteriology, PLoS Pathogens, Nucleic Acids Research, Frontiers in Microbiology, Frontiers in Cellular and Infection Microbiology, Molecular Immunology, Scientific Reports*

C. Contributions to Science

Characterization of bacterial collagen-like proteins: As a graduate student, I studied bacterial collagen-like proteins using the model pathogenic bacterium *Streptococcus pyogenes*. Previous work had described the presence and distribution of collagen-like protein in numerous bacteria, but very little was known about the biological function of these proteins. Our work determined that this family of proteins is capable of binding directly to host cell receptors via the collagen-like domain, and these interactions resulted in uptake of the bacteria by the cells. Moreover, our structure-function analyses revealed that domains in these proteins other than the collagen-like domain also possess unique ligand-binding properties that aid the bacterium in attaching to host cells and evading the immune system. Selected publications summarizing this work are listed below:

Caswell, C.C., Lukomska, E., Seo, N.-S., Höök, M., and Lukomski, S. (2007) Scl1-dependent internalization of group A *Streptococcus* via direct interactions with the $\alpha_2\beta_1$ integrin enhances pathogen survival and re-emergence. *Mol. Microbiol.* **64**:1319-1331. (PMID: 17542923)

Caswell, C.C., Han, R., Hovis, K.M., Ciborowski, P., Keene, D.R., Marconi, R.T., and Lukomski, S. (2008) The Scl1 protein of M6-type group A *Streptococcus* binds the human complement regulatory protein, factor H, and inhibits the alternative pathway of complement. *Mol. Microbiol.* **67:**584-596. (PMID: 18093091)

Caswell, C.C., Barczyk, M., Keene, D.R., Lukomska, E., Gullberg, D.E., and Lukomski, S. (2008) Identification of the first prokaryotic collagen sequence motif that mediates binding to human collagen receptors, integrins $\alpha_2\beta_1$ and $\alpha_{11}\beta_1$. *J. Biol. Chem.* **283**:36168-36175. (PMID: 18990704)

Caswell, C.C.†, Oliver-Kozup, H.†, Han, R., Lukomska, E., and Lukomski, S. (2009) Scl1, the multifunctional adhesin of group A Streptococcus selectively binds cellular fibronectin and laminin, and mediates pathogen internalization by human cells. *FEMS Microbiol. Lett.* **303**:61-68. (PMID: 20002194)
†Authors contributed equally to this work.

Description of novel virulence mechanisms in *Brucella* spp.: When I began my postdoctoral studies, I set out to characterize the molecular events that contribute to *Brucella* virulence, a goal that I maintain to this day. It had been shown previously in the laboratory that the RNA chaperone Hfq is essential for *Brucella* pathogenesis, and part of my work dealt with defining one of the links between Hfq and virulence. Additionally, we carried out several studies that characterized the systems required for *Brucella* strains to combat oxidative stress, and we described a new transcriptional regulator in *Brucella* that is required for pathogenesis. More recently, as an independent investigator, my lab has characterized the requirements of zinc homeostasis and proline utilization for the full virulence of *Brucella*. The publications related to this summary can be found below:

Caswell, C.C., Gaines, J.M., and Roop R.M. II (2012) The RNA chaperone Hfq independently coordinates expression of the VirB type IV secretion system and the LuxR-type regulator, BabR, in *Brucella abortus* 2308. *J. Bacteriol.* **194**:3-14. (PMID: 22020650)

Caswell, C.C., Baumgartner, J.E., Martin, D.W., and Roop, R.M. II (2012) Characterization of the organic hydroperoxide resistance system of *Brucella abortus* 2308. *J. Bacteriol.* **194:**5065-5072. (PMID: 22821968)

Caswell, C.C., Elhassanny, A.E.M., Planchin, E.E., Roux, C.M., Weeks-Gorospe, J.N., Ficht, T.A., Dunman, P.M., and Roop, R.M. II (2013) The diverse genetic regulon of the virulence-associated transcriptional regulator MucR in *Brucella abortus* 2308. *Infect. Immun.* **81:**1040-1051. (PMID: 23319565)

Sheehan, L.M., Budnick, J.A., Roop, R.M. II, and **Caswell C.C.** (2015) Coordinated zinc homeostasis is essential for the wild-type virulence of *Brucella abortus*. *J. Bacteriol.* **197:**1582-1591. (PMID: 25691532)

Caudill, M.T., Budnick, J.A., Sheehan, L.M., Lehman, C.R., Purwantini, E., Mukhopadhyay, B., and **Caswell C.C.** (2017) The proline utilization system in required for infection by the pathogenic α-proteobacterium *Brucella abortus*. *Microbiology* **In press**.

Identification and characterization of small RNAs in *Brucella* spp.: Along the same lines as the above section, one of the main goals of my postdoctoral research was to define the link between Hfq and *Brucella* virulence. It is interesting to note that *Brucella* was the first bacterium to which Hfq was linked to bacterial pathogenesis, but at the time of my arrival in the laboratory, no *Brucella* small RNAs had been identified. Given that Hfq is known to function as a chaperone for small RNA-mRNA interactions in order to regulate gene expression, it was hypothesized that *Brucella* strains express small RNAs. We employed a number of methodologies to identify *Brucella* small RNAs, and to date, we have confirmed the existence of 15 small RNAs in *B. abortus*. However, our focus remains on studying two related small RNAs, called AbcR1 and AbcR2, and the publications described and characterizing these *Brucella* small RNAs are listed below:

Caswell, C.C., Gaines, J.M., Ciborowski, P., Smith, D., Borchers, C.H., Roux, C.M., Sayood, K., Dunman, P.M., and Roop, R.M. II (2012) Identification of two small regulatory RNAs linked to virulence in *Brucella abortus* 2308. *Mol. Microbiol.* **85:**345-360. (PMID: 22690807)

Sheehan, L.M., Budnick, J.A., Blanchard, C., Dunman, P.M., and **Caswell, C.C.** (2015) A LysR-family transcriptional regulator required for virulence in *Brucella abortus* is highly conserved among the a-proteobacteria. *Mol. Microbiol.* **98:**318-328. (PMID: 26175079)

Saadeh, B., **Caswell, C.C.**, Chao, Y., Berta, P., Wattam, A.R., Roop, R.M. 2nd, and O'Callaghan, D. (2015) Transcriptome-wide identification of Hfq-associated RNAs in *Brucella suis* by deep sequencing. *J. Bacteriol.* **198:**427-435. (PMID: 26553849)

Sheehan, L.M., and **Caswell, C.C.** (2017) A 6-nucleotide regulatory motif within the AbcR small RNAs of *Brucella abortus* mediates host-pathogen interactions. *mBio* **In press**.

URL to full publication list: http://www.ncbi.nlm.nih.gov/pubmed/?term=caswell+cc

D. Research Support

Ongoing Research Support

15SDG23280044 Caswell, C.C. (PI) 01/01/2015-12/31/2018
American Heart Association, Scientist Development Grant
Characterizing virulence-associated small RNAs of *Brucella abortus*
The goal of this project is to characterize a novel pair of small, regulatory RNAs in *Brucella abortus*, particularly to define the molecular mechanisms governed by the small RNAs to contribute to *B. abortus* pathogenesis.

1R15AI117648-01 Caswell, C.C. (PI) 09/018/2015-08/31/2018
National Institute of Allergy and Infectious Diseases
Characterization of a novel genetic pathway required for *Brucella* virulence
The goal of this project is to define the molecular activity of a novel transcriptional regulator protein in the pathogenesis of *Brucella abortus*.

BIOGRAPHICAL SKETCH

Provide the following information for all key personnel.
Follow the sample format for each person found in **Biosketch Sample**. **DO NOT EXCEED FOUR PAGES.**

NAME	**POSITION TITLE**
S. Ansar Ahmed	Associate Dean for Research and Graduate Studies, College of Veterinary Medicine (VMCVM), Virginia Tech Professor of Immunology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
The University of Agricultural Sciences	BVSc (DVM)	1977	Vet. Med. Surg.
The Murdoch University, Australia	PhD	1984	Immunology and Immunopathology

A. Positions and Honors.

Positions:

1985-1989 Research Instructor ('85-87), Non-Tenure track Research Asst. Professor ('87-'89) Div. of Clinical Immunology Dept. of Medicine, The University of Texas Health Center at San Antonio, Texas
1989-1994 Assistant Professor in Immunology (Tenure track), Dept. of Pathobiology,V irginia-Maryland College of Veterinary Medicine (VMCVM), Virginia Tech, Blacksburg, Virginia.
1994- 2001 Tenured, Associate Professor, VMCVM, Virginia Tech , Blacksburg, VA
2001- to-date Tenured, Professor of Immunology, VMCVM, Virginia Tech, Blacksburg, VA
2002- to-2008 Director, Center for Molecular Medicine & Infectious Diseases, VMCVM, Virginia Tech
2007- to 2008 Interim Head, Biomedical Sciences & Pathobiology, VMCVM, Virginia Tech
2008 to 2017 Head, Biomedical Sciences and Pathobiology, VMCVM, Virginia Tech
2017-current Associate Dean for Research and Graduate Studies, VMCVM

Relevant Professional Memberships

American Association of Immunologists

Honors:

DVM (BVSc): **(1)** Awarded all four academic merit Gold Medals (1977): (i) *UAS gold Medal for General Academic Merit*, *(ii) Lions Club International Gold Medal,* (iii) *Dr. S. Mohyuiddin's Gold Medal for Veterinary Pathology* & *(iv) Dr. Rajkumar Gold Medal for Veterinary Medicine.* **(2)** Recipient of UAS MERIT Scholarship ('72-77); **(3)** Dr. Jawaharlal Nehru, National Award (1977), **(4)** State Govt. Award for Academic Merit (1978)
Ph.D.: **(1)** Upgraded from MS to Ph.D.; **(2)** Murdoch University Scholarship Award (Australia); **(3***)* Murdoch University Travel Award (*to present Papers at IVth International Immunology meetings Paris (1980)* and London (1980).
Post-doctoral: Leukemia Research Fellowship from the Leukemia Society of America, Inc. (1983-85)

Selected Other honors:Membership in Federal Govt. Study Sections and Grant review

(**1) ALTX-1 NIH, study section** *Ad Hoc Memb*er, 2001; **(2) ALTX-4 NIH study Section**, *Ad Hoc Member,*2003; **(3) IRPG/NIH (Special Emphasis Panel)/** - 2003;**(4**) Special Emphasis Panel/ ZRG1 GMA-3 /**NIH-**2003; **(5**) **XNDA-NIH** study section, *Ad Hoc Member* 2004, **(6) Innate Immunity and Inflammation**/ **(ZRG)** NIH, Nov. 04-05, 2004; **(7) NSF-** Integrative Animal Biology Program, Nov. 01, 2004; **(8) USDA**/SBIR –2004; **(9) Innate Immunity and Inflammation (ZRG 1 III)** 7/7-8 2005; **(10) USDA/ SBIR-2005; (11) NIH study section Special Emphasis Panel -**The Cooperative Study Group for Autoimmune Disease Prevention (Feb 28 March 1'06); (**12**) **NIH, XNDA**, Member conflict, Special Emphasis Panel,

06/21/07; (**13**) **NIH/NINDS**, Special Emphasis Panel, K99/R00 program, July 2, 2007; (14) **NIH/NINDS**, K99/R00 Review Group, 04/10/2008; (15) **NIH/NLS-2** meeting Oct 27-28, 2008; (19) NIH (Member Conflict study section): Feb 24, 2010; (21) **NIH, SEP** March, 2012; (22**) NIH,** July 5, 2012, ZRG1 CB-F(02) Special Emphasis Panel; (23) **NIH November**, SEP, 2012 (24) **NIH, MOSS Q02,** March 21, 2013; (25) **NIH, Member Conflict SEP**, IMM-N, J, April 8, 2014.

External Reviewer for Several Research Foundations::**(1)** The Blowitz-Ridgeway Foundation; **(2)** JW McLaughlin Foundation; **(3)** John Sealy Endowment Foundation: (4) Lupus Foundation of America

Research Awards and Other Academic Recognition: **(1) Smith Kline Beecham award for Excellence in Research** on Animal Health, 1994; **(2) Pfizer award for Research Excellence, 2003; (3) Member,** Phi Zeta National Honor Society and **(4)** Early Promotion and Tenure, 1994; **(5)** VMRCVM **Excellence in Teaching Award,** 1992; **(6) External** P&T**,** and reviewer of program for several Universities.

External Reviewer for Several Research Foundations::**(1)** The Blowitz-Ridgeway Foundation; **(2)** JW McLaughlin Foundation; **(3)** John Sealy Endowment Foundation: (4) **ASPIRES** Grant Review Panel, VT,

Research Awards and Other Academic Recognition: **(1) Smith Kline Beecham award for Excellence in Research** on Animal Health, 1994; **(2) Pfizer award for Research Excellence, 2003; (3) Member,** Phi Zeta National Honor Society and **(4)** Early Promotion and Tenure, 1994; **(5)** VMRCVM **Excellence in Teaching Award,** 1992; **(6) External** P&T**,** and reviewer of program for several Universities.

Selected Relevant Invited Presentations:

1) "*Unequal Immune capabilities between males and females: Implications for health and autoimmune diseases*".2011 American Physiological Society Conference: Physiology of Cardiovascular Disease: Gender Disparities, Jackson, MS on October 12-14, 2011.
2) "*Gender Differences in microRNAs in autoimmune diseases "Roundtable conference of experts*" sponsored by Society for Women's Health Research (SWHR) in Washington, DC, Oct 4-5, 2012.
3) "*MicroRNAs, a new Paradigm to understand autoimmune pathogenesis and Inflammation".* Workshop on Adjuvants & Vaccines: Focus on Autoimmunity, Amsterdam, October 18-19, 2012.
4) *"miRNAs may be small in size but have a big impact on inflammation and autoimmunity "* Invited Speaker for NIEHS supported distinguished lecture series at the University of Texas, Galveston", April, 2013.
5) "*New thoughts on Sex differences in inflammation/autoimmune diseases: role of microbiota and microRNA".* Invited speaker for the Society for Women's Research to discuss the current state of art relative to gender-based medicine. My talk title was at the "*What Difference an X Makes*: The State of Women's Health" Washington DC. July 18-19, 2013.
6) " *In Pursuit of understanding of why females are more susceptible to autoimmune diseases: It is more complex than initially postulated". Cancer and Inflammation Invited Speaker, NCI/NIH, June, 2015*

B. Selected peer-reviewed publications (Selected from 103 publications, listed in chronological order).

1. Dai R, Cowan, C, Heid B, Khan D, Liang Z, Pham C.T.N, **S. Ansar Ahmed**. Neutrophils and neutrophil serine proteases are increased in the spleens of estrogen-treated C57BL/6 mice and several strains of spontaneous lupus-prone mice. ***PLoS One***. In press.
2. Dai R, Lu R, **S. Ansar Ahmed.** The Upregulation of Genomic Imprinted DLK1-Dio3 miRNAs in Murine Lupus Is Associated with Global DNA Hypomethylation. ***PLoS One***. 2016 Apr 12;11(4):e0153509. PubMed PMID: 27070142; PubMed Central PMCID: PMC4829153.
3. Dai R and **S. Ansar Ahmed.** microRNA, an important epigenetic regulator of immunity and autoimmunity. In: Laurence J, editor. ***Translating MicroRNAs to the Clinic***: ELSEVIER; 2016. p. 223-58.
4. Khan, D., Dai, R., **S. Ansar Ahmed,** Sex differences and Estrogen regulation of miRNAs in lupus, a prototypical Autoimmune Disease. ***Cellular Immunology*** 294 (2) April 2015, Pages 70–79, 2015
5. Liao X, Ren J, Wei CH, Ross AC, Cecere TE, Jortner BS, Ahmed SA, Luo XM. (2015) Paradoxical effects of all-*trans*-retinoic acid on lupus-like disease in the MRL/lpr mouse model. ***PLoS One*** 10(3): e0118176.

6. Dai R, **S. Ansar Ahmed**. Sexual dimorphism of miRNA expression: a new perspective in understanding the sex bias of autoimmune diseases. ***Therapeutics and Clinical Risk Management***. 2014;10:151-163. PMID: 24623979.
7. Dai R, McReynolds S, LeRoith T, Heid B, Liang Z, **S. Anasr Ahmed**. Sex differences in the expression of lupus-associated miRNAs in splenocytes from lupus-prone NZB/WF1 mice. ***BMC Biology of sex differences*** 2013, 4:19. PMID: 24175965.
8. Deena Khan, Catharine Cowan and **Ansar Ahmed S** "Estrogen andSignaling in the Cells of Immune System" In: ***Advances in Neuroimmune Biology*** 3 (2012) 1–21, DOI 10.3233/NIB-2012-012039,IOS Press, 2012 (Edited Book Chapter)
9. Dai R and **S. Ansar Ahmed**. MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. ***Translational Research*** 2011,157(4):163-79. PMID: 21420027.
10. Liao X, Li S, Settlage RE, Sun S, Ren J, Reihl AM, Zhang H, Karyala SV, Reilly CM, **S. Ansar Ahmed**, Luo XM. (2015) Cutting Edge: Plasmacytoid Dendritic Cells in Late-Stage Lupus Mice Defective in Producing IFN-α. *Journal of Immunology*. 195:4578-4582.
11. Dai R, Zhang Y, Khan D, Heid B, Caudell D, Crasta O and **S. Ansar Ahmed**. Identification of a Common Lupus Disease-Associated microRNA Expression Pattern in Three Different Murine Models of Lupus. ***PLoS One*** 2010, 5 (12):e14302. PMID: 21170274.
12. Khan D, Dai R, Karpuzoglu E, S. **S. Ansar Ahmed**. Estrogen increases, whereas IL-27 and IFN-gamma decrease, splenocyte IL-17 production in wild type mice. ***European Journal of Immunology*** 2010, 40(9):2549-56. PMID: 20623549.
13. Ansar Ahmed S. Karpuzoglu, E, Deena Khan. "Effects of Sex Steroids on Innate and Adaptive Immunity" In: ***Sex and Susceptibility to Infection***. Edited by: S.L. Klein and C.W. Roberts, Springer-Verlag, John Hopkins, ISBN 978-3-642-02154-1 (e-ISBN ISBN 978-3-642-02155-8), pp-19-52, 2010 (Edited Book Chapter)
14. Dai, R., R. A. Phillips, E. Karpuzoglu, D. Khan, and **S. Ansar Ahmed**. 2009. Estrogen regulates transcription factors STAT-1 and NF-kappaB to promote inducible nitric oxide synthase and inflammatory responses. ***J Immunol*** 183:6998-7005. PMID: 19890039
15. Peairs, A., A. Radjavi, S. Davis, L. Li, **S. Ansar Ahmed**, S. Giri, and C. M. Reilly. 2009. Activation of AMPK inhibits inflammation in MRL/lpr mouse mesangial cells. ***Clin Exp Immunol*** 156:542-551. PMID: 19438609.
16. Karpuzoglu, E., R. A. Phillips, R. Dai, C. Graniello, R. M. Gogal, Jr., and **S. Ansar Ahmed**. 2009. Signal transducer and activation of transcription (STAT) 4beta, a shorter isoform of interleukin-12-induced STAT4, is preferentially activated by estrogen. ***Endocrinology*** 150:1310-1320. PMID:18988675.
17. Dai, R., R. A. Phillips, Y. Zhang, D. Khan, O. Crasta, and **S. Ansar Ahmed**. Suppression of LPS-induced Interferon-gamma and nitric oxide in splenic lymphocytes by select estrogen-regulated microRNAs: a novel mechanism of immune modulation. ***Blood*** 2008, 112:4591-4597. PMID: 18791161.
18. Dai, R., R. A. Phillips, and **S. Ansar Ahmed**. 2007. Despite inhibition of nuclear localization of NF-kappa B p65, c-Rel, and RelB, 17-beta estradiol up-regulates NF-kappa B signaling in mouse splenocytes: the potential role of Bcl-3. ***J Immunol*** 179:1776-1783. PMID: 17641044.
19. Karpuzoglu, E., R. A. Phillips, R. M. Gogal, Jr., and **S. Ansar Ahmed**. 2007. IFN-gamma-inducing transcription factor, T-bet is upregulated by estrogen in murine splenocytes: Role of IL-27 but not IL-12. ***Mol Immunol*** 44:1819-1825. PMID: 17046061
20. Reilly, C. M., S. Olgun, D. Goodwin, R. M. Gogal, Jr., A. Santo, J. W. Romesburg, **S. Ansar Ahmed**, and G. S. Gilkeson. 2006. Interferon regulatory factor-1 gene deletion decreases glomerulonephritis in MRL/lpr mice. ***Eur J Immunol*** 36:1296-1308. PMID:16541466.
21. Lengi, A. J., R. A. Phillips, E. Karpuzoglu, and **S. Ansar Ahmed**. 2006. 17beta-estradiol downregulates interferon regulatory factor-1 in murine splenocytes. ***J Mol Endocrinol*** 37:421-432. PMID: 17170083.
22. Karpuzoglu, E., J. B. Fenaux, R. A. Phillips, A. J. Lengi, F. Elvinger, and **S. Ansar Ahmed**. 2006. Estrogen up-regulates inducible nitric oxide synthase, nitric oxide, and cyclooxygenase-2 in splenocytes activated with T cell stimulants: role of interferon-gamma. ***Endocrinology*** 147:662-671.

PMID: 16293660.

Complete list of published work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1xg0wt73uBLAO/bibliography/48807843/public/?sort=date&direction=ascending.

C. Research Support.

Ongoing Research Supports:

(1) **NIH 9T35OD011887-07** *Summer Veterinary Student Research Program (SVSRP).* **S. Ansar** Ahmed (**Program Director**). *Aim: To train DVM students into biomedical research in animal models of diseases.* **03/09/12-03/09/17, Role: Program Director**

(2) **NIH 2T350DO11887-11,** *Summer Veterinary Student Research Program (SVSRP).* **S. Ansar** Ahmed (**Program Director**). *Aim: To train DVM students into biomedical research in animal models of diseases.* **03/09/17-03/09/22, Role: Program Director; Impact score- 21** (awaiting funding).

(3) **NIH 9T32OD010430-07,** Animal Model Research for Veterinarians (AMRV) The *Aim of this proposal is to train veterinarians in biomedical research by recruiting them in Ph.D. program.* **03/16/2012 - 02/28/2017 Role: Co-Investigator/Mentor.** (PI: X-J Meng)

(4) **1 R15 AR062883-01A1** NIH/NIAID "miRNA expression in the NZB/W lupus mice". This grant will identify if there are alterations in miRNA in specific cells and in urine as mice develop systemic lupus erythematosus. N*o overlap with the present proposal.* **3/1/2013-2/29/2017, Role: Co-I. (**PI: Reilly C.)

