



## **2018 Annual Report**

### ***Division of Infectious Diseases***

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#### **DIVISION DESCRIPTION**

The Division of Infectious Diseases cares for children with common, complex and potentially life-threatening infectious diseases and illnesses. The division also focuses on preventive health measures, and is active in overseeing infection control, antimicrobial stewardship and immunization programs.

Division research interests include international health, immunization efficacy, vaccine preventable disease epidemiology and policy, respiratory tract infections, urinary tract infections, congenital arbovirus infections, and fungal diseases, as well as education and training of future infectious disease experts.

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#### **2018 HIGHLIGHTS**

- **James Conway, MD**, was formally appointed as the University of Wisconsin School of Medicine and Public Health Director, Office of Global Health, responsible for overseeing international programs and student experiences, in collaboration with the other health professional schools. He will continue to serve as Associate Director for the UW-Madison Global Health Institute.

Medical student Samuel Starke (mentor: **James Conway, MD**) received a Shapiro Summer Research Award for the project, "Evaluation of School-Based LTBI Treatment Program for Tibetan Schoolchildren with Recent Exposure to Active TB."

- **J. Muse Davis, MD, PhD**, received a five-year, \$1,004,400 K08 career development award from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH/NIAID), for his project, "Fungal and Host Factors in Initiation of Cryptococcal Persistence." To improve understanding of disseminated fungal infections from both the host and pathogen perspectives, he will use a zebrafish larva model to directly monitor microbial pathogenesis *in vivo*, namely *Cryptococcus*. He will be supported by primary mentor **Anna Huttenlocher, MD**, and co-mentors **Bruce Klein, MD**, and Christina Hull, PhD (Biomolecular Chemistry).
- Infectious diseases fellow **Daniele Gusland, MD** (mentors: **James Conway, MD**, and Dawd Siraj, MD [Medicine]), received \$25,000 from the University of Wisconsin Global Health Institute for the project, "Etiology and Antimicrobial Resistance Patterns of Neonatal Sepsis in Jimma, Ethiopia (EARNEST)." The team will conduct a 12-month prospective study of 1,000 neonates and young infants admitted to Jimma University Hospital with possible serious bacterial infection, with the goals of identifying the most common organisms responsible for neonatal bacterial infection and estimating the likelihood of successful treatment based on resistance rates to first-line antibiotics.

- **Emma Mohr, MD, PhD**, was appointed to the UW Institute for Clinical and Translational Research's (ICTR) TL1 post-doctoral trainee program. The award provides funding support as she completes her research project, "Defining Maternal Antibody Responses in Congenital Zika Virus Infection." The project uses body fluid and tissue samples from a project studying pathogenesis of Zika virus during pregnancy to focus on the immune response to Zika virus infection.
- **Bruce Klein, MD**, received R01 research grant funding from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH/NIAID) for his four-year, \$1.85 million project, "Lung Epithelial Cell Regulation of Immunity to Inhaled Fungi." This project aims to increase knowledge about how the lung epithelial cells that line the respiratory mucosa sense and manage inhaled fungal spores, and identify new ways to therapeutically target early events that can optimize mucosal immunity to fungi and lung inflammation.

Dr. Klein also received a one-year, \$49,527 grant from the United States Geological Survey (USGS) National Wildlife Health Center for his project, "The Novel Method for Assessing Vaccines Against White Nose Syndrome Using a Mouse Model." The project aims to determine vaccine antigens that might be useful in protecting bats against white nose syndrome and to test those antigens in an alternative animal model.

- The State University of New York (SUNY) Downstate Medical Center Alumni Association presented Department of Pediatrics Chair **Ellen Wald, MD**, with an alumni achievement award in Pediatrics in recognition of her outstanding work as a leader.

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## RECENT PUBLICATIONS

Aliota MT, Dudley DM, Newman CM, Weger-Lucarelli J, Stewart LM, Koenig MR, Breitbart ME, Weiler AM, Semler MR, Barry GL, Zarbock KR, Haj AK, Moriarty RV, Mohns MS, **Mohr EL**, Venturi V, Schultz-Darken N, Peterson E, Newton W, Schotzko ML, Simmons HA, Mejia A, Hayes JM, Capuano S 3rd, Davenport MP, Friedrich TC, Ebel GD, O'Connor SL, O'Connor DH. Molecularly barcoded Zika virus libraries to probe in vivo evolutionary dynamics. *PLoS Pathog*. 2018 Mar 28;14(3):e1006964. doi: .1371/journal.ppat.1006964. eCollection 2018 Mar. PMID: 29590202; PMCID: PMC5891079.

