BIOGRAPHICAL SKETCH

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NAME: Monack, Denise

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POSITION TITLE: 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
University of California, Davis, California	B.S.	1984	Genetics
Stanford University	Ph.D.	2002	Microbiology & Immunology

A. Personal Statement

I have a broad training in bacterial pathogenesis, with greater than 30 years of experience working in the field of host-pathogen interactions, and have published many basic research articles on bacterial pathogens and immune responses to infection. The primary focus of my research is to understand the genetic and molecular mechanisms of bacterial pathogenesis. I am particularly intrigued by host-adapted pathogens that have evolved to persist within hosts for long periods of time. I have developed a mouse model to study mechanisms of asymptomatic persistent *Salmonella* infections and transmission. We use this model to study various aspects of systemic and gut colonization. We recently identified a *Salmonella*-driven mechanism of granuloma macrophage polarization that involves injection of a Type 3 secreted effector, SteE. This allows the pathogen to antagonize TNF-mediated pathogen restriction during persistent infection. In addition, we use this model to study the immune responses during chronic infection. For example, we described a unique dampened immune state in the hosts that are responsible for the vast majority of host-to-host transmission, supershedder hosts. We routinely perform unbiased genome-wide genome-wide screens in this mouse model, which has led to the identification of 280 *Salmonella* genes that are important for persistent colonization. In-depth studies of these genes have revealed examples of unique co-evolution between a pathogen and its mammalian host. Recent ly we have established a tool to study interactions with enteric pathogens that utilizes flipped and unflipped human-derived intestinal organoids. We are currently characterizing the interactions of typhoidal *Salmonella* strains (*S*. Typhi and *S*. Paratyphi A) with human macrophages and human intestinal organoids. We have discovered new type 3 secretion system effectors that are required for intracellular replication and are discovering human-specific host interacting proteins.

1. Co JY, Margalef-Catala M, Li X, Mah AT, Kuo CJ, **Monack DM***, Amieva MR*. Controlling Epithelial Polarity: A Human Enteroid Model for Host-Pathogen Interactions. Cell Rep. 2019;26(9):2509-20 e4. Epub 2019/02/28. doi: 10.1016/j.celrep.2019.01.108. PubMed PMID: 30811997; PMCID: PMC6391775
2. Ding S, Song Y, Brulois KF, Pan J, Co JY, Ren L, Feng N, Yasukawa LL, Sanchez-Tacuba L, Wosen JE, Mellins ED, **Monack DM**, Amieva MR, Kuo CJ, Butcher EC, Greenberg HB. Retinoic Acid and Lymphotoxin Signaling Promote Differentiation of Human Intestinal M Cells. Gastroenterology. 2020. Epub 2020/04/05. doi: 10.1053/j.gastro.2020.03.053. PubMed PMID: 32247021.

3. Jacobson, A., L. Lam, M. Rajendram, F. Tambuini, J. Honeycutt, T. Pham, W. Van Treuren, K. Pruss, S. Stabler, K. Lugo, D. Bouley, J. Vilches-Moure, M. Smith, J. Sonnenburg, A. Bhatt, K. Huang, **D.M. Monack**. 2018 A gut commensal-produced metabolite mediates colonization resitance to Salmonella infection. Cell Host and Microbe. Aug 8;24(2):296-307
4. Kortmann J., Brubaker, S.W. and **Monack, D.M.** 2015. Cutting Edge: Inflammasome activation in primary human macrophages is dependent on flagellin. J. Immunol. Jun 24 PubMed PMID:26109648; PubMed Central PMCID: PMC4505955

B. Positions and Honors Positions and Employment

1980-84	Undergraduate research under Dr. Richard Criddle, University of California at Davis, CA
1983	Summer Intern, Fermentation Department, Genentech, Inc., South San Francisco, CA
1989	Part-time work at Affymax Research Institute, Palo Alto, CA
1984-87	Life Science Technician, Department of Microbiology and Immunology, Stanford University School of Medicine, Dr. Stanley Falkow's Lab
1987-98	Research Assistant, Department of Microbiology and Immunology, Stanford University School of Medicine, Dr. Stanley Falkow's Lab
1998-02	Graduate Student, Department of Microbiology and Immunology, Stanford University School of Medicine, Dr. Stanley Falkow's Lab
2002-07	Senior Research Scientist, Department of Microbiology and Immunology, Stanford University School of Medicine
2007-2012	Assistant Professor, Department of Microbiology and Immunology, Stanford University School of Medicine
2012-2016	Associate Professor, Department of Microbiology and Immunology, Stanford University School of Medicine
2012-2017	Director, Graduate Admissions Program, Department of Microbiology and Immunology, Stanford University School of Medicine
2016-	Professor, Department of Microbiology and Immunology, Stanford University School of Medicine
2019-	Associate Chair, Department of Microbiology and Immunology, Stanford University, School of Medicine

Other Experience and Professional Memberships

Member of American Society of Microbiology

Editorial Board

2007-present	*PLoS Pathogens Section Editor*
2010-present	*Infection and Immunity*
	Journal of Immunology
	Pathogens and Disease

Scientific Advisory Boards and Committees

2009-2013	NIH/NIAID Systems Biology Working Group for Systems Biology Program at the University of Washington.
2007-2018	Department of Microbiology and Immunology Seminar Speaker Selection Committee
2008-present	Department of Microbiology and Immunology Graduate Admissions Committee

Study Sections for Grant Reviews

2007	NIH/NIAID Study Section for Regional Centers of Excellence
2012-2017	NIH/NIAID Host Interactions with Bacterial Pathogens Study Section

Honors

2008	Baxter Faculty Scholar, Donald E. and Delia B. Baxter Foundation
2008	Terman Fellow, Stanford University School of Medicine
2009	The Burroughs Wellcome Fund Recipient
2010	Society of Leukocyte Biology G.J. Thorbecke Award
2012	Stanford University Postdoc Association Mentor Award
2015	Chair-elect for Division B, American Society of Microbiologists

2015 American Academy of Microbiology Fellow
2016 Chair for Division B, American Society of Microbiologists
2018 Max Planck Sabbatical Award

C. Contribution to Science

1. Identification of novel *Salmonella* virulence determinants that mediate persistent infection.

The lifestyle of *Salmonella enterica* serovar Typhimurium during acute infections in the gastrointestinal tract and within macrophages in systemic tissues has been intensely studied. However, the mechanisms that lead to bacterial survival, systemic dissemination, and transmission during persistent infections are less well understood. Through genetic screens, my lab has discovered genes required for long-term survival in a mouse model of *Salmonella* infection that I developed and characterized as a graduate student. We have shown during colonization of systemic sites that *Salmonella* injects effector proteins through the type 3-secretion system encoded on *Salmonella* Pathogenicity Island 2 that mediate inhibition of dendritic cell (DC) chemotaxis. We have also shown that this inhibition of DC chemotaxis contributes to *Salmonella* persistence by dampening adaptive immune responses. In addition, we have shown that there are nutritional and virulence mechanisms that mediate intraspecies competition in the distal gut that influence transmission to naïve hosts.

a. Lawley, T.D., K. Chan, L.J. Thompson, C.C. Kim, G.R. Govoni, and **D.M. Monack**. 2006. Genome-wide screen for *Salmonella* genes required for long-term systemic infection of the mouse. PLoS Pathog. Feb;2(2):e11. Epub Feb 24.
b. McLaughlin LM, Xu H, Carden SE, Fisher S, Reyes M, Heilshorn SC, **D.M. Monack**. A microfluidic-based genetic screen to identify microbial virulence factors that inhibit dendritic cell migration. Integrative Biology. 2014 Apr 1;**6**: 438-449. PMCID: PMC4114769
c. Lam L. and **Monack D.M.** Intraspecies competition for niches in the distal gut dictate transmission during persistent Salmonella infection. PLoS Pathog. 2014 10(2)e1004527. PMCID: PMC4256465
d. Pham THM, Brewer SM, Thurston T, Massis LM, Honeycutt J, Lugo K, Jacobson AR, Vilches-Moure JG, Hamblin M, Helaine S, **Monack DM**. Salmonella-Driven Polarization of Granuloma Macrophages Antagonizes TNF-Mediated Pathogen Restriction during Persistent Infection. Cell Host Microbe. 2020;27(1):54-67 e5. Epub 2019/12/31. doi: 10.1016/j.chom.2019.11.011. PubMed PMID: 31883922.

2. Characterization of immune states that mediate tolerance and influence disease transmission. We have shown that oral infection of 129SvJ mice with *Salmonella* results in 20-30% of the mice being supershedders (shed $>10_8$ CFU/g feces), which rapidly transmit infection. Although supershedder mice develop colitis, they remain asymptomatic. Importantly, both supershedder and non-supershedder hosts carry identical pathogen burdens across all tissues except the intestinal tract. Our results strongly suggest that tolerance mechanisms play a role in the maintenance of the asymptomatic supershedder state. What is tolerance in the context of our model? An infected host can fight pathogenic infection by two distinct processes, resistance and tolerance. Resistance encompasses a diverse set of mechanisms employed by the host to control pathogen invasion and replication. Tolerance, on the other hand, employs different mechanisms that help the host organism tolerate the damage caused by the pathogenic infection and the resulting immune response. My lab has been testing the hypothesis that tolerance mechanisms play a role in the maintenance of the asymptomatic supershedder state. Although very little is known about the full spectrum of tolerance mechanisms, the few studies in animals suggest that since pathogens and immunopathology can potentially affect almost any physiological process, tolerance is not restricted to a single protective pathway. Thus, we are taking broad unbiased approaches to map the crosstalk between the host immune state and pathogen during asymptomatic carriage. Our initial studies have shown that supershedder hosts have a unique dampened immune state that not only facilitates disease transmission but also confers tolerance to antibiotic-induced disturbances of the microbial communities in the gastrointestinal tract.

a. Lawley, T.D., D.M. Bouley, Y.E. Hoy, C. Gerke, D.A. Relman and **D.M. Monack**. 2008. Host transmission of *Salmonella* enterica serovar Typhimurium is controlled by virulence factors and the indigenous intestinal microbiota. 76(1):403-16. PMCID: PMC2223630

b. Gopinath, S, Lichtman, JS, Bouley, DM, Elias, JE, and **Monack, D.M.** The role of disease-associated tolerance in infectious superspreaders. Proc Nat Acad Sci USA. 2014 Nov 4: 111(44):15789-15785. PMCID: PMC4226084
c. Eisele NA, Ruby T, Jacobson A, Manzanillo PS, Cox JS, Lam L, Makundan L, Chawla A, **Monack D.M**. Persistent Salmonella infection is controlled by PPARdelta, a host regulator of fatty acid metabolism. Cell Host and Microbe. 2013. **14**(2): p. 171-82. PMCID: PMC3785333
d. Broz P, Ruby T, Belhocine K, Bouley DM, Kayagaki N, Dixit VM, **Monack D.M.** 2012. Caspase-11 increases susceptibility to *Salmonella* infection in the absence of caspase-1. Nature. Aug 15. doi: 10.1038. PMCID: PMC3470772

3. Molecular dissection of cytosolic innate immune activation during bacterial infection.

It was first recognized several decades ago by Janeway and Medzhitov that there are pattern recognition receptors on the surface of mammalian cells that recognize microbial-associated molecular patterns. More recently, it has been discovered that there are similar "receptors" that monitor the sanctity of the host cell cytosol and respond to "danger" signals by initiating innate immune responses. My lab has been studying the molecular mechanisms of intracellular recognition of bacterial pathogens by comparing and contrasting infections with intracellular *Salmonella* and *Francisella*. We have recently shown that *Francisella* generates type I IFNs, which are required for the up-regulation of many innate immune genes including AIM2, and that this pathway is required for inflammasome assembly and downstream caspase-1 activation. Active caspase-1 cleaves pro-inflammatory cytokines and mediates macrophage death. Intracellular *Salmonella* also stimulate caspase-1 activation by different pathways compared to *Francisella*. In addition, we have shown that intracellular *Salmonella* activate a caspase-11-dependent cell death, but *Francisella* does not. These studies are key to increasing our understanding of innate immune mechanisms that lead to protection against bacterial pathogens and will likely lead to the identification of molecular targets for the design of new therapeutics.

a. Henry, T., A. Brotcke, D.S. Weiss, L.J. Thompson and **D.M. Monack**. 2007. Type I interferon signaling is required for activation of the inflammasome during *Francisella* infection. J. Exp. Med. 204:987-94.
b. Broz, P., J. von Moltke, J.W. Jones, R.E. Vance, and **D.M. Monack**. 2010. Differential requirement for Caspase-1 autoproteolysis in pathogen-induced cell death and cytokine processing. Cell Host Microbe *8*:471-483. PMCID: PMC3016200
c. Storek K, Gersvolf, NA, Ohlson MB, and **Monack, D.M.** cGAS and Ifi204 cooperate to produce Type I IFNs in response to Francisella infection. J Immunol. 2015 194(7):3236-45. PMCID: PMC4367159
d. Broz P, Ruby T, Belhocine K, Bouley DM, Kayagaki N, Dixit VM, Monack DM. Caspase-11 increases susceptibility to Salmonella infection in the absence of caspase-1. Nature. 2012;490(7419):288-91. Epub 2012/08/17. doi: 10.1038/nature11419. PubMed PMID: 22895188; PMCID: 3470772

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1t53USkYcz1/bibliography/45632945/public/?sort=date&direction=ascending