Recent Completed Research Supports:

(1) **IRC 175185, Virginia-Maryland Regional College of Veterinary Medicine (VMRCV)** "Epigenetic regulation of genomic imprinting miRNAs in murine lupus". *The goal of this internal small grant is to help the PI to develop necessary technical approaches for epigenetic analysis and to generate preliminary data for extramural funding.* **07/01/2014-06/30/2016, Role: Co-PI.** (PI: Rujuan Dai)

(2) **Award ID: 219631, Alliance for Lupus Research "**Targeting the miR-182-96-183 cluster to ameliorate lupus" The goal of this project is to define the pathogenic and therapeutic application of lupus associated miRNA, miR-182-96-183. *No overlap with the present proposal.* **02/01/2012-1/31/2015, Role: Co-PI.**

(3) **457654, Merial Ltd**, entitled "2014 merial Veterinary Scholars Program" *Aim is to expose DVM students to biomedical research in animal models of diseases.* **12/1/ 2007 – 11/30/2014, Role: PI/Program Director**

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Luo, Xin Mimi

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Peking University, Beijing, China	BS (honors)	07/1998	Molecular Biology
Pennsylvania State University, University Park	MS	08/2001	Nutrition
Pennsylvania State University, University Park	PhD	05/2006	Immunology
California Institute of Technology	Postdoc	07/2010	Immunology

A. Personal Statement

I obtained doctoral training at Penn State University with Catharine Ross, and postdoctoral training at Caltech with Nobel Laureate David Baltimore. My current research interests are immunological and microbial regulation of autoimmunity. This is an area distinct from my previous trainings. In the past 4 years as an independent investigator, I have successfully initiated my research program by publishing on high-impact journals (eight publications so far as the senior author) and supervising PhD and MD students.

B. Positions and Honors

Positions

1998-2001 Graduate Assistant, Dept. of Nutrition, Pennsylvania State University, University Park
2001-2006 Graduate Assistant, Integrative Biosciences, Pennsylvania State University, University Park
2006-2010 Postdoctoral Fellow, California Institute of Technology
2010-2011 Senior Research Scientist, California Institute of Technology
2011-2012 Scientist II, Cell Signaling Technology
2012- Assistant Professor, VA-MD Regional College of Veterinary Medicine, Virginia Tech
2014- Assistant Professor, Faculty of Health Sciences, Virginia Tech Carilion Research Institute

Professional Membership and Services

2001- Member of American Association of Immunologists (AAI)
2009- Member of Scientific Advisory Board, Immusoft Corporations
2014- Member of American Society for Microbiology (ASM)

Honors

1993 3rd Prize, Chinese Chemistry Olympiad
1994 Shuermei Scholarship for Outstanding Female Students, Shude High School
1994 Advanced Science Honor Program Fellowship
1998 Young Eagle Scholarship
2001 Integrative Biosciences Scholarship
2001 Life Science Consortium Fellowship
2011 AAI Trainee Abstract Award
2014 AAI Early Career Faculty Travel Grant
2016 AAI Early Career Faculty Travel Grant

C. Contribution to Science

1. ***Interaction between immunity and gut microbiota***. This is an area of research that I started to work on after becoming independent. Perturbation of gut microbiota had been shown to be associated with several autoimmune disorders, but little is known about the role of gut microbiota in lupus. My laboratory was the first to describe the gut commensal composition and diversity in lupus. We showed that certain "good" bacteria are associated with improved lupus symptoms, while certain "bad" bacteria are correlated with more severe disease. In addition to autoimmunity, we have also investigated the microbiome in immunodeficiency. So far much attention in the microbiome field has focused on how microbiota affects host immunity. We aimed to dissect the underappreciated, opposite function—how host immunity affects gut microbiota. Using Rag1-knockout mice and bone marrow transfer experiments, we provided direct evidence that host adaptive immune system can indeed shape the gut microbiota.

    a. Zhang H, Liao X, Sparks JB, Luo XM. (2014) Dynamics of gut microbiota in autoimmune lupus. *Applied Environmental Microbiology* 80(24): 7551-60.
    b. Zhang H, Sparks JB, Karyala SV, Settlage R, Luo XM. (2015) Host adaptive immunity alters gut microbiota. *ISME Journal* 9(3): 770-81.
    c. Mu Q, Zhang H, Luo XM. (2015) SLE: Another Autoimmune Disorder Influenced by Microbes and Diet? *Frontiers in Immunology* doi: 10.3389/fimmu.2015.00608.
    d. Zhang H., Luo XM. (2015) Control of Commensal Microbiota by the Adaptive Immune System. Invited review by *Gut Microbes* 6(2):156-60.

2. ***Mechanisms of lupus pathogenesis and regulation***. This is an area of research that I started to work on after becoming independent. Lupus is a complex autoimmune disease with no cure. A focus of my laboratory is on the roles of dendritic cells in lupus pathogenesis. We have found that IFNα-producing plasmacytoid dendritic cells (pDCs), while essential in the initiation of lupus, are defective at producing the pro-inflammatory cytokine in late-stage lupus disease. This suggests that pDCs might not be a good therapeutic target in patients with active lupus. In addition, my laboratory has shown that the effects of vitamin A on systemic autoimmunity are more complicated than previously thought. We have found that it may decrease inflammation in some organs while generating more severe disease in others. Moreover, we have shown that inhibition of HDAC6 ameliorates lupus-like disease in mice.

    a. Liao X, Li S, Settlage RE, Sun S, Ren J, Reihl AM, Zhang H, Karyala SV, Reilly CM, Ahmed SA, Luo XM. (2015) Cutting Edge: Plasmacytoid Dendritic Cells in Late-Stage Lupus Mice Defective in Producing IFN-α. *Journal of Immunology*. 195:4578-4582.
    b. Liao X, Ren J, Wei CH, Ross AC, Cecere TE, Jortner BS, Ahmed SA, Luo XM. (2015) Paradoxical effects of all-*trans*-retinoic acid on lupus-like disease in the MRL/lpr mouse model. *PLoS One* 10(3): e0118176.
    c. Regna NL, Vieson MD, Luo XM, Chafin CB, Puthiyaveetil AG, Hammond SE, Caudell DL, Jarpe MB, Reilly CM. (2016) Specific HDAC6 Inhibition by ACY-738 Reduces SLE Pathogenesis in NZB/W Mice. *Clinical Immunology*. 162: 58-73.
    d. Liao X, Reihl AM, Luo XM. (2016) Breakdown of Immune Tolerance in Systemic Lupus Erythematosus by Dendritic Cells. *Journal of Immunology Research*. (In press)

3. ***Lentiviral programming of immune response against HIV***. Because HIV had evolved to be highly resistant to antibody neutralization and all attempts to design an immunogen that would raise a broadly neutralizing response had failed, a new approach, even a far-fetched one, was desirable. Dr. David Baltimore and I explored the possibility of lentiviral programming of B cells to make a predefined, broadly neutralizing anti-HIV antibody. To closely study hematopoiesis and deliver the antibody, I created an *in vitro* culture system where human hematopoietic stem cells were allowed to differentiate into naïve B cells in the presence of stromal cell support (mimicking the bone morrow environment), and the naïve B cells were then activated by a cocktail of cytokines to become antibody-producing plasmablasts and plasma cells (mimicking splenic development of B cells). Using the culture system, we were the first to prove the concept that anti-HIV immunity could be provided by lentiviral programming of B cells. We published the method, and filed a patent application to cover the invention. The patent has been licensed by *Immusoft Corporations*. In addition, I have proposed and demonstrated the efficacy of using lentiviral delivery and backpacking of anti-HIV antibodies *in vivo* that can protect humanized mice from HIV challenge.

a. Luo XM, Maarschalk E, O'Connell RM, Wang P, Yang L, Baltimore D. (2009) Engineering human hematopoietic stem/progenitor cells to produce a broadly neutralizing anti-HIV antibody after in vitro maturation to human B lymphocytes. *Blood* 113(7): 1422-1431.
b. Luo XM, Yang L and Baltimore D. *In vitro* human B lymphopoiesis culture system. U.S. Patent No. 8,133,727 B2, Date of Patent March 13, 2012.
c. Luo XM, Lei MYY, Feidi RA, West AP, Balazs AB, Bjorkman PJ, Yang L, Baltimore D. (2010) Dimeric 2G12 as a potent protection against HIV-1. *PLoS Pathogens* 6(12): e1001225.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1xgezwbGp4N5K/bibliograpahy/47630445/public/?sort=date&direction=ascending

D. Research Support

CURRENT

NIH 5R03AI117597-02 Role: PI 4/1/2016 – 3/31/2018
Title: Effect of maternal immune factors in shaping the infant gut microbiota
The contribution of placenta-derived immune factors to infant microbiota composition has not been revealed. Lack of such information has prevented identification of specific risk factors in the microbiota. The proposed research aims to improve neonatal health by identifying these risk factors, which in turn will lead to the design of probiotic therapies against neonatal infections and related complications.

College Seed Grant Role: PI 7/1/2014 – 6/30/2016
Virginia Tech College of Veterinary Medicine
Title: Generation of two humanized lupus mouse models
The goal of this study is to provide a better platform for the study of human lupus pathogenesis and for the testing of treatments against lupus-related inflammatory flares in a system readily translatable to human use.

One Health Center Seed Grant Role: PI 7/1/2015 – 6/30/2016
Center for One Health Research, Edward Via College of Osteopathic Medicine and Virginia Tech College of Veterinary Medicine
Title: HDAC6 inhibition in SLE
The goal of this study is to understand the immunological effects of HDAC6 inhibition in lupus.

Fralin Seed Grant Role: PI 7/1/2015 – 6/30/2016
Fralin Life Science Institute
Title: The impact of antibiotics use on lupus progression
The goal of this study is to increase our understanding of how environmental triggers, such as antibiotics use, are associated with lupus.

COMPLETED

Internal Research Competition 7/1/2014 – 6/30/2015
Virginia Tech College of Veterinary Medicine
Mechanisms of retinoic acid-regulated lupus pathogenesis
The goal of this study is to elucidate the complex roles of vitamin A in autoimmunity.

Internal Research Competition 7/1/2012 – 6/30/2013
Virginia Tech College of Veterinary Medicine
Genetic engineering of stem cells as a novel immunotherapeutic approach against systemic lupus erythematosus
The goal of this study is to design effect treatments for lupus patients with severe lupus refractory to conventional treatments.

Genomics Research Laboratory Small Grant 7/1/2012 – 6/30/2013
VBI/Fralin, Virginia Tech

Probing cause-and-effect relationship between gut microbiota and host immunity using Next-Generation Sequencing

The goal of this study is to elucidate the cause-and-effect relationship between gut microbiota and host immunity. Ultimately, we hope to translate this knowledge into new treatment strategies (e.g. probiotics) for patients with B or T cell deficiencies, such as HIV-infected individuals.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Theus, Michelle Lee

eRA COMMONS USER NAME (credential, e.g., agency login): mtheus

POSITION TITLE: Assistant Professor of Biomedical Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ohio University, Athens Ohio	B.S.	1994-1998	Biological Sciences
University of Texas M.D. Anderson Cancer, Houston, TX	ASCP certified	1998-1999	Clinical Lab Sciences
Cleveland Clinic, Cleveland, Ohio	ASHI certified	1999-2001	Transplantation Sciences
Medical University of South Carolina, (MUSC), Charleston, South Carolina	Ph.D.	2001-2006	NeuroPathology
University of Miami, Miami, Florida	PostDoc	2006-2012	Neuroscience

A. Personal Statement

I have the research background, expertise and motivation required to accomplish the goals set out in this grant application. The objective of my research is to investigate a **novel suppressive pathway** regulating cerebral arteriogenesis involving Eph receptor signaling and angiopoietin and its effects on neurorestoration following traumatic brain injury (TBI). We plan to investigate the mechanism(s) underlying arteriole remodeling in the brain using cell-specific transgenic mice, gain- and reverse-of-function infusion approaches, unique reporter and arteriole-specific labeling strategies. Our long-term research goal is to identify highly relevant and potent drug targets capable of crossing the blood-brain barrier and promoting therapeutic arteriogenesis and neurorestoration. Overall, I have a great deal of experience with loss-of-function ephrin/Eph receptor knockout mice, gain-of-function infusion approaches, and *in vivo* injury model systems that is necessary to successfully carry out the proposed research. During my training at the Miami Project to Cure Paralysis, I gained critical knowledge and surgical skills related to TBI rodent models including controlled cortical impact (CCI), lateral fluid percussion (LFP) and blast injury. During this time I received several competitive NRSA grants, travel awards and have been twice recognized at the National Neurotrauma Symposium. I received a research award of excellence from the Women in Neurotrauma (WiNTR) Society for my research on adult TBI-induced neurogenesis in 2010 and the Michael Goldberger research award of excellence in 2011 for work involving dependence receptor-mediated cell death after TBI. Both presentations matured into peer-reviewed research publications. Within my first three active years as investigator at Virginia Tech, I have won three competitive internal grant competitions, had two fully independent publications accepted; one book chapter and two first author manuscript published and have recently been awarded an AREA training grant from NINDS. I have obtained the experience and knowledge to successfully complete the proposed studies as well as provide an environment for undergraduate, graduate and postdoctoral scholars to learn basic and translational neuroscience research. In addition, I offer leadership and administrative skills that were developed during my time in the clinical laboratory for organ transplantation and donation at the Cleveland Clinic. In summary, I have demonstrated a record of publication; external funding as well as extensive student training that has prepared me this training application and to establish myself as a leader in research and teaching in the neuroscience field.

B. Positions and Honors

Positions and Employment

1998-1999 Histocompatibility Scientist, MD Anderson Cancer Center, Transplantation lab, Houston,TX
1999-2001 Histocompatibility Scientist, Cleveland Clinic, Transplantation Lab, Cleveland, OH
2001-2006 Pre-Doctoral training, Dept. NeuroPathology, MUSC, Charleston, SC
2006-2012 Post-doctoral Fellow, Dept. Neurosurgery, University of Miami, Miami, FL
2012- Assistant Professor, Dept. Biomedical Sciences, Virginia Tech, Blacksburg, VA

Other Experience and Professional Memberships

1999 American Society of Clinical Laboratory Science (ASCLS)
1999 American Society of Clinical Pathologists (ASCP)
2000 American Society of Histocompatibility and Immunogenetics (ASHI)
2003 Society for Neuroscience
2007 American Association for the Advancement of Science

Board Certifications

1999 Medical Technologist (ASCP)
1999 Clinical Laboratory Scientist (National Crediting Agency)
2000 Histocompatibility Technical Specialist (ASHI)

Honors

2004 American Society for Neural Transplantation and Repair, Travel Award, Clearwater, FL
2005 American Society for Neural Transplantation and Repair, Travel Award, Clearwater, FL
2005 International Conference on Neural Transplantation and Repair, Travel Award, Taipei, Taiwan
2008 Margaret Whelan Postdoctoral Scholarship Fund, Medical Faculty Travel Award, Miami, FL
2010 National Neurotrauma Symposium, Travel Grant Award, Las Vegas NV
2010 WiNTR Research Award of Excellence, National Society for Neurotrauma Symposium, Las Vegas NV
2011 Michael Goldberger Research Award of Excellence, National Society for Neurotrauma Symposium, Fort Lauderdale, FL

C. Contribution to Science

1. The role of hypoxia and HIF1-alpha as a stimulus for growth promoting factors has been previously described. Under transient hypoxic conditions, cells up-regulate critical factors involved in survival and growth signaling including VEGF, erythropoietin, Bcl-2, etc. This priming or pre-conditioning prepares the cells for a subsequent insult, allowing them to better survive in harsh environments. I established a method for hypoxic pre-conditioning of transplantable embryonic stem cell (ES)-derived neural stem cells (NSCs) as a strategy for cell survival in the ischemic rat brain after stroke (Theus et al. *Experimental Neurology* 2008). I found that exposure of these cells to low levels of oxygen 24 hrs prior to transplantation greatly enhanced their survival and trophic factor release which significantly improved outcome in rats following stroke.

2. Efficient neuronal differentiation of embryonic stem cells represents a critical barrier in cell replacement therapy. Together with others, I improved our understanding of the signaling pathways required for proper neuron differentiation and synaptic maturation of ES-derived NSCs involving Src Kinases and ERK molecules (Theus et al. Exp Cell Res, 2006; Li Z Dev Growth Differ 2006). These pathways have important implications for improving the neuronal phenotype using ES cells in transplantation studies and in promoting neuronal replacement using endogenous subventricular (SVZ)-derived neural progenitors following brain injury. I also co-authored a review during this time highlighting the current state of ES cell therapy for stroke treatment and the role of angiogenesis in providing vascular support for neural stem cells (Wei L et al., Pathophysiology 2005). In addition to stroke, I aided in ES cell transplantation studies in the cochlea following murine auditory-neuropathy, which revealed a critical window after injury where the cells are vulnerable to apoptotic death when transplanted to early (Lang H et al., 2008).

3. Endogenous neurogenesis is a naturally occurring phenomenon in the adult brain that is involved in neuronal cell replacement during active learning and memory and olfaction. Neurogenic compartments

exist in the human and rodent brain and have been shown to respond to injured stimulus by migrating the areas of tissue damage. However, this response is limited and stem cells predominantly acquire an astrocytic phenotype. Moreover, the importance of these cells in brain repair is unclear. Together with others, we showed that genetically targeting these cells through ablation technology severely diminished their presence in the trauma cortex resulting in exacerbation of injury (Dixon K et al., J neurotrauma, 2015). I also discovered a novel inhibitory pathway that suppressed the neural stem cell response in trauma and development (Theus MH et al., Stem Cells, 2010, del Valle K et al, Dev Neurosci, 2011) and was involved in dependence receptor mediated cell death in the peri-lesion cortex (Theus MH et al., Cell Death and Dis, 2014). Upon transitioning into an assistant professor position, I also demonstrated hypoxic conditions in the trauma-injury SVZ and showed its effects on neural stem cells growth (Baumann G et al., Exp Biol Med, 2013). During this time I also developed a monolayer cell culture system for growing neural stem cells isolated from the subventricular zone. This system was critical for *ex vivo* evaluation of the stem cell response to trauma-induced signals; i.e. growth factor administration, gene manipulation, chemo-attractive and repulsive cues and cell death signals (Theus MH et al., Curr Protoc Stem Cell Biol. 2012).

4. My research efforts also include collaborations with several investigative teams focused on characterizing innate immune cell activation in the CNS and PNS. In particular, I collected data and co-authored a manscript involving in a transgenic rodent study where $IKK\beta^{f/f}$ mice were used to selective ablate NF-κB signaling in schwann cells as a model to study peripheral signals involved in proper myelination of the sciatic nerve (Morton P et al., J Neurosci, 2013). Moreover, using conventional Eph knockout mice, I also assisted in isolating and culturing astrocytes from the brain and performed stimulation experiments to characterize the release profile for D-serine, a critical regulator of NMDAR function (Zhuang Z et al., J Neurosci, 2010). This studies provided important information regarding the signals regulating neural activity in the hippocampus after TBI.

URL to a full list of my published work:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43608342/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01NS096281 Mechanisms Regulating Cerebral Arteriogenesis and Neurorestoration
National Institutes of Health, NINDS
Dates: 03/01/2016 – 02/28/2021
Objective: This grant will investigate the mechanisms regulating cerebral arteriogenesis after traumatic brain injury.

Laboratory Start-up Package, VRMCVM
Date: 1/01/2012-7/01/2015
Objective: Molecular and cellular mechanisms of neurogenesis, vascular injury and repair

SDG 16470021-Collateral formation and remodeling after ischemic stroke.
Scientist Development Grant, American Heart Association (AHA)
Dates: 07/01/13-06/30/17; *Relinquished for R15 support.*
Objective: This grant will investigate the mechanisms regulating collaterogenesis following permanent embolic stroke
Role: PI

R15 NS081623-Collateral formation and remodeling after ischemic stroke.
National Institutes of Health; NINDS
Dates: 09/01/13-06/30/16
Objective: This grant will investigate the mechanisms regulating collaterogenesis following stroke
Role: PI

Virginia Tech College of Veterinary Medicine, Internal Research Competition (IRC)
Dates:07/01/15-06/30/16
Objective: This grant will investigate the endothelial cell-specific effects of Eph signaling on stroke recovery
Role: PI

Completed Research Support

T32 NS007459-07- The role of ephrinB3 on neurogenesis in the adult brain
Dalton Dietrich (PI)
08/01/07-07/31/08
The goal of this study was to identify the role of ephrinB3 on the proliferation and survival of adult neural stem/progenitor cells in the subventricular zone using gene-targeted knockout mice.
Role: Post-Doctoral Trainee

F32 NS064699- Molecular mechanisms of adult neurogenesis following traumatic brain injury.
07/01/09-06/30/11
The goal of this study was to examine the role of ephrinB3 and its cognate receptors on neurogenesis in the adult brain after TBI.
Role: PI

Virginia Tech College of Veterinary Medicine, Internal Research Competition (IRC)
07/01/12-06/30/13
A transgenic approach to analyzing cerebrovascular development and repair.
The goal of this one year internal grant proposal was to create tissue-specific knockout mice. Using the loxP-Cre system, EphA4 receptor was ablated on Tie2-expressing endothelial cells and GFAP-positive astrocytes.
Role: PI

Virginia Tech College of Veterinary Medicine, Internal Research Competition (IRC)
Dates:07/01/14-06/30/15
Molecular and cellular mechanism(s) regulating pial arteriole collateral development
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: **Meng, Xiang-Jin**

eRA COMMONS USER NAME (credential, e.g., agency login): **XJMENG**

POSITION TITLE: **University Distinguished Professor**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Binzhou Medical College, Binzhou, PRC	M.D.	08/85	Medicine
Hubei Medical College, Wuhan, PRC	M.S.	07/88	Microbiology/Immunology
Iowa State University, Ames, Iowa	Ph.D.	08/95	Immunobiology/Virology
NIH, NIAID, Bethesda, MD	Postdoc	1995-98	Molecular Virology

A. Personal Statement

My research interest focuses on studying the molecular mechanisms of viral pathogenesis and developing effective vaccines against emerging and re-emerging viral diseases including hepatitis E viruses (HEV), porcine circovirus type 2 (PCV2), porcine reproductive and respiratory syndrome virus (PRRSV), torque teno sus virus (TTSuV), and porcine epidemic diarrhea virus (PEDV). Currently I am utilizing pigs, rabbits, and chickens as animal models to study the mechanisms of HEV replication and pathogenesis, define the mechanisms of HEV cross-species infection, and develop vaccines against HEV. Our group discovered swine hepatitis E virus in pigs in 1997 and avian hepatitis E virus in chickens in 2001. My lab also identified the first U.S. strain of HEV from rabbits. We have since established three unique animal model systems (pigs, chickens and rabbits) for HEV, and have extensively utilized these animal models for the study of HEV pathogenesis, cross-species infection, and vaccine trials. My group also established the first infectious clones for genotypes 3 and 4 HEV and avian HEV. By using the HEV infectious cDNA clones and the animal model systems, we have conducted extensive structural and functional studies of HEV genes. Additionally, my lab has also been actively studying the molecular mechanisms of virus replication and pathogenesis with emphasis on vaccine developments for 4 other economically-important swine viruses (PCV2, PRRSV, TTSuV, PEDV). I have authored or co-authored >305 peer-reviewed papers, book chapters and review articles. According to Google Scholar, Meng's publications have been cited for >20,700 times with an h-index of 78. I have demonstrated a successful track record for developing commercial vaccines against important viral diseases. I am an inventor of 21 awarded and 17 pending U.S. patents, as well as 40 awarded foreign patents on various virus vaccines and diagnostics. For example, I am the lead inventor for the first USDA-fully licensed vaccine, Fostera™ PCV, against porcine circovirus-associated diseases, which is currently marketed worldwide. I have served as the PI for numerous grants including 7 NIH grants and 8 USDA grants in the past, and have successfully administered those projects. Additionally I have extensive experience in training postdoctoral fellows and graduate students, and have served as Director for the NIH T32 PhD graduate training program on Animal Model Research as well as the Director of DVM/PhD combined dual doctoral degree program at Virginia Tech.

B. Positions and Honors

Positions and Employment

2013 – present University Distinguished Professor, Virginia Polytechnic Institute and State University (VPI&SU) (Virginia Tech), Blacksburg, VA
7/2007 – 2013 Professor of Molecular Virology, VA-MD College of Vet Medicine, VPI&SU, Blacksburg, VA
2006 – present Director, NIH T32 Post-DVM Training Program on Animal Model Research for Veterinarians.
2006 – 2008 Director, DVM/PhD Dual Degree Graduate Program, VMRCVM, VPI&SU, Blacksburg, VA
4/2003 – 6/2007 Associate Professor (with tenure) of Molecular Virology, VMRCVM, VPI&SU, Blacksburg, VA
3/1999 – 3/2003 Assistant Professor of Molecular Virology, VMRCVM, VPI&SU, Blacksburg, VA
8/1998 - 2/1999 Senior Staff Scientist, Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, MD
9/1995 - 8/1998 John E. Fogarty Visiting Scientist, Lab of Infectious Diseases, NIAID, NIH, Bethesda, MD
5/1991 - 8/1995 GRA, Iowa State University College of Veterinary Medicine, Ames, IA
8/1988 - 5/1991 Research Associate, Shandong Academy of Medical Science, Jinan, Shandong, P.R.C.
8/1985 - 7/1988 GRA, Hubei Medical College, Wuhan, Hubei, P.R.C.

8/1984 - 7/1985 Medical Intern, Affiliated Hospital of Binzhou Medical College, Binzhou, Shandong, P.R.C.

Other Experiences (selected recent ones)

2012-present: Editor for 5 international journals: *mBio* (Editor, 2013-present); *Veterinary Microbiology* (Editor-in-Chief, 2014-present); *Virus Research* (Editor, 2016-present); *Animal Health Research and Review* (Editor, 2012-present); *Proc Natl Acad Sci USA* (Editor, 2016-present).
2016-present: Board of Directors, Virginia Academy of Sciences, Medicine, and Engineering.
2012-2015: Member of selection committee for ASM's "Merck Irving S. Sigal Memorial Award".
2011: Chair, USDA-ARS Animal Health National Program NP 103 Panel I – Swine (2011).
2011: Chair, Novel Vaccine and Vaccination Strategy Workshop. December 2, 2011. Chicago, IL.
2011-2016: Co-chair, local planning committee, 2016 Annual Meeting of Am Soc for Virology, Blacksburg, VA.
2011: Co-Chair of "Vaccine and Antiviral" Session and Member of the Program Committee, XIIth Intl Nidovirus Symposium, Grand Traverse Resort & Spa, MI.
2009-2013: Permanent member, NIH Virology-A Study Section (VIRA).
2009-2012: Chair, USDA NC-229 committee on emerging viral diseases of swine.
2009-2011: Chair, The 2010 and 2011 International PRRS Symposia, Chicago, IL.
2009. Rapporteur, 7th Framework Programme for Research of the European Union Panel on PRRS, Brussels.
2008-2009. Chair, Scientific Program Committee, International PRRSV Symposiums. Chicago, IL.
2008. Chair, NIH Special Emphasis Panel IDM-B (15) Study Section.
2004-2008. Permanent Member, NIH DDR (Drug Discovery & Antimicrobial Resistance) Study Section.
2007. Member, NIH-NCRR Comparative Medicine Review Committee Special Emphasis Panel CMRC-03.
2007-2009. Secretary, U.S. Department of Agriculture NC-229 committee on PRRSV.
2005-2011. Chair, *Hepeviridae* Subcommittee, International Committee on Taxonomy of Viruses.
2006-2007. Member, National Pork Board Planning Committee on PCV2 and associated diseases.
2004-2005. Member, NIH Special Emphasis Panels ZRG1 IDM-N 90S; ZRG1DDR(01), and ZRG1 DDR01Q.
2004. Member, NIH Virology Study Section Special Emphasis Panel.
2002-2003. Member and site visit team, NIH-NCRR Comparative Medicine Study Section.
1999-2006. Member, Virology Panel, United States Military Infectious Diseases Research Program (MIDRP).
2000-2001. Chair, Viral Hepatitis Panel for FY1999-2000 Annual Reports, MIDRP, United States DOD.

Honors (selected recent ones)

2017: Recipient, 2017 Outstanding Faculty Award by State Council of Higher Education for Virginia (SCHEV), the highest honor for faculty at Virginia's public and private colleges and universities.
2016: Member, U.S. National Academy of Sciences, elected to NAS in May 2016.
2014: Fellow, National Academy of Inventors, elected to NAI in December 2014.
2013: Recipient of University Distinguished Professor title, a pre-eminent and lifetime title bestowed by the University Board of Visitors to no more than one percent of the university faculty at any given time.
2012: Fellow, American Academy of Microbiology, elected to the AAM in February 2012.
2008. Recipient, Inaugural Fralin Life Science Institute Senior Faculty Fellow Award.
2008. Recipient, Honorary Diplomat, American College of Veterinary Microbiologists.
2008. Recipient, the 2008 Alumni Award for Research Excellence, Virginia Tech.
2008: Honor, Thomson Scientific ranked Meng in the top 1% highly-cited scientists in the field of Microbiology based on total citations from January 1997 to August 2007.
2007. Recipient, The 2007 Pfizer Award for Research Excellence, Pfizer Inc.
2003, 2009. Recipient, "Outstanding Editorial Board Member", *Journal of Clinical Microbiology.*
2002. Recipient, Clifton Garvin Award (recognize faculty representing Virginia Tech's future), Virginia Tech.
2001. Recipient, The 2001 Pfizer Award for Research Excellence, Pfizer Inc.
1997. Recipient, NIH Fellows Award for Research Excellence, NIH, Bethesda, Maryland.
1996. Recipient, The Zaffarano Prize for Research Excellence, Iowa State University, Ames, Iowa.
1995. Recipient, Research Excellence Award, Iowa State University, Ames, Iowa.

C. Contributions to Science

1. **Discovery of swine hepatitis E virus (swine HEV) leading to the recognition of hepatitis E as a zoonotic disease**: Hepatitis E virus (HEV) is an important human pathogen. Each year, more than 20 million people worldwide are infected by HEV, and over 3 millions will develop symptomatic hepatitis E with more than 56,600 hepatitis E-related deaths. The source of HEV infection, especially in industrialized countries, has long been a mystery. In 1997, Meng discovered the first animal strain of HEV, designated swine HEV, from pigs in

the United States. Swine HEV is antigenically and genetically very similar to the genotypes 3 and 4 human HEV. This discovery led to the eventual recognition of hepatitis E as a zoonotic disease as swine HEV infects humans. Since the initial discovery of swine HEV from pigs in 1997, the host range of HEV has drastically been expanded and numerous novel HEV strains have now been identified from many other animal species (chicken, rabbit, ferret, rat, deer, mongoose, bat, fish, etc). Therefore, Meng's discovery of swine HEV from pigs revolutionized the way physicians and scientists used to think about this important human pathogen, and pave the way for developing new HEV animal models and therapeutics.

(1). Meng, X.J., R.H. Purcell, P.G. Halbur, J.R. Lehman, D.M. Webb, T.S. Tsareva, J.S. Haynes, B.J. Thacker, and S.U. Emerson (1997). A novel virus in swine is closely related to the human hepatitis E virus. *Proceedings of the National Academy of Sciences USA* 94:9860-9865. PMCID:PMC23282.

(2). Meng, X.J., P.G. Halbur, M. Shapiro, S. Govindarajan, J.D. Bruna, I. K. Mushahwar, R.H. Purcell, and S.U. Emerson (1998). Genetic and experimental evidence for cross-species infection by the swine hepatitis E virus. *Journal of Virology*. 72:9714-9721. PMCID:PMC110481.

(3). Emerson SU, Zhang M, **Meng X.J**., St. Clair M, Nguyen H, Huang Y, and Purcell RH (2001). Recombinant hepatitis E virus genomes infectious for primates: importance of capping and discovery of a cis-reactive element. *Proceedings of the National Academy of Sciences USA* 98:15270-75. PMC65019.

(4). Huang YW, G. Haqshenas, C. Kasorndorkbua, P. Halbur, S. Emerson, **X.J. Meng** (2005). Capped RNA transcripts of full-length cDNA clones of hepatitis E virus are replication-competent when transfected into Huh7 cells and infectious when intrahepatically inoculated into pigs. *Journal of Virology*. 79:1552-1558. PMCID:PMC544089.

2. **Discovery of avian hepatitis E virus (avian HEV) and establishment of small homologous animal model systems for HEV**: Due to the lack of a practical animal model system to study HEV, the biology and pathogenesis of the hepatitis E virus are poorly understood. In 2002, Meng's group discovered the first avian strain of HEV from chickens with hepatitis-splenomegaly syndrome (HS syndrome) in the United States. We subsequently demonstrated that the avian HEV is antigenically and genetically related to human HEV, and can cross species barrier and infect turkeys. Since avian HEV infection in chickens is associated with a clinical disease (HS syndrome), the discovery led us to develop a very useful chicken animal model system to study some of the clinical aspects of HEV infection in a homologous small animal model system. Furthermore, our group also successfully developed unique pig and rabbit model systems for HEV, and these animal models have been critical for the study of various aspects of HEV pathogenesis and replication.

(1). Haqshenas G., H.L. Shivaprasad, P. Woolcock, D. Read, **X.J. Meng** (2001). Genetic identification and characterization of a novel virus related to human hepatitis E virus from chickens with hepatitis-spleenomegaly syndrome. *Journal of General Virology*. **82**:2449-2462. PMID:11562538.

(2). Billam P, F. Huang, Z. Sun, F. Pierson, R. Duncan, F. Elvinger, D. Guenette, T.E. Toth, **X.J. Meng** (2005). Systematic pathogenesis and replication of avian hepatitis E virus in specific-pathogen-free adult chickens. *Journal of Virology*. 79:3429-37. PMCID:PMC1075698.

(3). Pudupakam RS, Y.W. Huang, P. Billam, S. Ramamoorthy, F.W. Pierson, and **X.J. Meng** (2009). The hypervarible region (HVR) in the ORF1 of the hepatitis E virus (HEV) is dispensable for virus replication *in vivo*. *Journal of Virology*. 83:384-95. PMCID:PMC2612298.

(4). Kenney SP, Pudupakam RS, Huang YW, Pierson FW, LeRoith T, and **X.J. Meng** (2012). The PSAP motif within the ORF3 protein of an avian strain of the hepatitis E virus is not critical for viral infectivity in vivo but plays a role in virus release. *Journal of Virology*. 86(10):5637-46. PMID: 22438540.

3. **Invention of the first U.S. Department of Agriculture (USDA) fully-licensed vaccine against porcine circovirus type 2 (PCV2)**: Porcine circovirus type 2 (PCV2) is one of the most economically-important swine pathogens causing immense economic losses to the global swine industry. By utilizing innovative vaccine development strategies, we develop a chimeric virus (PCV1-2) with the capsid gene of the pathogenic PCV2 inserted into the backbone of the non-pathogenic PCV1. The chimeric PCV1-2 virus is non-pathogenic but elicits protective immunity against the pathogenic PCV2. Meng is the lead inventor for the first USDA fully-licensed vaccine, Fostera™ PCV, against the porcine circovirus-associated diseases (PCVAD). This vaccine is licensed to Pfizer Inc in 2005, and is currently being marketed and sold in more than 55 different countries worldwide. The vaccine has already saved hundreds of millions dollars for the global swine industry. In 2014, another new commercial vaccine (Fostera™ PCV MH) against both PCV2 and M. *hyopneumonia* was released to the market. This new bivalent commercial vaccine has two-components: one is based on the Fostera™ PCV vaccine component, and the second is based Zoetis' mycoplasma hyopneumonia vaccine component.

(1). Fenaux, M., P.G. Halbur, G. Haqshenas, R. Royer, P. Nawagitgul, M. Gill, T.E. Toth, and **X.J. Meng** (2002). The cloned genomic DNA of the type-2 porcine circovirus (PCV-2) is infectious when injected into the liver and lymph nodes of SPF pigs: characterization of clinical course, virus distribution and pathological lesions. *Journal of Virology*. **76**:541-551.
(2). Fenaux, M., T. Opriessnig, P.G. Halbur, **X.J. Meng** (2003). Immunogenicity and pathogenicity of the chimeric infectious DNA clones between pathogenic type 2 porcine circovirus (PCV2) and non-pathogenic PCV1 in weaning pigs. *Journal of Virology.* **77**:11232-11243.
(3). Fenaux M, T. Opriessnig, P.G. Halbur, F. Elvinger, and **X.J. Meng** (2004). A chimeric porcine circovirus (PCV) with the capsid gene of pathogenic PCV2 cloned into the genomic backbone of non-pathogenic PCV1 induces protective immunity against PCV2 infection in pigs. *Journal of Virology*. **78**:6297-6303.
(4). Beach N.M., N.M. Juhan, L. Cordoba, and **X.J. Meng**. 2010. Replacement of the replication factors of porcine circovirus (PCV) type 2 with those of PCV type 1 greatly enhances viral replication *in vitro.* *Journal of Virology*. **84**:8986-8989.

4. **Cloning of the first U.S. strain of porcine reproductive and respiratory virus (PRRSV) and development of vaccines against PRRSV**: PRRSV is arguably the most economically-important global swine pathogen causing more than $640 million economic losses each year to the swine industry in the United States alone. Meng published the very first paper reporting the cloning and sequencing of the first U.S. strain of PRRSV from pigs in Iowa, and proposed the existence of two distinct genotypes of PRRSV. Over the years, we have since made significant contributions to the prevention and control of this economically-important disease by developing several experimental vaccines against PRRSV.

(1). **Meng**, **X.J.,** P.S. Paul, and P.G. Halbur (1994). Molecular cloning and nucleotide sequencing of the 3' terminal genomic RNA of porcine reproductive and respiratory syndrome virus. *Journal of General Virology* **75**:1795-1801.
(2). Opriessnig T., P.G. Halbur, K.J. Yoon, R.M. Pogranichniy, E.M. Vaughn, K.M. Harmon, R.Evans, K.F. Key, F.J. Pallares, P. Thomas, **X.J. Meng** (2002). Comparison of molecular and biological characteristics of a modified live PRRSV vaccine (RespPRRS/Repro™), the parent strain of the vaccine (ATCC VR2332), ATCC VR2385, and two recent field isolates of PRRSV. *Journal of Virology*. **76**:11837-11844.
(3). Ni YY, T. Opriessnig, L. Zhou, D. Cao, Y.W. Huang, P.G. Halbur, and **X.J. Meng**. 2013. Attenuation of porcine reproductive and respiratory syndrome virus by molecular breeding of the virus envelope genes from genetically divergent strains. *Journal of Virology*. **87:**304-313.
(4). Zhou L, Y.Y. Ni, P. Piñeyro, B.J. Sanford, C.M. Cossaboom, D.J. Cao, Y.W. Huang, and **X.J. Meng**. 2012. DNA shuffling of the GP3 genes of porcine reproductive and respiratory syndrome virus (PRRSV) produces a chimeric virus with an improved cross-neutralizing ability against a heterologous PRRSV strain. *Virology*. **434**:96-109.

5. **Establishment of infectious DNA clones of Torque teno sus virus and discovery of novel swine pathogens from pigs in the United States:** Torque teno sus virus (TTSuV) is an orphan virus that infects pigs. We developed the first infectious DNA clone of TTSuV and conducted pathogenicity studies in pigs using the infectious clone to determine the pathogenic potential of TTSuV. This work paved the way for future vaccine development against TTSuV. Additionally, we also first reported the evolution and genotyping of the porcine epidemic diarrhea virus (PEDV) which emerged for the first time in May 2013 in the USA causing immense economic losses. These findings pave the way for developing vaccines against TTSuV, and PEDV.

(1). Huang YW, A.W. Dickerman, P. Pineyro, L. Li, L. Fang, R. Kiehne, T. Opriessnig, and **X.J. Meng**. 2013. Origin, evolution, and genotyping of emergent porcine endemic diarrhea virus (PEDV) strains in the United States. *mBio*. **4(5)**:e00737-13. doi:10.1128/mBio.00737-13.
(2). Huang YW, A.R. Patterson, T. Opriessnig, B.A. Dryman**,** A. Gallei, K.K. Harrall, E.M. Vaughn, M.B. Roof, and X.J. Meng. 2012. Rescue of a porcine anellovirus (*Torque teno sus virus 2*) from cloned genomic DNA in pigs. *Journal of Virology*. **86**:6042-6054.
(3). Huang YW, K.K. Harrall, B.A. Dryman, T. Opriessnig, E.M. Vaughn, M.B. Roof, and **X.J. Meng**. 2012. Serological profile of Torque teno sus virus species 1 (TTSuV1) in pigs and antigenic relationships between two TTSuV1 genotypes (1a and 1b), between two species (TTSuV1 and 2), and between porcine and human anelloviruses. *Journal of Virology*. **86(19):**10628-10639.

Complete List of Published Work (Google Scholar): Total >305 publications, cited >20,700 times as of May 2017 with a h-index of 78 [https://scholar.google.com/citations?user=86WX4IUAAAAJ&hl=en].

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support (*Selected*)

NIH/NIAID R01 AI50611 Meng (PI) 06/15/2002 - 12/31/2018
A chicken model to study hepatitis E virus pathogenesis
The major goal of this project is to develop a chronic HEV infection animal model to delineate the immunological factors leading to chronic infection. No overlap.
Role: PI

NIH/NIAID R01 AI74667 Meng (PI) 03/01/2008 - 06/30/2018
Mechanism of Hepatitis E virus replication and pathogenesis
The major goal is to delineate mechanisms of HEV replication, and cross-species infection. No overlap.
Role: PI

NIH/NCRR T32 RR021819 Meng (PI) 10/01/2006 - 9/30/2017
Animal Model Research for Veterinarians
The major goal of this project is to train veterinarians as biomedical scientists in the area of animal models for human diseases including hepatitis E. No overlap.
Role: PI

USDA- AFRI-2013-67015-21342 Meng (PI) 09/01/2013 to 08/31/2018
Identification of CD8 T cell epitopes of multiple heterologous PRRSV strains for vaccine development
The major goal is to identify T cell epitopes from heterologous strains of PRRSV to facilitate the development of a broadly-protective vaccine. No overlap.
Role: PI

Pfizer Inc #457354 Meng (PI) 03/15/2011 - 03/14/2018
Development of next generation broadly protective marker vaccines against porcine circovirus type 2.
The major goal is to develop a broadly-protective vaccine against all known strains of PCV2. No overlap.
Role: PI

Boehringer Ingelheim #457926 Meng (PI) 02/15/2013 - 03/14/2018
Novel species of Torque teno sus virus (TTSuV) from pigs in the USA and its disease association
The major goal of the project is to characterize a novel species of TTSuV. No overlap.
Role: PI

Eli Lilly and Co #458262 Meng (PI) 06/1/2014 - 05/31/2018
Development of novel vaccines against the emerging porcine enteric coronaviruses in the United States
The major goal of the project is to develop vaccines against PEDV and PdCoV. No overlap.
Role: PI

Boehringer Ingelheim #458887 Meng (PI) 03/1/2015 - 02/28/2018
Development of piglet diarrhea orthoreovirus vaccines
The major goal of the project is to develop vaccines against the novel porcine orthoreovirus. No overlap.
Role: PI

Zoetis Inc #459338 Meng (PI) 10/1/2016 - 09/31/2019
Broadly-protective dendritic cell-targeted PRRSV subunit vaccines
The major goal of the project is to develop a subunit PRRS virus vaccine targeting directly to dendritic cells. No overlap.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Lijuan Yuan, PhD.

eRA COMMONS USER NAME (credential, e.g., agency login): Yuan21

POSITION TITLE: Associate Professor (tenured)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Beijing Health School, Beijing, PRC	Diploma	07/1981	Pharmaceutics
Beijing University, Beijing, PRC	Diploma	07/1985	Biochemistry
Capital Institute of Pediatrics, PRC	M.S.	08/1991	Immunology/Virology
The Ohio State University, Wooster, OH	Ph.D.	06/2000	Immunology/Virology
LID, NIAID, NIH, Bethesda, MD	Postdoc	06/2002	Molecular Virology and Immunology

A. Personal Statement

My research interest focuses on the host-pathogen interactions of human enteric viral diseases and evaluating intervention strategies to reduce vial diarrhea using gnotobiotic pig models, including wild type and genetically engineered gene-knockout pigs and human-gut-microbiota colonized pigs. As PI, Co-PI and contract PI on several current and previous NIH, Gates Foundation, PATH, and international vaccine-company grants, I studied the pathogenesis of human norovirus and rotavirus, the immunogenicity and protective efficacy of various vaccine formulations, as well as adjuvants and immunization routes. I successfully administered all of the projects (e.g. staffing, research protections, budget), coordinated research efforts with my trainees and other researchers, and produced peer-reviewed publications from each project. The resulting research findings established me as one of a few experts leveraging the gnotobiotic pig model to study human enteric viral pathogenesis, immunity, therapeutics, vaccines and influences of probiotics/prebiotics and gut microbiota. In the past 8 years, I have mentored 8 PhD students (major advisor for 7; 4 have graduated), 12 post-docs and visiting scholars. I have the leadership, training, expertise, facilities and motivation necessary to serve as a co-investigator on this T32 program.