**Brandhorst T, Klein B**. Uncertainty surrounding the mechanism and safety of the post-harvest fungicide Fludioxonil. *Food Chem Toxicol*. 2018 Nov 17. pii: S0278-6915(18)30839-1.

Carberry AR, Hanson K, Flannery A, Fischer M, Gehlbach J, Diamond C, **Wald ER**. Diagnostic error in pediatric cancer. *Clin Pediatr (Phila)*. 2018 Jan;57(1):11-18. doi: 10.1177/0009922816687325. Epub 2017 May 8. PubMed PMID: 28478722. \*\*

**Conway JH**. Strengthening immunization programs: Lessons learned on engaging stakeholders. In: DiPrete Brown L, ed. *Foundations of Global Health Practice*. Hoboken, NJ: Jossey-Bass, A Wiley Imprint. 2018; 405-411.

**DeMuri GP**, Gern JE, Eickhoff JC, Lynch SV, **Wald ER**. Dynamics of bacterial colonization with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* during symptomatic and asymptomatic viral upper respiratory tract infection. *Clin Infect Dis*. 2018 Mar 19;66(7):1045-1053. doi: 10.1093/cid/cix941. PubMed PMID: 29121208; PubMed Central PMCID: PMC6019034.

Dudley DM, Van Rompay KK, Coffey LL, Ardeshir A, Keesler RI, Bliss-Moreau E, Grigsby PL, Steinbach RJ, Hirsch AJ, MacAllister RP, Pecoraro HL, Colgin LM, Hodge T, Streblow DN, Tardif S, Patterson JL, Tamhankar M, Seferovic M, Aagaard KM, Martín CS, Chiu CY, Panganiban AT, Veazey RS, Wang X, Maness NJ, Gilbert MH, Bohm RP, Adams Waldorf KM, Gale M Jr, Rajagopal L, Hotchkiss CE, **Mohr EL**, Capuano SV 3rd, Simmons HA, Mejia A, Friedrich TC, Golos TG, O'Connor DH. Miscarriage and stillbirth following maternal Zika virus infection in nonhuman primates. *Nat Med*. 2018 Aug;24(8):1104-1107. doi: 10.1038/s41591-018-0088-5. Epub 2018 Jul 2. PMID: 29967348; PMCID: PMC6082723.

Fites JS, Gui M, Kernien JF, Negoro P, Dagher Z, Sykes DB, Nett JE, Mansour MK, **Klein BS**. An unappreciated role for neutrophil-DC hybrids in immunity to invasive fungal infections. *PLoS Pathog*. 2018 May 21;14(5):e1007073. doi: 10.1371/journal.ppat.1007073. eCollection 2018 May. PubMed PMID: 29782541; PubMed Central PMCID: PMC5983859.

Garfoot AL, Goughenour KD, **Wüthrich M**, Rajaram MVS, Schlesinger LS, **Klein BS**, Rappleye CA. O-mannosylation of proteins enables histoplasma yeast survival at mammalian body temperatures. *MBio*. 2018 Jan 2;9(1). pii: e02121-17. doi: 10.1128/mBio.02121-17. PubMed PMID: 29295913; PubMed Central PMCID: PMC5750402.

Heffron AS, **Mohr EL**, Baker D, Haj AK, Buechler CR, Bailey A, Dudley DM, Newman CM, Mohns MS, Koenig M, Breitbart ME, Rasheed M, Stewart LM, Eickhoff J, Pinapati RS, Beckman E, Li H, Patel J, Tan JC, O'Connor DH. Antibody responses to Zika virus proteins in pregnant and non-pregnant macaques. *PLoS Negl Trop Dis*. 2018 Nov 27;12(11):e0006903. doi: 10.1371/journal.pntd.0006903. eCollection 2018 Nov. PMID: 30481182; PMCID: PMC6286021.

Hernández-Santos N, Wiesner DL, Fites JS, McDermott AJ, Warner T, **Wüthrich M**, **Klein BS**. Lung epithelial cells coordinate innate lymphocytes and immunity against pulmonary fungal infection. *Cell Host Microbe*. 2018 Apr 11;23(4):511-522.e5. doi: 10.1016/j.chom.2018.02.011. Epub 2018 Mar 22. PubMed PMID: 29576482; PubMed Central PMCID: PMC5951304.

Johnson CJ, **Davis JM**, