
BIOGRAPHICAL SKETCH

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NAME: Petersen, Christine Anne

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POSITION TITLE: Associate Professor, Infectious Disease Epidemiology

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
Johns Hopkins University, Baltimore, MD	B.A.	05/1994	Biology
Cornell University, Ithaca, NY	D.V.M.	05/1998	Veterinary Medicine
Harvard University	Ph.D.	05/2005	Immun. and Infect. Dis.

A. Personal statement.

Since June 2013, I have been the Director of the Center for Emerging Infectious Diseases (CEID) at the University of Iowa housed within the Department of Epidemiology. The focus of this Center is to bring together transdisciplinary research teams to lessen the burden of emerging zoonotic infectious diseases across health settings. The work proposed in this U01 is a perfect example of these efforts; bringing together immunologists, vaccinologists and computational biologists/biostatisticians to attack the problem of vaccine-intractable infections through Bayesian hierarchical modeling of protective immunity. Through the coordination of CEID I developed a strong working relationship with Dr. Jacob Oleson, co-I on this proposal and point person for the statistical modeling core. I have served as scientific matchmaker to the faculty across Iowa health institutions and the globe to bring the team for this proposed work together. CEID-based efforts have led to published collaborative studies and became the launching point for this current proposal.

I am also the principal investigator and last author in studies that follow the immunopathology of visceral leishmaniasis (VL) and tick-borne diseases, including Borreliosis (LD) in a canine natural disease model, references 1-4, sections C1, 2 and 5. We have ongoing studies of dogs infected with visceralizing *Leishmania* spp in the US, Brazil and India and in people in Brazil and Ethiopia. I am Co-I of an R01 "*Epidemic modeling framework for complex, multi-species disease processes*", working with Drs. Oleson and Brown, also collaborators on this project, based on my laboratory's wet-lab discoveries of canine progressive leishmaniasis. The beginnings of this work is represented in (1,2). Regarding field and vaccine trials, I was PI on a sub-contract on a VL vaccine immunogenicity study with Meril from an NIAID R01 to the Infectious Disease Research Institute (IDRI). This subaward from IDRI led to further trials of experimental vaccine immunogenicity ex vivo in cells from my hunting dog cohort, published in *Vaccine* in 2015 and a large CONSORT-guided vaccine field trial completed in spring of 2017 and recently also published in *vaccine* (4). The safety portion of this trial was published in *AJTMH* in 2018. Our active research group is focused on the long term goal of understanding how to best protect people and animals from vector-borne diseases through effective treatment and/or vaccination.

1. Ozanne, M.V., Brown, G.D., Oleson, J.J., Lima, I.D., Queiroz, J.W., Wilson, M.E., **Petersen, C.A.**, Jeronimo, SMB, (2018) "Bayesian Epidemic Compartmental Model for an Infectious Disease with Dynamic Disease State Proportions: Analyzing Visceral Leishmaniasis in Brazil." Journal of Applied Statistics, (in press).
2. Toepp, A., Willardson, K., Scott, B., Johannes, A., Senesac, R., Larson, M., **Petersen, C.**, (2018) "Prevalence and risk factors for Lyme disease in companion animal caretakers". Vector Borne and Zoonotic Diseases. 10.1089/vbz.2017.2238.
3. Toepp, A., Larson, M., Wilson, G., Grinnage-Pulley, T., Leal-Lima, A., Bennett, C., Anderson, M., Fowler, H., Anderson, B., Jeffries, J., Beeman, G.M., Parrish, M., Hinman, J., Buch, J., Saucier, J.,

Gharpure, R., Cotter, C., **Petersen, C.**, (2018) "Randomized, controlled, double-blinded field trial to evaluate the efficacy of the Leish-Tec® vaccine as immunotherapy for canine leishmaniasis". Vaccine 36:6433-41.

4. Schaut RG, Lamb IM, Toepp AJ, Scott B, Mendes-Aguiar CO, Coutinho JF, Jeronimo SM, Wilson ME, Harty JT, Waldschmidt TJ, **Petersen CA.** (2016). Regulatory IgDhi B Cells Suppress T Cell Function via IL-10 and PD-L1 during Progressive Visceral Leishmaniasis. Journal of Immunology, Vol. 196: 4100-9. PMC4868652

B. Positions and Honors.

Positions and Employment

- 1999-2004 Graduate Student, Dept. of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA
- 2004-2005 Affiliate Assistant Professor, Department of Vet. Path., College of Veterinary Medicine, Iowa State University, Ames, IA (title given to NIH K08 mentored training grant funded scientists)
- 2005-2012 Assistant Professor, Department of Vet. Path., College of Veterinary Medicine, Iowa State University, Ames, IA
- 2006-2013 Adjunct Assistant Professor, Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA
- 2012-2013 Associate Professor, Department of Vet. Path., College of Veterinary Medicine, Iowa State University, Ames, IA . With tenure.
- 2013-present Associate Professor, and Director of the Center for Emerging Infectious Diseases, Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA

Recent Awards and Honors

President, American Council for Molecular, Cellular and Immunoparasitology. Nov. 2016-2018.