B. Positions and Honors

Positions and Employment

1996-2000	Graduate Research Associate, Food Animal Health Research Program, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH Ph.D. Dissertation: Studies of immunity to human rotavirus and candidate vaccines in a gnotobiotic pig model.
2000-2002	Post-Doctoral Fellow, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.
2002-2007	Adjunct Assistant Professor and Research Scientist, Food Animal Health Research Program, Department of Veterinary Preventive Medicine, The Ohio State University, Wooster, OH.
2007-2013	Assistant Professor of Virology, Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA.
2013-	Associate Professor of Virology (with tenure), Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA.
2013-	Associate Professor of Virology, Faculty of Health Sciences, Virginia Polytechnic

Institute and State University

Other Experience and Professional Memberships

1996-current, American Society for Virology (life member)
2002-current, American Society for Microbiology
2010-current, International Society for Vaccines
2006-current, American Association for the Advancement of Science
2002-current, Phi Zeta National Honor Society of Veterinary Medicine
1995-2012, Society for Mucosal Immunology
2012, American Association of Immunologists
1999-2007, American Association of Veterinary Immunologists
1998-2004, Phi Kappa Phi National Honor Society

Ad Hoc Reviewer for Journals:

Journal of Virology; Journal of Medical Virology; Future Virology; Viral Immunology; Virus Research; Virology; Archives of Virology; Virology: Research and Treatment; PLoS ONE; Scientific Reports, Vaccine; Clinical and Vaccine Immunology; Human Vaccines & Immunotherapeutics; Inflammation Research; Immunological Investigations; Clinical and Experimental Immunology; Anaerobe; Applied and Environmental Microbiology; Veterinary Immunology and Immunopathology; Veterinary Microbiology; BMC Microbiology; Future Microbiology; Microbial Ecology; Beneficial Microbes; Pediatric Research; Journal of Medical Primatology; Journal of Probiotics & Health; Microbes and Infection; Infection, Genetics and Evolution; Avian Pathology; Animal Health Research Reviews; Journal of Dairy Science; Veterinaria Italiana; African Journal of Pharmacy and Pharmacology; European Journal of Pharmaceutics and Biopharmaceutics; International Journal for Biotechnology and Molecular Biology Research; Nucleus Medical Media; The ILAR Journal; Elsevier Academic Press; Springer.

Grant Reviewer for funding agencies:

Academy of Sciences of the Czech Republic (June 2008).
NIAID Special Emphasis Panels for RFP NIH-NIAID-DMID-AI2008041 Animal Models of Infectious Diseases- (July 2009).
Wellcome Trust Technology Development Grant and Project Grant, UK (July 2009 and March 2010).
Portuguese Foundation for Science and Technology (September 2012).
NIAID, NIH Review panelist for RFA-AI-12-020 SEP ZAI1-JKB-M-J4 (December 2012).
NIH Comparative Medicine Special Emphasis Panel ZOD1 CM-6 (June 2013) and ZOD1 CG-9(01) (October 2013).
NSF Review panelist (December 2013 and December 2014).
NIH Special Emphasis Panel/Scientific Review Group 2014/05 ZRG1 IDM-S (55) R (March 2014).
Czech Science Foundation, Czech Republic (July 2014).
USDA-NIFA A1221, A1223, and A1224 Animal Health Panel A (Animal Health, Tools and Resources - Veterinary Immune Reagents) (October 2014).
NIAID, NIH Special Emphasis Panel/Scientific Review Group 2015/01 ZAI1 LG-M (J1) for RFA-AI-14-011 (Novel, Alternative Model Systems for Enteric Diseases U19) (November 2014).
The Research Foundation-Flanders (FWO), Brussel, Belgium, application for international collaboration programs (July 2014).
National Park Board (December 2014).
USDA Agriculture and Food Research Initiative Exploratory Research Program: Animal Health and Disease Prevention (May 2015).
Qatar National Research Foundation NPRP9 (January 6, 2016)
USDA-NIFA A1221 Animal Health Panel A (October 31- November 3, 2016)
National Pork Board (January 4, 2017).

Honors

1998	Membership of Phi Kappa Phi Honor Society, inducted May, 1998, The Ohio State University, Columbus, OH
1999 – 2000	Charles E. Thorne Memorial Assistantship Award from Ohio Agricultural Research and Development Center, The Ohio State University, Wooster, OH
1999 – 2000	Presidential Fellowship, The Ohio State University, Columbus, OH
2000	Membership of Phi Zeta Veterinary Medicine National Honor Society, inducted June, 2000, The Ohio State University, Columbus, OH

2001	William E. Krauss Director's Award for Excellence in Research from Ohio Agricultural Research and Development Center, The Ohio State University, Wooster, OH
2009	American Society for Microbiology International Professorship Award for Asia
2009	Honorary Professorship, Yunnan Agricultural University, China
2010	Virginia Tech Scholar of the Week, December 6-10, 2010
2011	Pfizer Award for Research Excellence 2011
2017	Outstanding Graduate Mentor Award, College of Veterinary Medicine, Graduate School, Virginia Polytechnic Institute and State University, 2016-2017

C. Contribution to Science

Vaccine development. I am engaged in developing various novel vaccines for rotavirus and norovirus and in developing novel approaches to enhance vaccine immunogenicity and protective efficacy.

a. Kocher J, Bui T, Giri-Rachman E, Wen K, Li G, Yang Y, Liu F, Tan M, Xia M, Zhong W, Jiang X, Yuan L. 2014. Intranasal P particle vaccine provided partial cross-variant protection against human GII.4 norovirus diarrhea in gnotobiotic pigs. *J Virol*. 88 (17):9728-9743 (doi:10.1128/JVI.01249-14). PMC4136312.
b. Wen K, Li G, Bui T, Liu F, Li Y, Kocher J, Lin L, Yang X, Yuan L. 2012. High dose and low dose *Lactobacilli acidophilus* exerted opposite immune modulating effects on T cell immune responses induced by an oral human rotavirus vaccine in gnotobiotic pigs. *Vaccine* 30:1198–1207 (doi:10.1016/j.vaccine.2011.11.107). PMC3269528.
c. Wen X, Wen K, Cao D, Li G, Jones RW, Li J, Szu S, Hoshino Y, Yuan L. 2014. Inclusion of a universal tetanus toxoid CD4+ T cell epitope P2 significantly enhanced the immunogenicity of recombinant rotavirus ΔVP8* subunit parenteral vaccines. *Vaccine* 32 (35):4420-7. PMC4104241.
d. Wen X, Cao D, Jones RW, Hoshino Y, Yuan L. 2015. Tandem truncated rotavirus VP8* subunit protein with T cell epitope as non-replicating parenteral vaccine is highly immunogenic. *Human vaccines & immunotherapeutics* 11: 2483-2489 (doi:10.1080/21645515.2015.1054583). PMC 4635725

Gnotobiotic pig model of human enteric virus infection and disease. To study host-pathogen interactions of human enteric viruses, an appropriate model system must be utilized. I am one of a few experts in the world developing gnotobiotic pig models of human enteric virus infection and diseases, which is an excellent animal model to study the human diseases. In addition to gnotobiotic pig models of human rotavirus and norovirus infection and diseases, my lab recently established the first gnotobiotic pig model of human enterovirus 71 infection and disease. My lab also established the first gnotobiotic pig model transplanted with newborn infant human gut microbiota and used the model for rotavirus infection and vaccine studies.

a. Bui T, Kocher J, Li Y, Wen K, Li G, Liu F, Yang X, LeRoith T, Tan M, Xia M, Zhong W, Jiang X, Yuan L. 2013. Median infectious dose of human norovirus GII.4 in gnotobiotic pigs is decreased by simvastatin treatment and increased by age. *J. Gen Virol*. 94:2005-2016. PMC3749057.
b. Yang X, Li G, Wen K, Bui T, Liu F, Kocher J, Jortner BS, Vonck M, Pelzer K, Deng J, Zhu R, Li Y, Qian Y, Yuan L. 2014. Neonatal gnotobiotic pig model of human enterovirus 71 infection and associated immune responses. *Emerging Microbes and Infections* 3, e35; doi:10.1038/emi.2014.35. PMC4051366.
c. Zhang H, Wang H, Shepherd M, Wen K, Li G, Yang X, Kocher J, Giri-Rachman E, Dickerman A, Settlage R, Yuan L. 2014. Probiotics and virulent human rotavirus modulate the transplanted human gut microbiota in gnotobiotic pigs. *Gut Patho*. 6:39 (doi:10.1186/s13099-014-0039-8). PMC4209515.
d. Wen K, Tin C, Wang H, Li G, Giri-Rachman E, Yang X, Kocher J, Bui T, Clark-Deener S, Yuan L. 2014. Probiotic *Lactobacillus rhamnosus* GG enhanced Th1 cellular immunity but did not affect antibody responses in a human gut microbiota transplanted neonatal gnotobiotic pig model. *PLoS ONE* 9(4): e94504. (doi:10.1371/journal.pone.0094504). PMC3983166.

Immunological responses to human enteric viruses. Rotavirus and norovirus are the leading causes of acute gastroenteritis, especially for infants and young children worldwide. The large clinical impact of this disease drives my research interest in the immunological responses to its etiological agents. Using the gnotobiotic pig model, my laboratory is able to examine immunological responses to rotavirus and norovirus infections on a clear background, effectively making me a porcine immunologist. Many of my studies have expanded the knowledge of the porcine immune system and immune responses to viral infections and their similarity and difference from responses in humans.

a. Wen K, Bui T, Weiss M, Li G, Kocher J, Yang X, Jobst PM, Vaught T, Ramsoondar J, Ball S, Clark-Deener S, Ayares D, Yuan L. B-cell-deficient and CD8 T-cell-depleted gnotobiotic pigs for the study of human rotavirus vaccine-induced protective immune responses. Viral Immunol. 2016 Jan 29. [Epub ahead of

print].

b. Wen K, Li G, Yang X, Bui T, Bai M, Liu F, Kocher J, Yuan L. 2012. CD4+CD25-FoxP3+ regulatory cells are the predominant responding regulatory T cells after human rotavirus infection or vaccination in gnotobiotic pigs. *Immunology*. 137: 160–171 (doi:10.1111/j.1365-2567.2012.03617.x). PMC3461397.
c. Wen K, Bui T, Li G, Liu F, Li Y, Kocher J, Yuan L. 2012. Characterization of immune modulating functions of γδ T cell subsets in a gnotobiotic pig model of human rotavirus infection. *Comp Immunol Microbiol Infect Dis.* 35:289-301 (doi:10.1016/j.cimid.2012.01.010). PMC3366054.
d. Wen K, Azevedo MSP, Gonzalez AM, Zhang W, Saif LJ, Li G, Yousef AE, Yuan L. 2009. Toll-like receptor and innate cytokine responses induced by lactobacilli colonization and human rotavirus infection in gnotobiotic pigs. *Vet Immunol Immunopathol* 127:304-315 (doi:10.1016/j.vetimm.2008.10.322). PMC2653198.

Probiotics and rice bran as therapeutics and vaccine adjuvants. Vaccines for rotavirus and other enteric pathogens often have low efficacy in low-income countries. Gut microbiome dysbiosis and associated enteropathy is hypothesized to be a major cause of compromised vaccine-induced immune response. I conducted the first NIH funded study (R01AT004789) using probiotics to enhance rotavirus vaccine immunogenicity, which was the impetus to the "probiotic adjuvant" concept. This concept, which is the use of probiotics as vaccine adjuvants, is now widely appreciated and several clinical trials utilizing this vaccine concept have been conducted. We demonstrated that rice bran can reduce rotavirus and norovirus diarrhea and enhance the immunogenicity of rotavirus vaccines.

a. Lei S, Ramesh A, Twitchell E, Wen K, Bui T, Weiss M, Yang X, Kocher J, Li G, Giri-Rachman E, Nguyen VT, Jiang X, Ryan EP, Yuan L. 2016. High protective efficacy of probiotics and rice bran against human norovirus infection and diarrhea in gnotobiotic pigs. Front. Microbiol. doi: 10.3389/fmicb.2016.01699. PMC5090003.
b. 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.
c. Yang X, Wen K, Tin C, Li G, Wang H, Kocher J, Pelzer K, Ryan E, Yuan L. 2014. Dietary rice bran protects against rotavirus diarrhea and promotes Th1 type immune responses to human rotavirus vaccine in gnotobiotic pigs. *Clin Vaccine Immunol*. 2014; 21:1396-1403 (doi:10.1128/CVI.00210-14). PMC4266357.
d. Liu F, Wen K, Li G, Yang X, Kocher J, Bui T, Jones D, Vonck M, Pelzer K, Yuan L. 2014. Dual functions of *Lactobacillus* acidophilus NCFMTM in protection against rotavirus diarrhea in gnotobiotic pigs vaccinated with a human rotavirus vaccine. *J Pediatr Gastroenterol Nutr*. 58: 171-178 (doi:10.1097/MPG.0000000000000197). PMC3908657.

Investigating human viral gastroenteritis – basic through applied. Much of my early career portfolio is made up of basic research studies investigating the pathogenesis and protective immunity to enteric viruses. Such studies identified a role for intestinal IgA antibody secreting cells and IFN-γ producing T cells in the protective immunity against human rotavirus diarrhea. However, my studies also traverse into applied research, such as performing pre-clinical testing of various candidate vaccines. For instance, my early work demonstrated that orally priming with live vaccine and boosting with a non-replicating vaccine using a different route is a highly effective vaccination approach. The combination of basic and applied research has provided insight into the immunological response to etiological agents of acute gastroenteritis, thereby also guiding the development of more effective vaccines.

a. Yuan L, Ward LA, Rosen BI, To TL, Saif LJ. 1996. Systemic and intestinal antibody-secreting cell responses and correlates of protective immunity to human rotavirus in a gnotobiotic pig model of disease. *J Virol.* 70:3075-3083. PMC190169.
b. Yuan L, Kang SY, Word LA, To TL, Saif LJ. 1998. Antibody-secreting cell responses and protective immunity in gnotobiotic pigs inoculated orally or intramuscularly with inactivated human rotavirus. *J Virol.* 72:330-338. PMC109380.
c. Yuan L, Iosef C, Azevedo MSP, Kim Y, Qian Y, Geyer A, Chang KO, Saif LJ. 2001. Protective immunity and antibody-secreting cell responses elicited by combined oral attenuated Wa human rotavirus and intranasal Wa 2/6 -virus-like-particles with mutant Escherichia coli heat-labile toxin (LT-R192G) adjuvant in gnotobiotic pigs. *J Virol.* 75:9229-9238. PMC114490.
d. Yuan L, Wen K, Azevedo, MSP, Gonzalez AM, Zhang W, Saif LJ. 2008. Virus-specific intestinal IFN-γ producing T cell responses induced by human rotavirus infection and vaccines are correlated with protection against rotavirus diarrhea in gnotobiotic pigs. *Vaccine* 26:3322-3331 (doi:

10.1016/j.vaccine.2008.03.085). PMC2574896.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/12aupwHx9npky/bibliography/40331096/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R21OD019934A Yuan (PI) 08/1/2015-05/31/2018
CRISPR/Cas9 guided production of genetically engineered pigs lacking CD8+ T cells
In this project, homology directed repair pathway at high frequency during CRISPR/Cas9 mediated genetic modification will be used to generate several types of immune-deficient pigs. The proof of concept study using CD8+ T cell deficient pigs for elucidating the mechanism of human norovirus vaccine-induced protection will provide insights that can facilitate the development of effective vaccines

Anhui Zhifei Longcom Biopharmaceutical, China Yuan (PI) 12/31/2016–12/31/2017
Evaluation of P-VP8* vaccine in gnotobiotic pig model of human rotavirus infection and diarrhea.
Our goal is to evaluate the immunogenicity and protective efficacy of the P-VP8* vaccine in the gnotobiotic pig model of human rotavirus infection and diarrhea.

5R01AI50611-10 X.J. Meng (PI) Role: Co-I 1/1/2013–12/31/2017
A chicken model to study hepatitis E virus pathogenesis
Our goal is to delineate the predictive immunological factors leading to the progression into chronicity and to understand the mechanisms of hepatitis E virus (HEV) immunopathogenesis. The results will be important for devising effective prevention and treatment strategies against HEV.

Completed Research Support

5R01AI089634 X. Jiang (PI) Role: subcontract PI 5/15/2010-4/30/2015
Novel vaccine against norovirus
Our goal is to develop a vaccine against noroviruses based on P particles and to evaluate the safety and immunogenicity of the vaccine in the gnotobiotic pig model of human norovirus infection and disease.

OPP1108188. Yuan (PI) 5/1/2014-10/31/2015
Bill and Melinda Gates Foundation Grand Challenges Exploration Grant Phase I
Gnotobiotic Pig Model for Dysbiosis and Enteric Immunity
Our goal is to develop a humanized neonatal gnotobiotic pig model that closely mimics dysbiosis and enteropathy in infants of developing countries and use the model for testing intervention strategies.

G-6298-1. Elizabeth Ryan (PI) Role: subcontract PI 6/15/2012-10/31/2015
Bill and Melinda Gates Foundation Grand Challenges Exploration Grant Phase II
Dietary rice bran supplementation for gut mucosal immunity and healthy rice crop improvement
Our goal is to determine whether selected rice bran can reduce the susceptibility to infection and diarrhea upon virulent human rotavirus infection in gnotobiotic pigs, examine the ability of rice bran to promote the immunogenicity and improve the protective efficacy of oral rotavirus vaccine, and evaluate the prebiotic effect of rice bran on the growth of probiotics and modulation of the metabolome.

R01AT004789 Yuan (PI) 8/1/2009-7/31/2014
Mechanisms of immune modulation by probiotics.
Our goal is to identify the mechanisms by which probiotics exert the adjuvant effects on rotavirus vaccines.
PATH-Program for Appropriate Technology in Health Yuan (PI) 12/17/2013-3/31/2015
Reduction of rotavirus diarrhea by neutral endopeptidase inhibitor racecadotril.
Our goal is to evaluate the effectiveness of a neutral endopeptidase inhibitor racecadotril in reducing rotavirus diarrhea in the neonatal gnotobiotic pig model of human rotavirus infection and diarrhea.

Lanzhou Institute of Biological Products, China Yuan (PI) 6/1/2010-08/30/2012
Evaluation of the immunogenicity and cross protection of Lanzhou trivalent reassortant rotavirus vaccine.
Our goal is to determine the immunogenicity and cross protective efficacy of the live oral trivalent vaccine in the gnotobiotic pig model of human rotavirus (G1P1A[8]) infection and disease and to identify the mechanism of cross protective immunity induced by rotavirus vaccines.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: **Allen, Irving Coy**

eRA COMMONS USER NAME (credential, e.g., agency login): **COY_ALLEN**

POSITION TITLE: **Assistant Professor**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
East Carolina University, Greenville, NC	BS	05/1997	Biology
University of North Carolina at Greensboro	MS	12/2000	Biology
University of North Carolina at Chapel Hill	PhD	12/2006	Genetics and Molecular Biology
University of North Carolina at Chapel Hill	Postdoc	06/2011	Immunology
North Carolina State University	MBA	12/2012	Bioscience Management

A. PERSONAL STATEMENT:

What are the critical factors associated with the initiation and resolution of inflammation? Likewise, overzealous inflammation is directly associated with a myriad of human and veterinary diseases. How can we control this overzealous immune response and maintain immune system homeostasis? These are the questions that our lab is attempting to address. My research program is focused on exploring the intersection between inflammatory diseases, host-microbe interactions, and cancer. Specifically, we are interested in understanding the contribution of unique families of pattern recognition receptors (PRRs) in modulating disease pathogenesis. PRRs are proteins that recognize pathogen-associated molecular patterns (PAMPs), which are present within viruses, bacteria, and other microbial species. PRRs are also responsible for sensing damage-associated molecular patterns (DAMPs), which are produced by host cells under a variety of pathologic conditions to coordinate the immune response to cellular damage and/or stress. PAMPs and DAMPs are recognized by three major classes of PRRs: the Toll-like receptors (TLRs); retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs); and the nucleotide-binding domain-leucine-rich repeat-containing molecules ("NOD-like" receptors; NLRs). These three protein families and their respective signaling cascades form the foundation of the innate immune system. **The overarching goal of our research program is to elucidate the mechanisms associated with PRR regulation of immune system homeostasis in human and veterinary health and to gain greater insight into the role of these proteins in modulating disease pathobiology.**

a. **Allen, I.C.**, Tekippe, E.M., Woodford, R.M., Uronis, J.M., Holl, E.K., Rogers, A.B.,Herfarth, H.H., Jobin, C., Ting, J.P.Y. (2010). The NLRP3 Inflammasome Functions as a Negative Regulator of Tumorigenesis during Colitis Associated Cancer. ***The Journal of Experimental Medicine***. May 10;207(5):1045-56. PubMed PMID: 20385749

b. **Allen,I.C.**, Wilson,J.E., Schneider, M., Lich,J.D., Authur,J.C., Woodford,R.M., Uronis,J.M., Davis,B.K., Roberts,R.A., Rogers,A.B., Herfarth,H.H., Jobin,C., and Ting, J.P.Y. (2012). NLRP12 Functions as a Negative Regulator of Noncanonical NF-κB Signaling and Tumorigenesis during Colitis Associated Cancer. ***Immunity*.** May 25;36(5):742-54. PubMed PMID: 22503542

c. Williams, T.M., Leeth R.A., Rothschild D.E., Coutermarsh-Ott, S.L., McDaniel D.K., Simmons A.E., Heid B., Cecere T.E., **Allen,I.C.** (2015). The NLRP1 Inflammasome Attenuates Colitis and Colitis Associated Tumorigenesis. ***The Journal of Immunology*.** Apr 1;194(7):3369-80. PMID: 25725098.

d. Coutermarsh-Ott, S.L., Simmons, A., Capria, V., LeRoith, T., Wilson, J.E., Heid, B., Washington, C., Qin, Q., Ting, J., Hontecillas-Magarzo, R., Bassaganya-Riera, J., Dervisis, N., **Allen, I.C.** (2016).

NLRX1 Suppresses Tumorigenesis and Attenuates Histiocytic Sarcoma through the Negative Regulation of NF-κB Signaling. ***Oncotarget.*** May 31;7(22):33096-110. PMID: 27105514

B. POSITIONS AND HONORS:

Research and Professional Experience:

1996	Microbiologist: North Carolina State Government Internship, NC Department of Agriculture, Plant Industry Division, Raleigh, NC
1997-2001	Laboratory Technologist I: Laboratory Corporation of America, Paternity Testing Division, Burlington, NC
2001-2002	Molecular Biology Laboratory Technologist (part-time): North Carolina State University, Center for Applied Aquatic Ecology, Raleigh, NC
2001-2002	Research Analyst: Duke University, Center for Human Genetics, Durham, NC
2007-2011	Postdoctoral Research Fellow: UNC Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
2011-2012	Research Associate/Research Assistant Professor: UNC Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC
2012-present	Assistant Professor: Virginia Polytechnic Institute and State University, Virginia Maryland Regional College of Veterinary Medicine, Department of Biomedical Sciences and Pathobiology, Blacksburg, VA
2014-present	Assistant Professor of Health Sciences: Virginia Tech, Translational Biology, Medicine, and Health Program, Virginia Tech Carilion School of Medicine and Research Institute, Roanoke, Virginia 24016
2017-present	Assistant Professor, Department of Biomedical Sciences, Virginia Tech Carilion School of Medicine, Roanoke, Virginia 24016

Academic and Professional Honors:

2000	UNC Greensboro University Excellence Award
2008	UNC Chapel Hill Postdoctoral Award for Research Excellence
2009	NIH Individual National Research Service Award
2009	UNC Chapel Hill Graduate Education Advancement Board Impact Award
2009	The Lineberger Comprehensive Cancer Center Joseph S. Pagano Award
2010	American Cancer Society Postdoctoral Fellowship
2011	NIH K01 Career Development Award
2014	The 2014 Chambers-eBioscience Memorial Award, AAI
2014	The 2014 Travel for Techniques Award, AAI
2015	AAI Early Career Faculty Travel Grant
2016	AAI Early Career Faculty Travel Grant
2016	AAI Travel Grant for the International Congress of Immunology (ICI 2016)
2017	AAI Early Career Faculty Travel Grant

Service and Other Experience:

2013-2016	*PLoS One* Editorial Board Member (Academic and Section)
2013-2015	Society of Mucosal Immunology, Website Committee
2014-2016	Society for Leukocyte Biology Development Committee
2014	AAAS Panelist at the USA Science and Engineering Festival
2014-2017	Research Committee, VMCVM
2015	NSF Peer Review Committee: Graduate Research Fellowship Program
2015 – 2019	Associate Editor of *The Journal of Immunology*
2015 – 2018	Section Editor of *PLoS One*
2015 - 2018	Society of Mucosal Immunology, Website Committee Chairman
2016	NIH Study Section: Tumor Microenvironment (TME)

C. CONTRIBUTIONS TO SCIENCE:

1. Inflammatory Disease: Elucidating the contribution of PRRs in inflammatory diseases is an essential pillar of my laboratory. My research program is focused primarily on mechanisms associated with mucosal inflammatory diseases, such inflammatory bowel disease (IBD). Over the last 7 years, we have made significant progress in this field. Crohn's disease and ulcerative colitis are common and debilitating

manifestations of IBD. Together, these two disorders afflict approximately 1.4 million Americans and over 4 million people worldwide. IBD is considered to be an autoimmune disease that is characterized by an imbalance of pro-inflammatory and anti-inflammatory signaling pathways in the gastrointestinal system. My team's work in this field generated some of the first studies to associate PRRs with protective roles in disease pathobiology. For example, when we first began exploring the NLR family in IBD, we hypothesized that attenuation of the pro-inflammatory NLRs and associated pathways would attenuate disease pathogenesis. However, our findings surprisingly revealed that these pro-inflammatory proteins are actually essential in maintaining immune system homeostasis in the gut and removing any of these proteins actually worsens disease progression, suggesting that they actually play a vital protective role in the gut. Together, our work suggests that each NLR attenuates IBD through cell type, temporal, and stimuli specific mechanisms in response to specific elements of the host microbiome. This line of research has resulted in publications in several high profile journals, including *The Journal of Experimental Medicine* (IF: 14.10), *Inflammatory Bowel Diseases* (IF: 5.475) and *The Journal of Immunology* (5.67). In addition to the pro-inflammatory sub-group of NLRs, I was also one of the first people to identify a role for the anti-inflammatory NLR NLRP12 in IBD. This unique NLR functions through the negative regulation of NF-κB signaling. NF-κB is a master regulator of gene transcription and is a critical modulator of the immune response. NF-κB signaling is divided into 2 distinct cascades, termed the canonical pathway and non-canonical pathway. My research revealed a role for NLRP12 modulation of the non-canonical NF-κB signaling pathway in disease pathogenesis. This is a very unique finding and resulted in a publication in the journal *Immunity* (IF: 20.72). These findings were also the basis for a successfully funded NIH R03 grant and a series of internal IRC grants to better evaluate the role of PRRs in the modulation of inflammatory signaling pathways. Together, the work from my research teams in these areas of study have resulted in a paradigm shift in the way we think about not only NLRs, but also other PRRs, pro-inflammatory cytokines and signaling pathways in the gut and identified protective roles for the NLR family in not only IBD, but a range of other inflammatory diseases. We are now exploring the contribution of not only NLRs, but also other PRRs in other inflammatory diseases beyond IBD. Furthermore, we are also translating these findings from bench-to-bedside by elucidating methods to target PRR signaling pathways with novel therapeutic approaches.

a. **Allen,I.C.**, Wilson,J.E., Schneider, M., Lich,J.D., Authur,J.C., Woodford,R.M., Uronis,J.M., Davis,B.K., Roberts,R.A., Rogers,A.B., Herfarth,H.H., Jobin,C., and Ting, J.P.Y. NLRP12 Functions as a Negative Regulator of Noncanonical NF-κB Signaling and Tumorigenesis during Colitis Associated Cancer. ***Immunity***. May 25;36(5):742-54. 2012. PMID: 22503542.

b. Williams, T.M., Leeth,R.A., Rothschild,D.E., McDaniel,D.K., Coutermarsh-Ott,S.L., Simmons,A.E., Kable,K.H., Heid,B., **Allen,I.C.** Caspase-11 Attenuates Gastrointestinal Inflammation and Experimental Colitis Pathogenesis. ***AJP-Gastrointestinal and Liver Physiology***. Jan 15;308(2):G139-50. 2015. PMID: 25414099.

c. McDaniel, D., Jo, A., Ringel, V., Coutermarsh-Ott, S., Powell, M., Long, T., Oestreich, K., Davis, R., and **Allen, I.C.** (2017). PEO-PDLLA Core-Shell Nanoparticles have Similar Cellular Uptake Dynamics and Biodistribution in Th1 and Th2 Microenvironments. **Nanomedicine: Nanotechnology, Biology, and Medicine**. (In Press). doi: 10.1016/j.nano.2016.12.015. [Epub ahead of print]. PMID: 28040495

d. Andrew L., Hontecillas, R., Philipson, C., Tubau-Juni, N., Abedi, V., Heltzel, C., Philipson, N., Kale, S., Carbo, A., Uren, A., Dickerman, A., Michalak, P., Corl, B.A., Eden, K., **Allen, I.C.**, and Bassaganya-Riera, J. (2017). NLRX1 regulates effector and metabolic functions of CD4+ T cells. ***Journal of Immunology***. Mar 15;198(6):2260-2268.

2. <u>Cancer Immunology:</u> There is an intimate link between inflammation and tumorigenesis. Nowhere is this more apparent than in the context of IBD and colon cancer. While the association is clear, the mechanism is not well understood. For example, which comes first, inflammation or cancer? To address some of the fundamental questions associated with tumor immunology, our laboratory is currently utilizing both common and novel models of inflammation driven tumorigenesis in the gut. We are continuing to focus on the contribution of the PRRs in these processes. Our current work is associated with both NLR and TLR modulation of tumorigenesis. As with IBD, my early work in this field generated some of the first studies to associate NLR proteins with epithelial cell barrier function and the attenuation of tumorigenesis in the gut. Indeed work conducted since arriving at Virginia Tech and published in *The Journal of Immunology* (5.570) has revealed that each NLR appears to attenuate tumorigenesis, likely through cell type, temporal, and stimuli specific mechanisms associated with recognition of atypical components of the host microbiome. We are now extending these

findings to regulators of the TLR and RLR families and exploring the contribution of these PRRs in other cancer models with a connection to aberrant immune system function, including lung cancer and breast cancer.

- **a.** Williams, T.M., Leeth,R.A., Simmons,A.E., Heid,B., Cecere, T.E., **Allen,I.C.** The NLRP1 Inflammasome Attenuates Colitis and Colitis-Associated Tumorigenesis. ***The Journal of Immunology***. Apr 1;194(7):3369-80. 2015. PMID: 25725098.
- **b.** Coutermarsh-Ott, S.L., Simmons, A., Capria, V., LeRoith, T., Wilson, J.E., Heid, B., Washington, C., Qin, Q., Ting, J., Hontecillas-Magarzo, R., Bassaganya-Riera, J., Dervisis, N., **Allen, I.C.** NLRX1 Suppresses Tumorigenesis and Attenuates Histiocytic Sarcoma through the Negative Regulation of NF-κB Signaling. ***Oncotarget.*** May 31;7(22):33096-33110. 2015. PMID: 27105514.
- **c.** Goswami, I., Morrison, R.G., Coutermarsh-Ott, S., **Allen, I.C.**, Davalos, R.V., Verbridge, S.S., Bickford, L.R. (2016). Influence of electric field ablation on cell signaling in triple negative breast cancer cells. ***Bioelectrochemistry.*** 113(2017):42-50. IF: 4.172.
- **d.** Rothschild, D.E., Zhang, Y., Diao, N., Lee, C., Chen, K., Caswell, C.C., Slade, D.J., Helm, R.F., LeRoith, T., Li, L., **Allen, I.C.** (2016). Enhanced mucosal defense and reduced tumor burden in mice with the compromised negative regulator IRAK-M. **EBioMedicine** Feb;15:36-47. PMID: 27939424.

3. Host-Microbe Interactions: The PRRs were originally identified due to their role in initiating the host innate immune response following pathogen exposure. My earliest work in the NLR field focused on the contribution of both inflammasome forming NLRs and regulatory NLRs in host-pathogen interactions. Indeed, many of my original publications in this field were some of the first studies evaluating the physiological and clinical contribution of NLRs following pathogen exposure using genetically modified mice. For example, my work with influenza virus and inflammasome forming NLRs was published in *Immunity* (IF: 20.72) and underlie the current paradigm of NLR function, whereby pathogens are sensed at early time-points of infection resulting in NLR signaling activation and subsequent optimization of host-pathogen immune responses. Subsequent studies using a diverse range of viruses and bacteria have been essential in elucidating mechanistic insight associated with unique members of the NLR family. For example, I published the first *in vivo* study associated with NLRX1, which is a member of a novel sub-group of NLRs. I am the first author on this manuscript, which is the original paper characterizing NLRX1 in the mouse (*Immunity;* IF: 20.72). Likewise, I am either the author or a co-author on the first papers published describing the roles of the related NLRs, NLRP12 (*The Journal of Immunology; IF: 5.67*) and NLRC3 (*Nature Immunology; IF: 26.20*), which also function as negative regulators of inflammation in the mouse following exposure to pathogens. These proteins function through the regulation of signaling cascades driven by other classes of PRRs, including the TLRs and RLRs. We are continuing to study the role of the inflammasome forming NLRs and regulatory NLRs in a variety of pathogen models. Likewise, we are also studying the contribution of these proteins and the signaling pathways they modify in the recognition of components of the host microbiome in support of the inflammatory disease and cancer research focus areas.

- **a.** **Allen, I.C.,** Scull, M.A., Moore, C.B., Holl, E.K., Taxman, D.J., Guthrie, E.H., Pickles, R.J., Ting, J.P.Y. The NLRP3 Inflammasome Is Essential for the Regulation of Innate Immune Responses to Influenza A Virus Infection. ***Immunity***. Apr;30(4):556-65. 2009. PMID: 19362020.
  Featured in Editorial: Owen,D.M. and Gale,M., Jr. (2009). Fighting the Flu with Inflammasome Signaling. *Immunity*. Apr;30(4):556-65.
- **b.** Perkowski, E.F., McCann, J.R., Sullivan, J.T., Malik, S., **Allen, I.C.**, Godfrey, V., Hayden, J.D., Braunstein, M. (2016). An orphaned Mce-associated protein of *Mycobacterium tuberculosis* is a virulence factor that stabilizes Mce transporters. ***Molecular Microbiology***. April 1;100(1):90-107. PMID: 26712165.
- **c.** Coutermarsh-Ott, S.L., Doran, J.T., Campbell, C., Williams, T.M., Lindsay, D.S., **Allen, I.C.** Caspase-11 Modulates Inflammation and Attenuates *Toxoplasma gondii* Pathogenesis. ***Mediators of Inflammation***. Volume 2016, 9848263, 14 pages. 2016. PMID: 27378827
- **d.** Yuan, L., Wang, H., Gao, K., Wen, K., **Allen, I.C.**, Li, G., Zhang, W., Kocher, J., Yang, X., Giri Rachman, E., Li, G., Clark-Deener, S. (2016). Lactobacillus rhamnosus GG modulates innate immune response to rotavirus vaccine through Toll-like 9 signaling pathway in intestinal mononuclear cells of gnotobiotic pigs transplanted with human gut microbiota. ***BMC Microbiology.*** Jun 14;16(1):109. 2016. PMID: 27301272

Complete List of Published Work in My Bibliography (53 Total Publications):
Google Scholar Metrics: 3231 citations as of May 9, 2017; h-index = 24
http://www.ncbi.nlm.nih.gov/sites/myncbi/1JGsSayNaPXQL/bibliography/43334079/public/?sort=date&direction=descending

D. RESEARCH SUPPORT:

Active Support:

1. **Evaluating NLR Modulation of Canonical and Non-Canonical NF-kB Signaling in IBD**
   R03-DK105975 (**PI: Allen**; Co-I: Cecere) 07/01/15 – 06/30/17 National Institutes of Health – NIDDK
2. **Harnessing CRISPR Technology for Gene Therapy Applications**
   JFC Seed Proposal (**PI: Allen**; Co-I: Davis) 07/01/15 – 06/30/18 VT/ICTAS
3. **Evaluation of H-FIRE and IRE in Cancer**
   (PI: Davalos; **Co-PI: Allen**; Co-PI: Verbridge) 03/01/17 – 12/31/17 Boston Scientific (Industry Support)
4. **Role of the Non-Canonical NF-xB Inflammatory Cascade in Therapeutic Response and Pathogenesis of Inflammatory Bowel Disease**
   (Co-PI: Sorrentino; **Co-PI: Allen**; Co-I: Vu; Knight) 03/01/17 – 06/30/18 Carilion Clinic RAP T-I
5. **Evaluation of pro-inflammatory TH2 mediated biomarkers and NF-kB signaling pathways in the Diagnosis and Treatment of Eosinophilic Esophagitis (EoE)**
   (PI: Michael Hart; **Co-I: Allen**; Knight; Grider; Katoh; Tenzer) 03/01/17 – 06/30/18 Carilion Clinic RAP T-II
6. **Defining the roles of inflammasomes in Zika virus infection**
   (**Co-PIs:** Lukens; Ewald; Hahn; **Allen**) 05/01/17 – 04/30/18 4-VA
7. **Defining Roles for Noncanonical NF-kB Signaling in Eosinophilic Esophagitis**
   (**PI: Allen**; Co-I: Verbridge; Eden) 07/01/17 – 06/30/18 VMCVM - IRC

Completed Support:

1. **NLR Regulation of Innate Immune Responses to Respiratory Virus Infection**
   F32-AI082895 (**PI: Allen**) 09/01/09 – 12/31/10 National Institutes of Health/NIAID
2. **NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis**
   PF-10-053-01-LIB (**PI: Allen**) 01/01/10 – 06/30/11 The American Cancer Society
3. **NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis**
   P30-DK34987 (**PI: Allen**) 07/01/09 – 2/29/11 UNCCH/CGIBD
4. **Elucidating the Contribution of Negative Regulators of TLR Signaling in Inflammatory Bowel Disease and Tumorigenesis**
   Pilot Grant (**PI: Allen**) 07/01/13 - 06/30/14 VMCVM/IRC
5. **NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis**
   K01-DK092355 (**PI: Allen**) 07/01/11 – 06/30/16 National Institutes of Health/NIDDK
6. **Novel vaccine system against viral infections**
   Seed Grant (**Co-PI: Allen**; Co-PI: Zhang) 07/01/15 – 06/30/16 VT/UMD CVM Joint Seed Grant
7. **Elucidating the Contribution and Therapeutic Potential of NLRX1 Signaling in Histiocytic Sarcoma**
   Pilot Grant (**PI: Allen**; Co-I: Dervisis; Co-I: Coutermarsh-Ott) 07/01/15 – 06/30/16 VMCVM/IRC
8. **Evaluating Novel Inflammatory Signaling Pathways from Patients with Inflammatory Bowel Disease**
   Pilot Grant (**PI: Allen**; Co-I: Sorrentino; Co-I: Eden) 07/01/16 – 06/30/17 VMCVM/IRC
9. **Evaluating Novel Inflammatory Signaling Pathways from Patients with Inflammatory Bowel Disease**
   (**PI: Allen**; Co-I: Sorrentino; Eden) 07/01/16 – 06/30/17 VMCVM/IRC
10. **The Contribution of NLR Proteins in Modulating Gastrointestinal Inflammation Following Exposure to Wheat Gluten**

(**Co-PI: Allen**; Co-PI: Berglind) 11/10/15 – 06/30/17 Edward Via College of Osteopathic Medicine

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Nammalwar Sriranganathan	Professor of Microbiology
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Agricultural Sciences, Bangalore,	B.V.Sc. M.V.Sc,	06/1966 06/1968	Veterinary Medicine and Surgery Veterinary Microbiology
Oregon State University, Corvallis, OR	Ph.D.	12/1975	Molecular Biology
American Veterinary Medical Association	E.C.V.G	06/1978	Veterinary Medicine

A. Personal Statement

One of the current goals of my research is to develop a multivalent vaccine *Brucella abortus* RB51 leucine auxotroph expressing synthetic protective antigens Ag85B, ESAT-6, and Rv2660c from *M. tuberculosis* and *M. bovis* under Brucella promotors for expression. *B. abortus* RB51 is a Stable rough mutant and USDA approved vaccines for cattle is from our laboratories of Schurig, Boyle and Sriranganathan. We have generated a *Leu*B deletion mutant of RB51 and constructed a plasmid with the *Leu*B serving as selection marker and expressing the TB antigens in place of a drug resistance marker. We have demonstrated the candidate vaccine is cleared in six weeks and does provide significant level protection against intraperitoneal challenge with *B. abortus* wild type 2308 and *M. tuberculosis*. We have initiated primary followed by and booster vaccination experiments and would like to evaluate its ability to protect against a challenge with *M. bovis*. My long-term research effort has been focused on the development of vaccines against brucellosis and tuberculosis in animals and humans. I have a strong interest in the areas of targeted drug delivery against intracellular pathogens. In the last 5 years, I have concentrated on the development and testing of drug-loaded nanoparticle targeted delivery systems against intracellular pathogens like *Salmonella*, *Brucella*, *Listeria*, and *Mycobacerium*. I have been able to develop highly productive collaborations with Drs. Judy Riffle, a chemist, and Dr. Gary Pickrell, a materials science engineer, Dr. Subbiah Elankumaran a veterinary virologist who are well-respected scientists at VT. Our collaboration has led to 16 publications in the area of nanomedicine and 66 publications in the area of *Brucella* and their recombinants.

C. Selected Peer-reviewed Publications:

Most Recent Brucella Relevant publications:

1. Nol P, Olsen SC, Rhyan JC, **Sriranganathan** N, McCollum MP, Hennager SG, Pavuk AA, Sprino PJ, Boyle SM, Berrier RJ, Salman MD.Vaccination of Elk (Cervus canadensis) with **Brucella** abortus Strain RB51 Overexpressing Superoxide Dismutase and Glycosyltransferase Genes Does Not Induce Adequate Protection against Experimental **Brucella** abortus Challenge. Front Cell Infect Microbiol. 2016 Feb 10;6:10.
2. Dorneles EM, Lima GK, Teixeira-Carvalho A, Araújo MS, Martins-Filho OA, **Sriranganathan** N, Al Qublan H, Heinemann MB, Lage AP. Immune Response of Calves Vaccinated with **Brucella** abortus S19 or RB51 and Revaccinated with RB51. PLoS One. 2015 Sep 9;10(9):e0136696.
3. Dabral N, Jain-Gupta N, Seleem MN, **Sriranganathan** N, Vemulapalli R. Overexpression of **Brucella** putative glycosyltransferase WbkA in B. abortus RB51 leads to production of exopolysaccharide. Front Cell Infect Microbiol. 2015 Jun 24;5:54.
4. Dorneles EM, **Sriranganathan** N, Lage AP. Recent advances in **Brucella** abortus vaccines. Vet Res. 2015 Jul 8;46:76. Review.
5. Dorneles EM, Teixeira-Carvalho A, Araújo MS, **Sriranganathan** N, Lage AP. Immune response triggered by **Brucella** abortus following infection or vaccination. Vaccine. 2015 Jul 17;33(31):3659-66. Review.

6. Dabral N, Martha-Moreno-Lafont, **Sriranganathan** N, Vemulapalli R. Oral immunization of mice with gamma-irradiated **Brucella** neotomae induces protection against intraperitoneal and intranasal challenge with virulent B. abortus 2308. PLoS One. 2014 Sep 16;9(9):e107180.
7. Dorneles EM, Teixeira-Carvalho A, Araújo MS, Lima GK, Martins-Filho OA, **Sriranganathan** N, Lage AP. T lymphocytes subsets and cytokine pattern induced by vaccination against bovine brucellosis employing S19 calfhood vaccination and adult RB51 revaccination. Vaccine. 2014 Oct 21;32(46):6034-8.
8. Lauer SA, Iyer S, Sanchez T, Forst CV, Bowden B, Carlson K, **Sriranganathan** N, Boyle SM. Proteomic analysis of detergent resistant membrane domains during early interaction of macrophages with rough and smooth **Brucella** melitensis. PLoS One. 2014 Mar 18;9(3):e91706.
9. Jain-Gupta N, Contreras-Rodriguez A, Smith GP, Garg VK, Witonsky SG, Isloor S, Vemulapalli R, Boyle SM, **Sriranganathan** N. Immunotherapeutics to prevent the replication of **Brucella** in a treatment failure mouse model. Vaccine. 2014 Feb 12;32(8):918-23.
10. Islam MA, Khatun MM, Werre SR, **Sriranganathan** N, Boyle SM. A review of **Brucella** seroprevalence among humans and animals in Bangladesh with special emphasis on epidemiology, risk factors and control opportunities. Vet Microbiol. 2013 Oct 25;166(3-4):317-26.
11. Avila-Calderón ED, Lopez-Merino A, **Sriranganathan** N, Boyle SM, Contreras-Rodríguez A. A history of the development of **Brucella** vaccines. Biomed Res Int. 2013;2013:743509.
12. Surendran N, **Sriranganathan** N, Boyle SM, Hiltbold EM, Tenpenny N, Walker M, Zimmerman K, Werre S, Witonsky SG. Protection to respiratory challenge of **Brucella** abortus strain 2308 in the lung. Vaccine. 2013 Aug 28;31(38):4103-10.
13. Rajasekaran P, Alexander JC, Seleem MN, Jain N, **Sriranganathan** N, Wattam AR, Setubal JC, Boyle SM. Peptide nucleic acids inhibit growth of **Brucella** suis in pure culture and in infected murine macrophages. Int J Antimicrob Agents. 2013 Apr;41(4):358-62.
14. Jain-Gupta N, Contreras-Rodriguez A, Vemulapalli R, Witonsky SG, Boyle SM, **Sriranganathan** N. Pluronic P85 enhances the efficacy of outer membrane vesicles as a subunit vaccine against **Brucella** melitensis challenge in mice. FEMS Immunol Med Microbiol. 2012 Dec;66(3):436-44.
15. Jain N, Boyle SM, **Sriranganathan** N. Effect of exogenous erythritol on growth and survival of **Brucella**. Vet Microbiol. 2012 Dec 7;160(3-4):513-6
16. Avila-Calderón ED, Lopez-Merino A, Jain N, Peralta H, López-Villegas EO, **Sriranganathan** N, Boyle SM, Witonsky S, Contreras-Rodríguez A. Characterization of outer membrane vesicles from **Brucella** melitensis and protection induced in mice. Clin Dev Immunol. 2012;2012:352493.
17. Surendran N, Hiltbold EM, Heid B, Akira S, Standiford TJ, **Sriranganathan** N, Boyle SM, Zimmerman KL, Makris MR, Witonsky SG. Role of TLRs in **Brucella** mediated murine DC activation in vitro and clearance of pulmonary infection in vivo. Vaccine. 2012 Feb 14;30(8):1502-12.
18. Chen F, Ding X, Ding Y, Xiang Z, Li X, Ghosh D, Schurig GG, **Sriranganathan** N, Boyle SM, He Y. Proinflammatory caspase-2-mediated macrophage cell death induced by a rough attenuated **Brucella** suis strain. Infect Immun. 2011 Jun;79(6):2460-9.
19. Rajasekaran P, Surendran N, Seleem MN, **Sriranganathan** N, Schurig GG, Boyle SM. Over-expression of homologous antigens in a leucine auxotroph of **Brucella** abortus strain RB51 protects mice against a virulent B. suis challenge. Vaccine. 2011 Apr 12;29(17):3106-10.
20. Surendran N, **Sriranganathan** N, Lawler H, Boyle SM, Hiltbold EM, Heid B, Zimmerman K, Witonsky SG. Efficacy of vaccination strategies against intranasal challenge with **Brucella** abortus in BALB/c mice. Vaccine. 2011 Mar 24;29(15):2749-55.