Inducted as member of Leishvet, the governing body that determines treatment and control guidelines for global veterinary Leishmaniasis. 2014- present.

Editor for PLoS Neglected Tropical Diseases, Infection and Immunity and guest editor for PLoS Pathogens.

Ad-hoc reviewer NIH NIAID Tropical Disease Research Centers P50, Sept. 2011, IHD study section, Feb. 2013, DVM-oriented T35/32 review Nov. 2014, SBIR/STTR review, June, Nov. 2016, March 2017, VMD Oct. 2018, Feb. 2019.

Keynote speaker, Woods Hole Immunoparasitology meeting, April 2019.

Brazilian Society of Protozoology Annual Conference invited speaker, Caxambu, MG, Brazil, Oct. 2012.

Inaugural International Society for Companion Animal Infectious Diseases Symposium invited speaker, Toulouse, France, 2010.

Patents from work

Christine Petersen and Angela Toepp No US 62/630,053 filed Feb. 13, 2018
"Immunotherapy for canine leishmaniasis".

C. Contribution(s) to Science

1. Immune alterations during progressive *L. infantum* infection expanded a large population of regulatory B cells, induced T cell exhaustion and led to clinical disease.

- U.S. and Brazilian infected with *L. infantum* have pronounced production of immunosuppressive IL-10 as disease progresses (Boggiatto *et al.* 2010, Esch *et al.*, 2013). IL-10 production is produced by naïve-like, IgD^{hi} B regulatory cells and less so T regulatory cells (Schaut *et al.*, 2016).
- Concomitant with production of IL-10 and high levels of immunoglobulin, CD4+ T cells from U.S. hounds infected with *L. infantum* progressing to clinical VL have reduced ability to respond via T cell proliferation to any specific antigen. (Boggiatto *et al.* 2010), (Esch *et al.*, 2013), (Vida *et al.*, 2015).
- Effector responses by CD4+ T cells and to a lesser extent CD8+ T cells were significantly recovered after blockade of the inhibitory receptor ligand B7.H1. (Esch *et al.*, 2013).
- Altered immunity and increased hypergammaglobulinemia leads to NLRP3 and autophagy-driven renal failure during clinical VL (Esch *et al.*, 2015).

These findings identified that during progressive *L. infantum* infection there is robust production of IL-10 from B cells which can co-opt other B cells and T cells into a regulatory phenotype. The canine model for VL has similar tissue pathology and immune responses to human disease in endemic areas, including T cell

exhaustion concomitant with progressive disease. This work substantiates that our cohorts of dogs are valid and useful model system for studying immunopathogenesis of visceral leishmaniasis, particularly given our ability to evaluate paired physical exams, repeated whole blood sampling across progression of disease and euthanasia with full tissue collection data. I served as the primary investigator in all of these studies.

2. Transmission of *Leishmania infantum* in dogs in non-endemic regions is primarily vertical, but retains ability for vector transmission.

My lab group determined and published the primary means of *Leishmania* transmission in U.S. dogs; vertical transmission, answering a question that had confounded multiple scientists and veterinarians for the last decade - how this disease is spreading focally in specific breeds without evidence of human infection or introduction into the U.S. canine population as a whole. This finding is significant to disease transmission throughout the 98 VL endemic countries, as focus on vector elimination alone will not eliminate VL. Without canine population control, mom-to-pup transmission will promote continued disease. We also determined that despite the fact that transmission has been predominantly amastigote-based and transplacental, the parasite has retained its ability to form infective metacyclic promastigotes once taken into *Lu. longipalpis* and infect other mammals.

- A very high percentage of pups born to a seropositive, *L. infantum*-infected bitch have disseminated parasites at birth. Twelve weeks after birth, at the time when the maternal immune response should have waned within the pups, there is decreased parasite dissemination. (Toepp *et al.* 2018)
 - Despite evidence of parasite transmission while *in utero*, which can interfere with the ability to distinguish parasite antigen from self, T lymphocytes from pups both at birth and twelve weeks after birth are able to make this self/non-self distinction as demonstrated by proliferation in response to parasite antigen. (Boggiatto *et al.* 2011)
 - Parasites from infected dogs can still actively infect *Lu. longipalpis*, become highly infectious metacyclic promastigotes and via sand fly infect additional mammals; have maintained the ability for vector borne transmission. (Schaut *et al.*, 2015)
 - Vertical transmission of *L. infantum* occurs in multiple vertebrate hosts, including people and dogs. This is also true of parasitic family-member, *Trypanosoma cruzi*. (Grinnage-Pulley *et al.*, 2016)
- These findings determined a novel means of *L. infantum* transmission without vectors, which maintains infection within the population and does not itself lead to additional pathology as the neonatal immune system is able to identify parasite antigen as non-self. These parasites have not lost their ability for vector transmission.

3. Dendritic cells and macrophages have altered maturation and subsequent function after *L. amazonensis* infection both *in vitro* and *in vivo* induced through MAP kinase ERK activation and alteration of NADPH oxidase function.

- Amastigote infection of bone marrow derived dendritic cells (BMDC) and bone-marrow macrophages (BMM) leads to rapid and significant activation of MAP kinase ERK, not seen in BMDC infected with the benign/healing disease causing parasite *L. major*. (Mukbel *et al.*, 2008, Boggiatto *et al.*, 2009, 2014)
- *L. amazonensis*-mediated ERK activation leads to a less mature DC population both *in vitro* and *ex vivo*. This defective DC phenotype can be recovered both *in vitro* and *in vivo* by blocking activation of ERK (Boggiatto *et al.*, 2009)

These findings are important as they identified a specific signaling pathway (ERK1/2 phosphorylation) and location (the late endosome) as the unique signal and site of activation by non-healing chronic *L. amazonensis* infection as compared to healing *L. major* infection, promoting parasite persistence and chronic disease within the host.

4. Pathogen-derived oligosaccharide cap sugars differentially alter the immune response, these and other adjuvants can effectively recover immune responsiveness during progressive VL.

- Creation of pathogen-derived cap sugars provides a model system to discover how sugars alter the immune response. Pathogen-derived cap sugars differentially alter production of the critical cell mediated immunity cytokine IL-12 (Song *et al.* 2010, Osanya *et al.*, 2011)
- Pathogen-derived cap sugars differentially alter production of other critical cell mediated immunity cytokines using toll-like receptor (TLR) 2 and mannose receptor *in vitro* and TLR2 *in vivo* (Osanya *et al.*, 2011)

- Use of an acid-labile linker and carbohydrates attached to this linker in a dendrimer array provided a pseudo-pathogen model system to assess carbohydrate release within the phagolysosome and effector interaction(s) of carbohydrates with T cells (Choudhury *et al.*, 2015)
- TLR agonist adjuvants, including those specific to glycolipids, or oligosaccharides themselves were able to recover T cell responsiveness from cells obtained from animals across the VL spectrum (Schaut *et al.*, 2016), and improve lesion resolution in *L. major*-infected mice (Grinnage-Pulley *et al.*, 2017).
With an invaluable team of collaborators, we have evaluated how structurally similar oligosaccharides with only one sugar difference can lead to very different innate immune responses, using different lectin-binding, leading to differences in clinical outcomes. Further studies used novel “pseudopathogen” particles to determine further how these sugars, provided in a multimeric display, are recognized by antigen presenting cells and promote effector functions in T cell subsets.

5. Exposure to domestic animals, whether dead-end or reservoir hosts, which are preferred vector blood meal sources, can greatly increase human vector exposure and subsequent likelihood of vector-borne infection. These interactions can be modeled, and effect of interventions predicted, using Bayesian statistical modeling.

- Caretakers of multiple hunting dogs had 5.89 greater risk of tick exposure than people out in tick environments without birds (Toepp *et al.* 2018)
- Exposure to tick borne diseases greatly increased the likelihood of clinical progression of leishmaniasis in dogs. (Toepp *et al.*, 2018)
- Using serology exposures of different hosts and knowledge of vector patterns, a predictive model can be designed. (Ozanne *et al.*, 2018)

With an invaluable team of collaborators, we have evaluated how dog exposure increased the risk of people working with dogs to find embedded ticks on their body. We found that after controlling for time spent outdoors and other variables, people working with large kennels of hunting dogs were at much higher risk of tick and therefore tick-borne disease exposure. We have used similar approaches to look at how tickborne diseases can alter another vector borne disease, Visceral Leishmaniasis. Collaboratively we have used data sets from these and other studies to use compartmental Bayesian statistical modeling to predict changes in transmission and how interventions may alter vector borne disease exposure.

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/christine_a.petersen.1/bibliography/40335669/public/?sort=date&direction=ascending.