RECENT THESES AND DISSERTATIONS DIRECTED AS MAJOR ADVISOR (Out of 22):

Dr. Mohamed Naguieb Serry: Ph.D., Dissertation Defended August 23rd, 2006: *Ochrobactrum anthropi*: A soil bacterium as a gain of function model for the study of *Brucella* Virulence. Received Outstanding Dissertation Award on Science, Technology, Engineering and Mathematics at Virginia Tech. Joined my laboratory back from Cornell University (after a year of postdoctoral) as a postdoctoral ICTAS fellow in my laboratory from 2007-2009. Now he is an Assistant professor at Purdue University and being promoted with tenure.

Dr. Ashish Ranjan: Successfully defended on September 10th 2009. Title of his dissertation: Development of core-shell nanostructure encapsulating gentamicin as efficient drug delivery system for intracellular Salmonella. Now he is a

Postdoctoral Fellow in Dr. Bradford Wood, Chief Interventional Radiology Research Laboratory at NIH. Now he is an Assistant Professor at Oklahoma State University.

Dr. Neeta Jain: Successfully defended her doctoral on January 19th, 2012 and is now a post-doctoral fellow in Dr. Sean at University of Chicago. College Outstanding Dissertation Award (VMCVM).

Dr. Eva Marie Restis: Successfully defended her doctoral on September 20th, 2013. Laboratory Animal Veterinarian at Merck, Omaha, NE.

Dr. Hamzeh Al Qublan successfully defended his doctoral on August 29th, 2014. Received Outstanding Dissertation Award on Science, Technology, Engineering and Mathematics at Virginia Tech. He is now pursuing his doctoral in dental medicine in University of Maryland. He will be an excellent academician.

VISITING Scientists:

Dr. Araceli Contreras Postdoc 2005-2007. NIH R21: Effect of aging on immune response against Brucella. Professor, Microbiology, University in Mexico.

Dr. Shrikrishna Isloor: Visiting Professor from Karnataka Veterinary, Animal and Fishery Sciences University, Hebbal Bangalore, India. 2012.

Dr Jasbir Singh Bedi: Assistant Professor, School of Public Health and Zoonoses,. College of Veterinary Science, Guru Angad Dev Veterinary and Animal Sciences University, Punjab, India Sept, 2013, March 2014.

Dr. Elaine Maria Seles Dorneles, Visiting Doctoral Student from Prof. Andrey Pereira Lage, Laboratório de Bacteriologia Aplicada, Universidade Federal de Minas Gerais, BRAZIL. October 2013, April 2014.

Dr. Satparkash Singh: Associate Professor, College of Veterinary Science, Guru Angad Dev Veterinary and Animal Sciences University, Punjab, India, August 2016 October 2016.

Current Visiting Professor and Doctoral students:

1. Dr. Neet Jain-Gupta: Senior Research Associate. May 2015-Present.
2. Dr/ Enas Soliman Visiting Scientist, Channell Student, Benha University Egypt.
3. MS. Betsy Schoeder PhD/DVM student, final year of both DVM and PhD.
4. Mr. Garrett Smith PhD/DVM student, Third year of both DVM and PhD.
5. Mr. Steven Waldrop: PhD/DVM student, Second year of PhD.

D. Research Support:

Ongoing extramural Research Support:

1. Smithfield Foods Murphy-Brown PI: Sriranganathan, N., E. Subbiah, S. M. Boyle. Title:"A Novel Recombinant Safe Vaccine to Control Boar Taint." $865,489. Jan 2015- Dec 2017.

2. NIH: T35 RR021311----01: Ansar Ahmed S (PD) (7/2012----2017) $ Summer. Veterinary Student Research Program (SVSRP) Role: N. Sriranganathan Mentor for summer veterinary students. OVERLAP: None.

3. NIH: T32 RR021819, Postdoctoral Training Grant, Meng, X.J (PD) 6/2012----5/2017. Animal Model Research For Veterinarians, N. Sriranganathan Mentor for Dr. Eva Restis NIH Stipend for 4 years. OVERLAP: None Role: Mentor.

4. VMCVM-VCOM Center for One Health Seed Grant: Nanoparticles to deliver antisense nucleic acid constructs as therapeutics for intracellular bacterial infections. PI: N. Sriranganathan & Stephen Boyle (VMCVM) Renee Prater & Shaadi Elswaifi (VCOM). $56,014: Dec 2015 – June 2017.

5. Enhancing Collaboration between Universidad Austral de Chile and Virginia Tech (ICTAS): Soil Microbiome of Chilean Patagonia by metagenomics and their potential applications. PI: N. Sriranganathan (NS), G. Schurig (GS), R. Mahajan (RM), O. Martinez (OM). $27,000. 2014-2016.

Pending Support:

1. XXII Concurso Nacional de Proyectos de Investigación Científica y Tecnológica Antártica, 2016. PI: O.A. Martinez, CO-I: O A. Thiers, N. Sriranganathan and G. Schurig. Title: "Soil Antarctic microbiome as source of new antimicrobials." $182,396. 2016-2018.
2. VT-UACh joint Research Program Seed grant. VT-UACh research team building project; Prevention of *Brucella ovis* induced pathobiology in rams through vaccination: VT: G. Schurig, N. Sriranganathan UACh: M. Moroni, and O. Martinez and B. Otto $15,000 July 2016.

Recently Completed (Last 5 years):

1. NanoRx: **"**Effect of Metadichol® on the gene expression of THP-1 monocytes: Transcriptome**."** N. Sriranganathan and G. Kimsawatde. $20,700 From: 10/2014-3/2015.

2. USDA-APHIS Wild Life: Nammalwar Sriranganathan and Stephen M Boyle: Preliminary evaluation in a murine model: a bivalent immunocontraceptive vaccine against brucellosis in feral swine. $11,000. 7/1/12 to 6/30/13.

3. USDA: Nammalwar Sriranganathan (PD), Stephen M. Boyle (CO-I), Steve Olsen (CO-I), Jack Ryan (CO-I), Pauline Nol (CO-I) and Katheline Fagerstone. SIPMC, Enhancement Gant. 5/2013 to 4/2014. $29,402:

4. NIH----RO1: Purdue # 4102----27485. R. Vemulapalli, (PI) (No cost Extension) 12/1/2008 to 11/30/13. N. Sriranganathan (5%) Role: Subcontract: Animal Challenge studies: $280,223.00/Total "Non----replicative vaccine for human brucellosis." " Development and testing in mice of candidate vaccines against Brucellosis for humans." Overlap: None Role: Co-PI. (Finalizing publications)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Thomas Joseph Inzana

eRA COMMONS USER NAME (credential, e.g., agency login): tinzana

POSITION TITLE: Tyler J. and Frances F. Young Chair in Bacteriology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Georgia, Athens, GA	B.S.	06/1975	Microbiology (maga cum laude)
University of Georgia, Athens, GA	M.S.	02/1978	Medical Microbiology
University of Rochester School of Medicine, Rochester, NY	Ph.D.	11/1982	Microbiology
Baylor College of Medicine	Postdoc	06/1984	Fellowship in Medical Laboratory Microbiology and Public Health

A. Personal Statement

I am a Board-certified (ABMM) clinical microbiologist, and have spent a substantial part of my research career in the development of diagnostic tests for bacterial agents, including methicillin-resistant *Staphylococcus aureus*. The interpretation and application of susceptibility testing following the Clinical Laboratory Standards Institute guidelines are standard protocols in our laboratory. In my research laboratory much or our work is focused on biofilm formation by respiratory pathogens, and we have demonstrated in a bovine model of respiratory disease biofilm formation in the host by *Histophilus somni* and *Pasteurella multocida*. We have also worked on biofilm formation by *Francisella tularensis*, and we have identified novel bacterial exopolysaccharides that form the matrix of the biofilms of each of these bacteria. We are currently examining how biofilms and other virulence factors are regulated in these respiratory pathogens through small RNAs. Most of my focus on virulence factors is directed toward the bacterial polysaccharides that comprise the lipopolysaccharide, capsules, and exopolysaccharides. I have also mentored summer research undergraduate students in the MAOP (Multicultural Academic Opportunities Program), minority students interested in pursuing veterinary school, students engaged in the NSF-funded program Research Experiences for Undergraduates, summer undergraduate research fellowships, and VT-PREP (Post-baccalaureate Research and Education Program).

B. Positions and Honors

Positions and Employment

7/84-6/87 Assistant Professor, Col. of Vet. Med. Dept. Vet. Microbiol. Pathol. Washington State University
7/87-4/91 Assistant Professor and Director, Clinical Microbiology VA-MD Coll. Vet. Med. Virginia Tech
6/92-8/92 Visiting Associate Professor, SUNY at Buffalo School of Medicine,
4/91-4/96 Associate Professor and Director, Clinical Microbiology. VA-MD Coll.Vet. Med. Virginia Tech
4/96-present Professor and Director, Clinical Microbiology, VA-MD Reg. Coll. Vet. Med., Virginia Tech
1/98-7/02 Director, Cent. Molecular Medicine & Infect. Dis., VA-MD Reg. Coll. Vet. Med., Virginia Tech
1/00-5/00 Visiting Professor, Univ. Penn. School of Medicine
10/06-6/10 Associate Vice President for Research Programs, Virginia Tech
7/07-present University Research Integrity Officer
4/03-present Tyler J. and Frances F. Young Prof. Bacteriol., VA-MD Reg. Coll. Vet. Med., Virginia Tech

Professional Memberships

American Society for Microbiology
American Academy for Microbiology
American Association of Veterinary Laboratory Diagnosticians
American Association for the Advancement of Science
Conference of Research Workers in Animal Diseases (CRWAD)
International Endotoxin and Innate Immunity Society
Phi Kappa Phi Honor Society
Phi Zeta National Veterinary Medicine Honor Society

Service and other experience (last 5 years):

2007-present Member of Editorial Board for Clinical Microbiology Reviews
2011 Panel member: USDA National Program 103: Animal Health Swine Program
2011-2012 Panel Member: NIAID Clinical Trial Planning and Implementation Grants
2012 Panel Member: NIAID Partnerships for Development of Therap. and Diagnostics for Biodefense (RO1)
2013 Panel Member**:** ZAI1-JRR-M-J4 AI-13-013 Partnerships for Biodefense (RO1)
2013 Panel Member: ZAI-RCU-M-J2 AI-13-013 Partnerships for Biodefense (RO1)
2016 Panel Member: NIH-USDA Dual Purpose with Dual Benefit grants
2016 Chair and Panel member: NIAID Investigator Initiated Program Project and Resource Applications
2017 Panel member: Dual Purpose with Dual Benefit: Research in Biomedicine and Agriculture Using Agriculturally Important Domestic Animal Species

Honors

1989 Beecham Award for Research Excellence
1992 Diplomate, American Board of Medical Microbiology
1996 Phi Zeta National Veterinary Medicine Honor Society
1997 Fellow, American Academy of Microbiology
2003 Pfizer Award for Research Excellence
2011 Division Z lecturer for 111th General Meeting of the American Society for Microbiology

C. Contribution to Science

Development of diagnostic tests and immunological assays

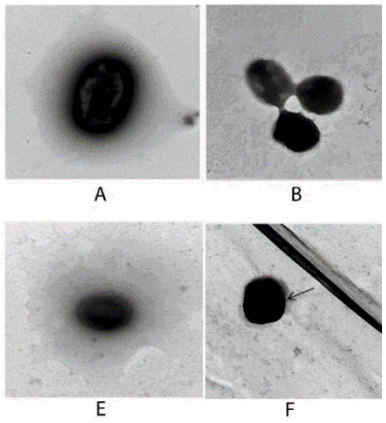
As a clinical microbiologist I have developed a wide array of diagnostic tests, many based upon the immunological response to carbohydrate antigens. My group was the first to purify and characterize the capsular polysaccharide of *A. pleuropneumoniae*, demonstrate it is the serotype-specific antigen, and develop type-specific reagents for this species, including antigen detection assays for clinical specimens. My lab was also the first to develop a multiplex PCR assay for detection of the bacterial species and serotype simultaneously based on multiplex PCR. This type of assay has seen been used for a wide variety of human and animal bacterial pathogens. I have also shown that detection of antibodies to the EPS of *H. somni* makes an excellent diagnostic test in cases where the pathogen cannot be isolated because the EPS is only made during systemic infection and not during colonization. Currently, my lab group has also teamed with the PI of this proposal, a photonic physicist, to develop biosensors based on detection of a specific antigen or DNA sequences. The assay is based on coupling antibodies or DNA to a highly specialized optical fiber that detects binding of antigen or complementary DNA by interference of the light path after binding. The assay is capable of detecting as few as 100 cells in a sample without the need for PCR. We have also used the carbohydrate antigens and/or genetic sequences of *F. tularensis, B. abortus*, and *Histophilus somni* to develop novel photonic biosensor diagnostic tests to identify these agents without the need for PCR.

1. Inzana, T.J.* 1995. A simplified procedure for preparation of sensitized latex particles to detect capsular polysaccharides: application to typing and diagnosis of *Actinobacillus pleuropneumoniae*. J. Clin. Microbiol. 33:2297-2303. PMID: 7494018.
2. Lo, T.M., C.K. Ward, and T.J. Inzana*. 1998. Detection and identification of *Actinobacillus pleuropneumoniae* serotype 5a by multiplex PCR. J. Clin. Microbiol. 36:1704-1710. PMID: 9620404.
3. Inzana, T.J. *, and A. Champion. 2007. Use of an inhibition-enzyme-linked immunosorbent assay for quantification of capsular polysaccharide or proteins in vaccines. Clin. Vaccine Immunol. 14:323-327. PMID: 17267591.
4. Cooper, K.L., A.B. Bandara, Y. Wang, A. Wang, and T.J. Inzana*. 2011. Photonic biosensor assays to detect and distinguish subspecies of *Francisella tularensis*. Sensors. 11:3004-3019. PMID: 22163782.

5. Bandara, A.B., Z. Zuo, S. Ramachandran, A. Ritter, J.R. Heflin, and T.J. Inzana*. 2015. Detection of Methicillin-Resistant Staphylococci by Biosensor Assay Consisting of Nanoscale Films on Optical Fiber Long-Period Gratings. Biosens Bioelectron. 70:433-440. PMID 25845336.

<u>*Francisella tularensis* and other select agents, pathogenesis, and virulence factors</u>

My lab works primarily on bacterial polysaccharides, their role in virulence, the host response to these antigens, and their application to vaccines and diagnostic tests. In *Francisella tularensis* we have focused on what appears to be a capsule around the bacterium under some growth conditions by transmission electron microscopy (EM), and on the lipopolysaccharide. We determined the "capsule" seen by EM is actually an electron dense complex of glycoproteins that are over-expressed under particular growth conditions. The genes responsible for glycosylating these proteins were identified, and following mutagenesis of two of these genes in the live vaccine strain (LVS) the capsule-like complex (CLC) was no longer present, but was restored by complementation. The LVS mutant was no longer virulent in a mouse model, and immunization of mice with the mutant protected the animals from intranasal challenge with the parent strain. Recently, a similar mutant was made in the highly virulent type A strain SchuS4, but was not adequately attenuated (unpublished).



Negative stain electron microscopy of the CLC of *F. tularensis*. Panel A, type B strain LVS_P10 passed and grown at 32°C on defined medium (CDMA); B, glycosyl transferase mutant LVSΔ1423/1422 _P10; E, complemented strain LVSΔ1423/1422[1423/1422+]_P10; F, LVS not passed in defined medium.

We were among the first groups to obtain lipopolysaccharide (LPS) O-antigen mutants of *F. tularensis*, which are highly attenuated and serum-sensitive. We have also made similar mutants in type A strains, one of which is much more virulent than SchuS4. Although highly attenuated, O-antigen mutants are cleared too quickly to induce a protective immune response against type A challenge. However, we have shown that this protection can be enhanced if the LPS conjugated to a strongly immunogenic protein is combined with the mutant (submitted for publication). Because this type A strain is more virulent than SchuS4, we use this strain for our vaccine studies and have published its full genome and that of its O-antigen mutant. I have also collaborated with colleagues on the LPS of *Brucella* spp. Recently we demonstrated that recently identified *Brucella* spp. produced a novel LPS that was initially identified using a bioinformatics approach, but was confirmed by biochemical analyses.

1. Bandara, A.B., A. Champion, X. Wang, G. Berg, M.A. Apicella, M. McLendon, P. Azadi, D.S. Snyder, and T.J. Inzana*. 2011. Characterization and Mutagenesis of a Capsule-Like Complex from *Francisella tularensis* LVS. PLoS ONE. 6(4): e19003. PMID: 21544194.
2. Li, J., C. Ryder, M. Mandal, F. Ahmed, P. Azadi, D.S. Snyder, R.D. Pechous, T. Zahrt, and T.J. Inzana*. 2007. Attenuation and protective efficacy of an O-antigen-deficient mutant of *Francisella tularensis* LVS. Microbiol. 153:3141-3153. PMID: 17768257.
3. Apicella, M.A., D.M.B. Post., A.C. Fowler, B.D. Jones, J.A. Rasmussen, J.R. Hunt, S. Imagawa, B. Choudhury, T.J. Inzana, T.M. Maier, D.W. Frank, T.C. Zahrt, K. Chaloner, M.P. Jennings, M.K. McLendon, B.W. Gibson. 2010. Identification, characterization and immunogenicity of an O-Antigen capsular polysaccharide of *Francisella tularensis*. PLoS ONE. 5(7): e11060. PMID: 20625403.
4. Modise, T., C. Ryder, S. Mane, A. Bandara, R. Jensen, and T. Inzana*. 2012. Genomic comparison between a virulent type A1 strain of *Francisella tularensis* and its attenuated O-antigen mutant. J. Bacteriol. 194:2775-2776. PMID: 22535949.
5. Champion, A.E., K.C. Freudenberger-Catanzaro, A.B. Bandara, and T.J. Inzana*. 2016. Biofilm formation by *Francisella tularensis* is dependent upon cell surface glycosylation, growth medium, and a novel glucan exopolysaccharide. Submitted.

<u>Gram-negative respiratory pathogens, host response, biofilm formation, and vaccine development</u>

I was the first to show that *Haemophilus influenzae* type b produces a LPS that lacks O-antigen, which later we termed lipooligosaccharide (LOS), and that this LOS undergoes phenotypic and antigenic phase variation. Following development of the capsule-protein conjugate vaccine for *H. influenzae* type b, I moved on to work on other *Haemophilus* spp. that infect animals. An advantage of this approach is that because *Haemophilus* spp. are host-specific, I could work on pathogenesis within the natural host to further understand host-pathogen interactions. An understanding of the role of the capsule and exotoxins in the disease process, and the host protective response, resulted in 3 vaccine patents and a commercial vaccine to prevent swine

pleuropneumonia due to *Actinobacillus (Haemophilus) pleuropneumoniae*. The live attenuated non-encapsulated vaccine strain was developed based on work that determined that neutralizing antibodies to the RTX exotoxin were required for protection, that neutralizing antibodies were primarily made to native toxin and not a toxoid, and that the capsule was required for virulence, but not protection. The bovine pathogen *Histophilus (Haemophilus) somni* is very similar in its virulence properties and antigenic makeup to *H. influenzae*. We have shown that during disease in the natural host that the LOS of *H. somni* undergoes antigenic phase variation, which it uses to escape the host immune response. To aid in these experiments, we made the first isogenic allelic exchange mutant of *H. somni.* The oligosaccharide side chains of the LOS are identical to those on glycosphingolipids on host cells, and are sialylated. In addition, the bacteria can attach phosphorylcholine to the LOS in a phase variable manner to aid in colonization (through attachment to platelet activating factor) or turn off its expression to avoid binding complement when the bacterium disseminates. Again these experiments were not done in animal models, but in the natural hosts. More recently, I have placed our focus on investigation and characterization of biofilm formation by *H. somni* in the bovine host, and its interaction with another common pathogen: *Pasteurella multocida*. My group has determined that not only does *H. somni* make an excellent biofilm in vitro, but also makes a prominent biofilm during pneumonia and systemic disease in its natural bovine host. A novel exopolysaccharide (EPS) has been identified as making up most of the biofilm matrix, and a diagnostic test developed to distinguish disease by *H. somni* rather than only colonization. In addition, I have identified a typical AI-2 quorum sensing system, and that a *luxS* mutant of *H. somni* is avirulent, but still forms a biofilm. Recently IL-18 was cloned into the *luxS* mutant to evaluate it as a vaccine candidate in experimental infection of cattle. Currently, I am also determining the role of small RNAs in regulation of *H. somni* virulence factors, particularly biofilm formation.

1. Wu, Y., J.H. McQuiston, A. Cox, T.D. Pack, and T.J. Inzana*. 2000. Molecular cloning and mutagenesis of a DNA locus involved in lipooligosaccharide biosynthesis in *Haemophilus somnus*. Infect. Immun. 68:310-319. PMID: 10603403.
2. Sandal, I. and T.J. Inzana*. 2010. *Histophilus somni* Host-Pathogen Interactions: A Genomic Window into Virulence. Trends Microbiol. 18:90-99.
3. Siddaramappa, S., et al. and T.J. Inzana*. 2011. Horizontal gene transfer in *Histophilus somni* and its role in the evolution of pathogenic strain 2336, as determined by comparative genomic analyses. BMC Genomics. 12:570. PMID: 22111657.
4. Sandal, I., T.J. Inzana*, A. Molinaro, C. De Castro, J.Q. Shao, M.A. Apicella, A.D. Cox, F. St. Michael, and G. Berg. 2011. Identification, structure, and characterization of an exopolysaccharide produced by *Histophilus somni* during biofilm formation. BMC Microbiol. 11:186.
5. Inzana, T.J. (Ed.). 2016. *Histophilus somni*: Biology, Molecular Basis of Pathogenesis, and Host Immunity. Curr. Topics Microbiol. Immunol. Vol 396. Springer, London. ISBN 978-3-319-29554-1.

Complete list of peer-reviewed published work (111) in MyBibliography
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48978963/?sort=date&direction=ascending

D. Research Support
Current Research Support

USDA-NIFA T.J. Inzana (PI) 4/17 to 3/21
The role of small RNAs and Hfq in regulation of *Histophilus somni* virulence factors.

The goal of this project is to determine which small RNAs are controlled by the global chaperone Hfq, and which virulence factors, particularly biofilm, are regulated by small RNAs. The small RNAs bound by Hfq will be determined, and mutagenesis of *hfq* and over-expression of small RNAs will be used to gain insight on which factors known to be related to virulence are regulated by these components.

USDA-NIFA T.J. Inzana (PI) 10/2013-9/17
Biofilm formation by *Pasteurella multocida* and its co-habitive interaction with *Histophilus somni* biofilm in vitro and in the bovine host.

The goal of this project is to characterize biofilm formation by *P. multocida* and how *P. multocida* and *H. somni* interact in a biofilm together in vitro and in the bovine host. The expression of genes by the bacteria and by the host will be determined to assess how polymicrobial infections influence gene expression.

Center for One Health Research Seed Grant T.J. Inzana (PI) 7/1/16-6/30/18
Investigation of the cause of chronic Lyme Disease in humans and dogs

The goal of this project is to develop an improved and rapid assay to detect *Borrelia burgdorferi* DNA in blood, urine, or synovial fluid and if chronic Lyme Disease is due to active, persistent spirochetes in the patient.

Virginia-Maryland College of Veterinary Medicine T.J. Inzana (PI) 7/1/16-6/3017
Regulation of Virulence Factors in the Bovine Respiratory Pathogen *Histophilus somni*.

The goal of this project is to obtain preliminary data on the role of Hfq and small RNAs in regulation of biofilm and other virulence factors in *H. somni*.

COMPLETED RECENT PROPOSALS

USDA-NIFA T.J. Inzana (PI) 9/11-8/14
Development of a DNA-based nanoscale optical fiber biosensor assay to detect *Brucella*.

The objective of this proposal was of develop photonic biosensors to detect DNA from *Brucella* species in samples from Elk and Bison in the Yellowstone National Park area without the need for PCR.

Virginia Tech-University of Maryland Joint Seed Grant T.J. Inzana (PI) 7/15-6/16
Novel vaccine delivery system against infectious diseases.

The goal of this project is to determine if cloning IL-18 or another cytokine into an attenuated, live bacterial pathogen will enhance the immune response and protective efficacy. *Histophilus somni* is being used as the initial model organisms, but if successful will be applied to *F. tularensis*.

Virginia-Maryland College of Veterinary Medicine. T.J. Inzana (PI) 7/15-6/16
Sustained Delivery of a Live *Francisella tularensis* Vaccine Strain by Encapsulation.

The goal of this project is to obtain preliminary data to demonstrate that encapsulation of attenuated live bacteria in alginate spheres can provide a protective immune response, but would otherwise be cleared before an immune response can be induced.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Hungerford, Laura

eRA COMMONS USER NAME (credential, e.g., agency login): lhungerford

POSITION TITLE: Professor and Head

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE	START DATE	END DATE	FIELD OF STUDY
Michigan State University, E. Lansing, MI	DVM	07/1977	06/1980	
University of Illinois School of Public Health, Chicago, IL	MPH	01/1985	06/1987	Biostatistics and Epidemiology
University of Illinois College of Veterinary Medicine, Urbana, IL	PHD	07/1981	06/1989	Veterinary Epidemiology
University of Illinois College of Veterinary Medicine , Urbana, IL	Other training	07/1980	06/1981	Food Animal Medicine and Surgery Intern
University of Illinois College of Veterinary Medicine, Urbana, IL	Resident	07/1981	06/1986	Veterinary Diagnostic Microbiology

A. Personal Statement

This proposal is designed to integrate successful research and teaching programs to bring them to bear on the multifaceted interplay between environmental contamination, microbiomes, and animal and human health. This will position VT to address societal grand challenges through generation of innovative solutions and creation of the next generation of innovative problem solvers. My extensive experience in teaching and mentoring students (primary mentor or chair for 2 postdoctoral fellow, 7 MS, 14 MPH and 4 PhD students and committee membership for an additional 17 MS and 18 PhD students), recognized by my academic appointments, promotions and awards, and by the success of my previous students, will allow me to strongly contribute to this effort. I have blended academic and federal leadership roles which provides additional experiences for both traditional research, mentoring and finding innovative funding sources. My work at both the university and FDA has been and remains largely as an integrator and problem-solver in team science; which is well suited to working with the multidisciplinary approach of this proposal. My specific research experience in vector-borne disease, transdisciplinary studies, geographic health, dynamic modeling and quantitative epidemiology align well with the project aims.

B. Positions and Honors

Positions and Employment

1980 - 1981 Food Animal Medicine and Surgery Intern, University of Illinois College of Veterinary Medicine, Urbana, IL

1981 - 1986 Veterinary Diagnostic Microbiology Resident, University of Illinois College of Veterinary Medicine, Urbana, IL

1989 - 1996 Assistant Professor, University of Illinois College of Veterinary Medicine, Urbana, IL

1996 - 1998 Associate Professor with Tenure, University of Illinois College of Veterinary Medicine, Urbana, IL

1998 - 2002 Associate Professor with Tenure, Great Plains Veterinary Educational Center, University of Nebraska, Clay Center, NE

2002 - 2005 Associate Professor, Univeristy of Maryland School of Medicine, Baltimore, MD

2002 - 2016 Senior Advisor for Science and Policy, US FDA Center for Veterinary Medicine, Rockville, MD

2004 - 2006 Interim head, Division of Foodborne and Emerging Pathogens, Univeristy of Maryland School of Medicine, Baltimore, MD

2005 - 2016	Professor with Tenure (2006), Univeristy of Maryland School of Medicine, Baltimore, MD
2012 - 2015	Director, Graduate Program in Epidemiology and Human Genetics, GPILS, Univeristy of Maryland School of Medicine, Baltimore, MD
2015 - 2016	Vice Chair for Academic Programs, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD
2016 -	Professor and Head, Department of Population Health Sciences, Virginia-Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA

Other Experience and Professional Memberships

1980 -	Member, American Veterinary Medical Association
1987 -	Founding member, Beta Tau Chapter, University of Maryland, Baltimore and Delta Mu Chapter, Virginia Tech; Chapter President, 2010-2012, 2017-, DELTA OMEGA Honorary Society for Public Health
1990 -	Executive Board (1990-1996, 2001-2008), President Elect (2001-2002), President (2003-2004); Schwabe Symposium Co-Chair (2002, 2004), Schwabe Symposium Chair (2005), Association for Veterinary Epidemiology and Preventive Medicine
1991 -	External Reviewer, USDA/ARS and USDA/CSRS
1997 -	Section Head (2000-2010), Executive Board (2005-2009), Vice President (2009-2010), President (2010-2011), Co-Chair of Epidemiology Session (1991, 1992, 1994, 1997, 1998, 1999, 2003), Leader, Epidemiology Section (1998-1999), Nominations Committee (1999), ACVPM Awards Committee (1999), Section founder and Companion Animal Epidemiology Section Co-Chair (2010 - present), CRWAD - Conference of Research Workers in Animal Disease
1998 -	Panel member (1998, 1999, 2008, 2014), U.S.D.A., NRI Competitive Grants
2002 -	Member, Maryland Veterinary Medical Association
2005 -	Panel member (2005, 2006, 2008); external reviewer in other years, N.S.F, EID Competitive Grants

Honors

1975	National Merit Scholar, National Merit Scholarship Corporation
1983	Inductee, PHI KAPPA PHI Honorary Society
1986	Inductee, SIGMA XI Honorary Scientific Research Society
1987	Inductee, PHI ZETA Honorary Society for Veterinary Medicine
1987	Inductee, DELTA OMEGA Honorary Society for Public Health
1990	Teachers Rated as Excellent (and 1992, 1994, 1996), University of Illinois
2008	Outstanding Teacher Award, Department of Epidemiology and Preventive Medicine, University of maryland School of Medicine
2009	Honorary Diploma, American Veterinary Epidemiology Association
2011	First Annual Student Teaching Award in Recognition of Outstanding Teaching and Mentoring, University of Maryland School of Medicine MPH Program
2013	Distinguished Scholar and Fellow, National Academies of Practice, Veterinary Medicine Academy

C. Contribution to Science

1. My initial engagement in infectious disease epidemiology was a direct response to questions that I developed as a clinician about the extent and transmission patterns at the species interface between cattle and deer. To address these questions, I have applied a blend of quantitative epidemiologic methods with approaches from other disciplines. For anaplasmosis, this allowed us to map and analyze disease patterns; find key factors associated with disease at the animal and county level; provide information to veterinarians and regulators; and suggest interventions. For sheep diseases, we combined environmental monitoring, risk factors, production practices, producer preferences, economics and simulation modeling to understand the impact of mortality and management in sheep. In raccoons, by integrating health questions into ongoing wildlife ecology studies, we examined

infection in the context of animal behavior and population dynamics. For E. coli O157:H7, we developed a novel pen-level sampler and used laboratory methods and longitudinal designs to demonstrate the ubiquitous nature and sources of variability in the occurrence of this pathogen. More recently, I have used this same transdisciplinary approach to collaborate on studies of a range of human microparasites.

a. Hungerford LL, Smith RD. Variations in seroprevalence and host factors for bovine anaplasmosis in Illinois. Vet Res Commun. 1997 Jan;21(1):9-18. PubMed PMID: 9060138.

b. Hungerford LL, Mitchell MA, Nixon CM, Esker TE, Sullivan JB, Koerkenmeier R, Marretta SM. Periodontal and dental lesions in raccoons from a farming and a recreational area in Illinois. J Wildl Dis. 1999 Oct;35(4):728-34. PubMed PMID: 10574532.

c. Nash ML, Hungerford LL, Nash TG, Zinn GM. Risk factors for perinatal and postnatal mortality in lambs. Vet Rec. 1996 Jul 20;139(3):64-7. PubMed PMID: 8857578.

d. Smith D, Blackford M, Younts S, Moxley R, Gray J, Hungerford L, Milton T, Klopfenstein T. Ecological relationships between the prevalence of cattle shedding Escherichia coli O157:H7 and characteristics of the cattle or conditions of the feedlot pen. J Food Prot. 2001 Dec;64(12):1899-903. PubMed PMID: 11770614.

2. Throughout my research, I've pioneered transdisciplinary approaches to health research, building partnerships that introduced new methodologies that subsequently became inculcated in the field. I was one of the first to promote use of geographic information systems (GIS) and spatial statistics in animal disease epidemiology, working with pioneers outside the veterinary or health fields. I worked with other faculty to develop methods for outside assessment of veterinary training to guide curriculum reform; a practice now commonly used in program review. We used detailed follow-up of individual raccoons to show that drugs used to handle the animals have behavioral impacts and can affect population estimates, which had never been considered. We used recognition of the natural curiosity and 'mouthing' behavior of cattle to design a new, efficient, pen-level, bacterial sampling system that allowed us to conduct many studies and is now widely used in research and monitoring. We used molecular epidemiology to examine the influence of the microbiome on health of children in the developing world. Currently, with the enormous advancement of methods within disciplinary silos, the potential for new insights through cross-disciplinary fertilization continues to grow rapidly.

a. Gehrt SD, Hungerford LL, Hatten S. Effects of immobilization agents on post-release behavior and population estimates of raccoons. Wildlife Society bulletin. 2001; 29:833-7.

b. Hungerford L. Use of spatial statistics to identify and test significance in geographic disease patterns. Prev Vet Med. 1991 December; 11(3-4):237-42.

c. Smith DR, Gray JT, Moxley RA, Younts-Dahl SM, Blackford MP, Hinkley S, Hungerford LL, Milton CT, Klopfenstein TJ. A diagnostic strategy to determine the Shiga toxin-producing Escherichia coli O157 status of pens of feedlot cattle. Epidemiol Infect. 2004 Apr;132(2):297-302. PubMed PMID: 15061505; PubMed Central PMCID: PMC2870106.

d. Lindsay B, Oundo J, Hossain MA, Antonio M, Tamboura B, Walker AW, Paulson JN, Parkhill J, Omore R, Faruque AS, Das SK, Ikumapayi UN, Adeyemi M, Sanogo D, Saha D, Sow S, Farag TH, Nasrin D, Li S, Panchalingam S, Levine MM, Kotloff K, Magder LS, Hungerford L, Sommerfelt H, Pop M, Nataro JP, Stine OC. Microbiota that affect risk for shigellosis in children in low-income countries. Emerg Inf Dis. 2015 21:242-50.

3. Many diseases, particularly zoonotic and vector-borne infections, have inherently heterogeneous and meaningful geographic distributions. I have helped develop, used, and taught GIS and spatial methodology throughout my career. This was key to understanding the epidemiology of anaplasmosis in Illinois. In another project, we worked with geographers to develop methods to use satellite data to understand tsetse fly distributions. With ecologists, we used mapping and regression to examine relationships predicting the vulnerability and resiliency of endangered amphibian populations and found associations that were later confirmed by laboratory studies. We used similar approaches to examine individual-, environmental-, and hamlet-level associations with malaria in a low transmission setting. This success has led to significant funding and, most recently, to a grant to foster inter-campus collaborations to build new partnerships in health geography for other faculty.

a. Hungerford LL, Smith RD. Spatial and temporal patterns of bovine anaplasmosis as reported by Illinois veterinarians. Preventive veterinary medicine. 1996; 25:301-13.

b. Kitron UD, Otieno LH, Hungerford LL, Odulaja A, Brigham WU, Okello OO, Joselyn Mark, Mohamed-Ahmed MM, Cook E. Spatial analysis of the distribution of tsetse flies in the Lambwe Valley, Kenya, using Landsat TM satellite imagery and GIS. The Journal of animal ecology. 1996; 65:371-80.

c. Lawpoolsri S, Chavez IF, Yimsamran S, Puangsa-Art S, Thanyavanich N, Maneeboonyang W, Chaimungkun W, Singhasivanon P, Maguire JH, Hungerford LL. The impact of human reservoir of malaria at a community-level on individual malaria occurrence in a low malaria transmission setting along the Thai-Myanmar border. Malar J. 2010 May 26;9:143. PubMed PMID: 20504308; PubMed Central PMCID: PMC2887882.

d. Witte CL, Sredl MJ, Kane AS, Hungerford LL. Epidemiologic analysis of factors associated with local disappearances of native ranid frogs in Arizona. Conserv Biol. 2008 Apr;22(2):375-83. PubMed PMID: 18261148.

4. Epidemiologic methods traditionally focus on identification of risk factors in a dataset. However, this describes the risk in the past. We may infer the future, but dynamic modeling provides explicit methodology for conceptualizing complex future results or consequences. In addition to using modeling to study sheep disease management costs and options, we used preliminary models to explore if distemper epidemics in raccoons and measles epidemics in humans could be generated by pathogen shifts rather than the traditional herd immunity explanation. This led us to molecular studies to explore this finding and the resulting discovery of previously unrecognized strain diversity in a raccoon outbreak. We also used modeling to explore cross-species transmission risk from primates to humans and enhanced treatment schemes for malaria in low transmission areas. A current student is using modeling to examine potential effects of a new vaccine for Salmonella. At a larger scale, we have combined spatial analysis and modeling to create transmission risk maps for avian influenza and are applying this to raccoon rabies.

   a. Engel G, Hungerford LL, Jones-Engel L, Travis D, Eberle R, Fuentes A, Grant R, Kyes R, Schillaci M. Risk assessment: A model for predicting cross-species transmission of simian foamy virus from macaques (M. fascicularis) to humans at a monkey temple in Bali, Indonesia. Am J Primatol. 2006 Sep;68(9):934-48. PubMed PMID: 16900504.

   b. Lawpoolsri S, Klein EY, Singhasivanon P, Yimsamran S, Thanyavanich N, Maneeboonyang W, Hungerford LL, Maguire JH, Smith DL. Optimally timing primaquine treatment to reduce Plasmodium falciparum transmission in low endemicity Thai-Myanmar border populations. Malar J. 2009 Jul 15;8:159. PubMed PMID: 19604346; PubMed Central PMCID: PMC2718908.

   c. Lednicky JA, Dubach J, Kinsel MJ, Meehan TP, Bocchetta M, Hungerford LL, Sarich NA, Witecki KE, Braid MD, Pedrak C, Houde CM. Genetically distant American Canine distemper virus lineages have recently caused epizootics with somewhat different characteristics in raccoons living around a large suburban zoo in the USA. Virol J. 2004 Sep 2;1:2. PubMed PMID: 15507154; PubMed Central PMCID: PMC524033.

   d. Prosser DJ, Hungerford LL, Erwin RM, Ottinger MA, Takekawa JY, Ellis EC. Mapping avian influenza transmission risk at the interface of domestic poultry and wild birds. Front Public Health. 2013;1:28. PubMed PMID: 24350197; PubMed Central PMCID: PMC3854848.

5. A final area of work has been to use my strong quantitative expertise, my background in clinical medicine, and my communication skills to advance clinical epidemiology and population health in veterinary medicine. In general, these collaborations have resulted in publications with co-authors from fields outside of population health. Among the many examples across my career are articles with clinical pathologists, equine clinicians, and animal behaviorists. All of these collaborations focused on answering clinical questions in an evidence-based manner. This approach is also a fundamental aspect of my role with FDA. As an example, we conducted and published a study that demonstrated the potential for use of systematic review and meta-analysis in drug review. This led to a paradigm shift in viewing evidence for safety and effectiveness that provided a new path recently used for approval of a new cattle drug.

a. Austin SM, Foreman JH, Hungerford LL. Case-control study of risk factors for development of pleuropneumonia in horses. J Am Vet Med Assoc. 1995 Aug 1;207(3):325-8. PubMed PMID: 7628934.
b. Baird-Heinz HE, Van Schoick AL, Pelsor FR, Ranivand L, Hungerford LL. A systematic review of the safety of potassium bromide in dogs. J Am Vet Med Assoc. 2012 Mar 15;240(6):705-15. PubMed PMID: 22380809.
c. Gaskins LA, Hungerford L. Nonmedical factors associated with feather picking in pet psittacine birds. J Avian Med Surg. 2014 Jun;28(2):109-17. PubMed PMID: 25115039.
d. Solter PF, Hoffmann WE, Hungerford LL, Peterson ME, Dorner JL. Assessment of corticosteroid-induced alkaline phosphatase isoenzyme as a screening test for hyperadrenocorticism in dogs. J Am Vet Med Assoc. 1993 Aug 15;203(4):534-8. PubMed PMID: 8407509.

D. Additional Information: Research Support and/or Scholastic Performance

Recently Completed Research Support

FDA IPA: Hungerford, Laura
06/01/13-10/25/16
Innovation in Science and Regulatory Decision-making for Animal Drugs
Role: PI

Zoological Society of San Diego
11/01/15-10/01/16
Systems Modeling and Network Analysis of Disease Epidemiology among Wild and Captive Species
Role: PI

State MPowering Maryland Initiative
01/01/15-06/01/16
Piloting Collaboration between the UMCP Center for Geospatial Information Science and the UMB Schools of Medicine, Nursing and Pharmacy
Role: Multiple PI

Zoological Society of San Diego
08/01/13-10/01/15
Developing Population Health-based Research among Wildlife Species
Role: PI

AHRQ, Johns Hopkins University subaward
01/01/12-08/01/13
MidAtlantic Public Health Training Center
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Pierson, Frank William

eRA COMMONS USER NAME (credential, e.g., agency login): PIERSON

POSITION TITLE: Professor, Biosecurity and Infection Control; Clinical Specialist, Poultry Health

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Delaware, Newark, DE	B.S.	05/1978	Animal Science
Purdue University, West Lafayette, IN	M.S.	12/1980	Animal Physiology
Virginia Tech, Blacksburg, VA	D.V.M.	05.1984	Veterinary Medicine
Virginia Tech, Blacksburg, VA	Ph.D.	05/1993	Infectious Diseases
American College of Poultry Veterinarians (Board Specialization), Jacksonville, FL	Diplomate	07/1994	Poultry Health

A. Personal Statement

During my time in academia, my investigatory work has primarily focused on infectious diseases of poultry (pathogenesis, multi-agent / factorial disease interactions, vaccine development) as well as food safety (*Salmonella* and *Salmonella* bioremediation). As an adjunct to research, my service and instructional activities have included such areas as biosecurity, agrosecurity (anti-terrorism / biologicals and toxicants), and animal disaster response (partial funding for the latter two areas from DHS). A specific outgrowth from my work on biosecurity has been to oversee the infection control program (ICP) of Veterinary Teaching Hospital at Virginia Tech. This has involved the design / development of Standard Operating Procedures for cleaning and disinfection (C&D), training of personnel, compliance, and investigation of hospital -acquired infections (HAIs) and zoonoses. My specific role relative to the oversight and implementation of the hospital ICPs position's me well for participation in this project i.e., monitoring of environmental exposure to the quaternary ammonium compounds used by personnel in the C&D process. I also served as hospital director and veterinarian-in-charge from 2007-2014, with administrative responsibility for the 120+ staff that will comprise the study pool. I recently returned from a 6 mo. research sabbatical leave split between the Southwest Border Food Protection and Emergency Preparedness Center, New Mexico State University, Las Cruces, NM and the Max Planck Institute for Infection Biology, Berlin, Germany.

B. Positions and Honors

Positions and Employment

1984-1987 Private Veterinary Practitioner, Londonderry Animal Hospital, Middletown, PA
1987-1990 Graduate Research Assistant, Department of Large Animal Clinical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
1990-1991 Research Associate, Department of Large Animal Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.

1991-1993	Research Scientist, Department of Large Animal Clinical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
1993-1999	Assistant Professor, Department of Large Animal Clinical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
1999-2011	Associate Professor, Poultry Health, Department of Large Animal Clinical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
2002-Present	Coordinator, Biosecurity and Infection Control, Veterinary Teaching Hospital, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
2007-2008	Interim Director and Veterinarian-in-Charge, Veterinary Medical Teaching Hospital, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
2008-2014	Director and Veterinarian-in-Charge, Veterinary Medical Teaching Hospital, Virginia-Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.
2011-Present	Professor, Biosecurity and Infection Control; Clinical Specialist, Poultry Health; Department of Population Health Sciences, Virginia-Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA.

Other Experience and Professional Memberships (selected)

1978-Present	Poultry Science Association
1984-Present	American Veterinary Medical Association
1988-Present	American Association of Avian Pathologists
1992-Present	Association of Avian Veterinarians
1999-Present	Member, Virginia Poultry Disease Task Force
2000-2013	Secretary, Northeastern Conference on Avian Diseases
2007-2013	Secretary / Chair, Northeastern Conference on Avian Diseases
2007-2014	Member, Executive Board, Virginia-Maryland Regional College of Veterinary Medicine
2007-2014	Member, University Outreach Council, Virginia Tech
2011-Present	Member, Organizing Committee, Virginia Agroterrorism Conference (annual)
2011-Present	Chair, Committee on Diseases of Public Health Significance, American Association of Avian Pathologists.
2011-2013	Member, National Institute for Occupational Safety and Health, National Occupational Research Agenda, Subcommittee-Veterinary Medicine and Allied Professions.

Honors (selected)

1992	College Teaching Award, Virginia-Maryland Regional College of Veterinary Medicine
1992	Virginia Tech Certificate of Teaching Excellence
1998	Recognized by the Distinguished Professors, Division of Research and Graduate Studies, Virginia Tech, for research contributions in the area of poultry health
2007	Virginia Tech Scholar of the Week, Office of the Vice President for Research, Virginia Tech, for research contributions in the area of poultry health
2012	Virginia Tech Scholar of the Week, Office of the Vice President for Research, Virginia Tech, for contributions in the areas of agroterrorism risk assessment and mitigation; food and agriculture infrastructure protection, biosecurity.
2015	Nominated, Excellence in Graduate Advising Award, Virginia Tech

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C. Contribution to Science

1. My early work focused on diseases of turkeys, especially the interactions of multiple infectious agents in the production of respiratory colibacillosis. I eventually concentrated on the role of hemorrhagic enteritis virus; a member of the family-*Adenoviridae*, genus-*Siadenovirus*. This is a rather unique virus with a small genome compared to other adenoviruses and it has an unusual coding sequence for a sialidase homolog. We continue to work on this virus (one of two labs worldwide); specifically pathophysiology, genomics, and

vaccinology. In addition to the publications below, three new manuscripts are in process based on the work of a recent PhD student; now post-doc.

a. Beach, N.M., R.B. Duncan, C.T. Larsen, X.J. Meng, N. Sriranganathan, and **F.W. Pierson**, 2009, Comparison of 12 turkey hemorrhagic enteritis virus isolates allows prediction of genetic factors affecting virulence. J Gen Virol, 90:1978-1985.
b. Beach, N.M., R.B. Duncan, C.T. Larsen, X.J. Meng, N. Sriranganathan, and **F.W. Pierson**, 2009. Persistent infection of turkeys with an avirulent strain of turkey hemorrhagic enteritis virus. Avian Dis 53:370-375.

2. I continue to work on other diseases of importance to the poultry industry in a manner consistent with my academic service appointment. In this respect, research flexibility is an important characteristic, both in scholarly pursuit and research support acquisition. Generally this research addresses diagnostics, epidemiology, pathophysiology, and vaccinology.

a. McQuiston, J.H., L.P. Garber, B.A. Porter-Spalding, J.W. Hahn, **F.W. Pierson**, S.H. Wainwright, D.A. Senne, T.J. Brignole, B.L. Akey, T.J. Holt, 2005. Risk factors for spread of low pathogenicity H7N2 avian influenza virus among commercial poultry farms in Virginia, 2002. J Amer Vet Med Assoc 226:767-772.
b. Elvinger, F., B. L. Akey, D. A. Senne, **F. W. Pierson**, B. A. Porter-Spalding, E. Spackman, D. L. Suarez. 2007. Characteristics of diagnostic tests used in the 2002 low pathogenicity avian influenza H7N2 outbreak in Virginia. J Vet Diagn Inves 19:341-348.
c. Walters, J., R. Evans, T. LeRoith, N. Sriranganathan, A. McElroy, and **F. W. Pierson**, 2014. Experimental Comparison of Hemolytic and Non-Hemolytic *Ornithobacterium rhinotracheale* Field Isolates *In Vivo.* Avian Diseases 58:78-82.
d. Lighty, M.E., F. Elvinger, R.D. Evans, N. Sriranganathan, T. LeRoith, and **F.W. Pierson**, 2016. Incidence of Clostridial Dermatitis (Cellulitis) and Factors for the Development of Disease in Turkeys. J Appl Poult Res 25:104-112.

3. Food safety as it relates to poultry, specifically *Salmonella* detection and bioremediation has been a parallel interest of my lab. We have specifically looked at novel, bacteriophage-mediated methodologies to reduce *Salmonella* load on poultry products as well as early detection methods to facilitate timely diversion of product for reprocessing or repurposing.

a. Whichard, J.M., N. Sriranganathan, and **F.W. Pierson**, 2002. Bacteriophage Felix O1: Suppression of Salmonella growth by wild-type and large-type plaque isolates in liquid culture and on poultry frankfurters. J. Food Protect 66:220-225.
b. Whichard, J.M., L.A. Weigt, D.J. Borris, L.L. Li, Q. Zhang, V. Kapur, **F.W. Pierson**, E.J. Linghor, Y. She, A.M. Kropinski, and N. Sriranganathan, 2010. Complete genomic sequence of bacteriophage Felix O1. Viruses 2:710-730.
c. Evans, N.P., R.D. Evans, J. Regalado, J.F. Sullivan, V. Dutta, F. Elvinger and **F.W. Pierson**, 2015. Preharvest *Salmonella* Detection for Evaluation of Fresh Ground Poultry Product Contamination. J Food Prot 78:1266-71.

4. Finally, I have also been part of a research team working on hepatitis E virus, a member of the family-*Hepeviridae*, genus-*Orthohepevirus*. The virus has a broad host range, most notably humans, swine and poultry. Hepatitis E virus can produce anything from subclinical infection to significant mortality in humans (approaching 20% among pregnant women in industrializing / developing countries) as well as fulminant disease in poultry. The latter inspired the development and validation of an avian (chicken) model to study viral replication and pathogenesis with the ultimate goal of advancing treatment and prophylaxis.

a. Billam, P., F.F. Huang, Z.F. Sun, **F.W. Pierson**, R.B. Duncan, F. Elvinger, D.K. Guenette, T.E. Toth, and X.J. Meng, 2005. Systematic Pathogenesis and Replication of Avian Hepatitis E Virus in Specific-Pathogen-Free Adult Chickens. J Virol 79:3429-3437.
b. Pudupakam, R.S., Y. W. Huang, T. Opriessing, P.G. Halbur, **F.W. Pierson**, and X.J. Meng, 2009. Deletions of the hypervariable region (HVR) in open reading frame 1 of hepatitis E virus do not abolish virus infectivity: Evidence for attenuation of HVR deletion mutants in vivo. J Virol 83:384-395.
c. Pudupakam, R.S., S.P. Kenny, L. Cordoba, Y.W. Huang, B. A. Dryman, T. LeRoith, **F.W. Pierson**, and X.J. Meng, 2011. Mutational Analysis of the hypervariable region of hepatitis E virus reveals its involvement in the efficacy of viral RNA replication. J Virol 85:10031-100040.
d. Kenney S.P., R.S. Pudupakam R, Y.W. Huang, **F.W. Pierson**, T. LeRoith, and X.J. Meng, 2012. The PSAP motif within the ORF3 protein of an avian strain of the hepatitis E virus is not critical for viral infectivity in vivo but plays a role in virus release. J Virol 86:5637-46.

5. My scholarly work includes: 77 authored or co-authored peer-reviewed papers, reviews, book chapters, and manuals, 31 research presentations given at regional / national / international meetings (excluding keynotes and continuing education presentations), and 106 co-authored papers / posters presented at regional / national / international meetings. A list of published work in NCBI cataloged journals (up to Dec 31, 2015) can be found at: **http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/bibliography/49614900/**

D. Research Support

Ongoing Research Support

NIH R01 AI050611 (competitive) Meng, X.J. (PI) 2013-2018
A Chicken Model to Study Hepatitis E Virus Pathogenesis.
Chickens are one of the few species in which distinct clinical signs and lesions can be produced following experimental hepatitis E virus inoculation. The goal of this project is to better define the pathogenic mechanisms (likely immune mediated) responsible for disease in humans.
Role: Co-I

NIH/NCRR T32 (competitive) Meng, X.J. (PI) 2011-2016
Animal Model Research for Veterinarians.
The goal of this training grant is to provide graduate research support funding for post-DVM students and aid in the development of animal models for human disease.
Role: Co-I

NIH T35 (competitive) Ahmed, S.A. 2011-2016
Summer Veterinary Research Program.
The purpose of this grant is to provide DVM students with financial support and other structured opportunities that will encourage the selection of alternative career paths in research.
Role: Co-I

Cargill Turkey, LLC and Virginia Poultry Growers Cooperative (solicited) 2015-2017
Control of Hemorrhagic Enteritis in the Shenandoah Valley and Continued Research for Disease Prevention.
The purpose of this project is to support improvements in the control of hemorrhagic enteritis of turkeys (Siadenovirus) and address other diseases of importance to the turkey industry.
Role: Co-PI

Phibro Animal Health (solicited) 2015-2016
Development of a model for Testing the Efficacy of a Feed-Based Antiprotozoal against *Cochlosoma anatis.*
The goal of this project is to test a proprietary product for anti-protozoal activity in turkeys.
Role: Co-PI

Land-O-Lakes (solicited) 2015-2016
Investigation of Medium Chain Fatty Acids for Salmonella Reduction in Poultry with the In Vivo Imaging System (IVIS).
The goal of this grant is to determine the effect of dietary medium chain fatty acids on *Salmonella* load and location in gastrointestinal tract of experimentally infected poultry.
Role: Co-PI

Agri-King (solicited) 2015-2016
IVIS Evaluation of Avi-lution for Reduction of *Salmonella* in Poultry.
The goal of this research is to determine the effect of the pro-biotic (direct-fed microbial) Avi-lution on *Salmonella* load and location in the gastrointestinal tract of experimentally infected chickens.
Role: Co-PI

Virginia Department of Environmental Quality (solicited) 02/2016-09/2016
Systematic Review of 9 VAC 20-120 - Regulated Medical Waste Regulations and Recommended Changes to Ensure Proper Handling of Highly Infectious Materials.
The goal of this project is to review, update and strengthen 9 VAC 20-120 (Virginia Administrative Code) so that VDEQ has the flexibility and operational authority to deal with emerging and / or unforeseen issues related to the management of regulated medical waste in the Commonwealth of Virginia.
Role: PI

Completed Research Support (selected, last 5 years)

NIH 2R01 (competitive) Meng, X.J. 2008-2012
A Chicken Model to Study Hepatitis E Virus Pathogenesis.
The goal of this project was to develop and validate an experimental chicken model to study hepatitis E infection
Role: Co-I

DHS Training Grant (sub-award, federal flow-through) 2009-2011
Training to Enhance Timely Sharing of Information and Intelligence on the Importation and Transportation of Food, Food Ingredients, and Animal Feed in the US.
Role: PI

Cargill Turkey, LLC and Virginia Poultry Growers Cooperative (solicited) 2011-2014
Characterization and Control of Diseases Responsible for Significant Losses to the Commercial Turkey Industry in the Shenandoah Valley.
The goal of this project was to provide veterinary support for the treatment, control and prevention of diseases of economic concern to the turkey industry.
Role: PI

USDA-NRI (competitive) 2009-2014
Integrated Education and Biodegradable Litter Amendment Development to Enhance Adoption of Ammonia Emissions Mitigation Practices in Poultry Houses.
The goal of this research was to evaluate the ability of an agricultural plant-based byproduct to reduce ammonia emissions from poultry house litter.
Role: Co-PI

VA-MD College of Veterinary Medicine – Internal Research Competition (competitive) 2012-2014
A mammalian model for testing the efficacy of an acute stress vaccination protocol for protection against acute and chronic tubercular lesions induced by *Mycobacterium avium*.
The goal of this research was to develop a mammalian model for Maa vaccine protocol that was previously proven to be effective prophylactically and therapeutically in chickens**.**
Role: PI

BIOGRAPHICAL SKETCH
NAME: Cassidy L. Rist

POSITION TITLE: Assistant Professor, Department of Population Health Sciences, Virginia-Maryland College of Veterinary Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion MM/YYYY	FIELD OF STUDY
University of Florida, Gainesville, FL	DVM	06/2005	Veterinary Medicine
Emory University, Atlanta, GA	MPH	06/2014	Global Epidemiology

A. Professional Summary

Veterinary epidemiologist with strength of knowledge in One Health and zoonoses, infectious disease prevention and control strategies, and emergency preparedness and response. Prior experience in small animal private practice; Research Fellow with the One Health Office at the Centers for Disease Control and Prevention; postdoctoral researcher with Emory University and Harvard Medical School; and Veterinary Medical Officer with the U.S. Department of Agriculture. Interest in promoting the role of livestock health in global food and economic security, strengthening domestic and international veterinary capacity for disease detection and response, and building collaborative research and development programs at the intersection of human, animal and environmental health.

B. Positions and Honors

Positions and Employment

2016 – Assistant Professor, Department of Population Health Sciences, Virginia-Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA

2015 – 2016 Veterinary Medical Officer, United States Department of Agriculture, Richmond, VA

2014 – 2016 Contractor, Centers for Disease Control and Prevention, Atlanta, GA

2014 – 2015 Postdoctoral Research Fellow, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA

2012 – 2014 Research Fellow, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA

2011 – 2012 Veterinarian, General Practice, Trenton Animal Hospital, Trenton, FL

2009 – 2011 Veterinarian, Emergency and Critical Care, Affiliated Pet Emergency Services, Gainesville, FL

2007 – 2009 Veterinarian, Emergency and Critical Care, Veterinary Emergency and Specialty Center, Santa Fe, NM

2006 – 2007 Intern, Small Animal Surgery, Wheat Ridge Veterinary Specialists, Wheat Ridge, CO

2005 – 2006 Intern, Small Animal Emergency and Critical Care, New England Animal Medical Center, West Bridgewater, MA

Honors and Awards

2013 Emory Global Health Institute, Multidisciplinary Team Field Scholar
2004 Dr. Mark Bloomberg Memorial Scholarship for Excellence in Academics and Leadership
2004 Allen H. Hart/IDEXX Scholarship for Excellence in Clinical Pathology

C. Contributions to Science

Select Publications

Rist CL, Arriola CS, Rubin C (2014). Prioritizing zoonoses: A proposed One Health tool for collaborative decision-making. PLoS ONE 9(10): e109986. doi:10.1371/journal.pone.0109986

Rist CL, Ngonghala CN, Garchitorena A, Brook CE, Ramananjato RH, Miller AC, Randrianarivelojosia M, Wright PC, Gillespie TR, Bonds MH (2015). Modeling the burden of poultry disease on the rural poor in Madagascar. One Health, vol 1:p60-65. doi:10.1016/j.onehlt.2015.10.002

Rist CL, Garchitorena A, Ngonghala CN, Gillespie TR, Bonds MH (2015). The burden of livestock parasites on the poor. Trends in Parasitology, 31(11):p527-530. doi:10.1016/j.pt.2015.09.005

Select Invited Presentations:

International Society for Veterinary Epidemiology and Economics, October 3rd, 2015. *"A coupled epidemiological-economic model for measuring the burden of poultry disease on the rural poor in Madagascar"*

Education and Research Center for Occupational Safety and Health Seminar Series at the **Johns Hopkins University, Bloomberg School of Public Health**, April 6th, 2015. *"Reaching National Consensus for Disease Control: Prioritization at the Human, Animal and Environmental Health Interface"*

Division Seminar at the **Centers for Disease Control and Prevention**, Division of High-Consequence Pathogens and Pathology, April 2, 2014. *"Lemurs In the Backyard, Chickens In the Kitchen: Finding One Health Solutions for Madagascar".*

Professional Memberships

- American Veterinary Medical Association
- International Society for Veterinary Epidemiology and Economics
- International Society for Infectious Diseases
- International Society for Disease Surveillance – One Health Surveillance Working Group
- United States Animal Health Association
- Network for the Evaluation of One Health

D. Research Support

Ongoing Research Support

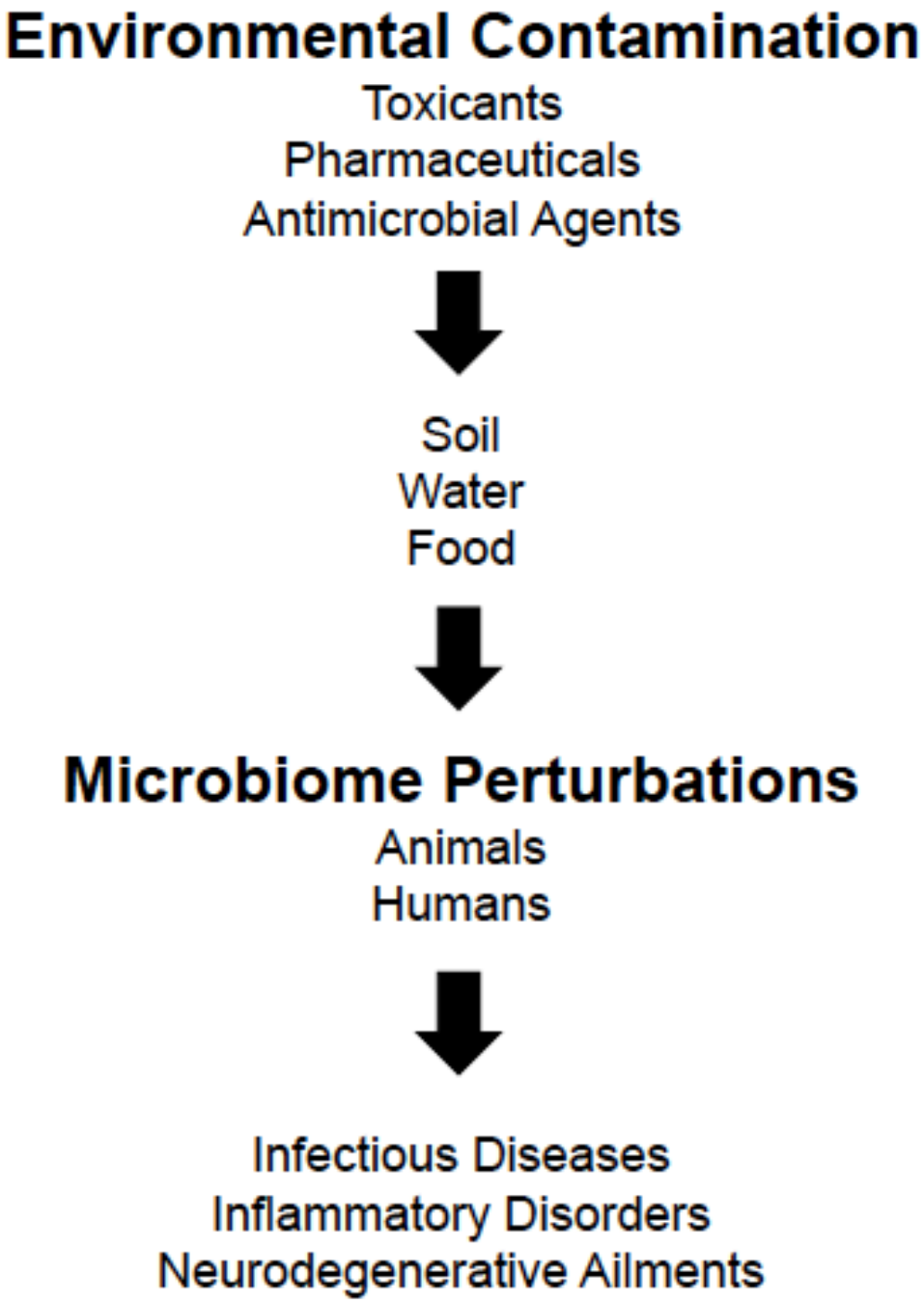
PIVOT Research Grant 10/01/16 – 09/30/17
Design and deployment of a regional dried blood spot sampling program for improved tuberculosis diagnostics in Ifanadiana District, Madagascar.
Role: Co-PI

Faculty Resources Grant, Virginia-Maryland College of Veterinary Medicine 12/01/16 – 08/01/17
Environmental conditions incurred by dried blood spot samples under drone transport.
Role: PI

Completed Research Support

Bill and Melinda Gates Foundation, Phase I Grand Challenges Explorations 07/01/14 – 09/01/15
The economic burden of disease: A combined metric of human and animal health in rural Madagascar.
Role: Co-Investigator

Appendix II


Environmental Contamination
Toxicants
Pharmaceuticals
Antimicrobial Agents
Soil
Water
Food
Microbiome Perturbations
Animals
Humans
Infectious Diseases
Inflammatory Disorders
Neurodegenerative Ailments

Appendix III

Hypothetical job posting for cluster hire related to this Concept

The complexity of global challenges related to microbiomes and their relationship to animal and human health and natural environments requires a multi-prong approach that is grounded in the understanding of environmental, animal, and human systems, as well as the fundamental mechanisms of microbial physiology. In order to build a more comprehensive approach to understanding and solving these modern challenges, Virginia Tech is assembling a transdisciplinary microbiome-related consortium to engage in research, education, and engagement through a program called Destination Areas. The Global Systems Science Destination Area (http://provost.vt.edu/destination-areas/da-global-systems.html) is focused on addressing critical problems that cross the nexus of natural, animal, and human systems. Virginia Tech has a long record of excellence in the fields of environmental science, engineering, and infectious diseases, which has positioned the university to become an innovative leader in global systems science. As part of this mission, the University has established a microbiome initiative for the hiring of several faculty positions to begin in August 2018. The following positions are being sought:

-Microbiome Specialist
-Environmental Systems Analyst (Modeler)
-Infectious Diseases Specialist (Agriculture)
-Infectious Diseases Specialist (Animal/Human)
-Environmental Toxicologist
-Systems Analyst

Research Resources

Virginia Tech has developed a supportive infrastructure for microbiome research, such as cutting-edge microbial laboratories and animal isolation facilities, gnotobiotic animal facilities, animal housing to accommodate a wide range of laboratory and domestic animal research and teaching, an insectary, and state of the art instrumentation and computational facilities. The University also has strengths in data analytics (including biostatistics, epidemiology, geospatial analysis and decision modeling) as well as an emerging health science and technology initiative in Roanoke, VA.

About Virginia Tech

Virginia Tech recognizes the critical importance of diverse teams of scholars. It seeks to diversify its faculty along multiple dimensions, including those that have been historically marginalized and excluded given the institutional history and legacy of the university. Virginia Tech is a public land-grant university, committed to teaching and learning, research, and outreach to the Commonwealth of Virginia, the nation, and the world. Building on its motto of *Ut Prosim* (that I may serve), Virginia Tech is dedicated to InclusiveVT- serving in the spirit of community, diversity, and excellence. We seek candidates who adopt and practice the Principles of Community, which are fundamental to our on-going efforts to increase access and inclusion and to create a community that nurtures learning and growth for all of its members. Virginia Tech actively seeks a broad spectrum of candidates to join our community in preparing leaders for the world.

Applicants must hold a Ph.D. in a relevant discipline. Applicants should apply using the online system at www.jobs.vt.edu. Please refer to individual job listings above for other application requirements.

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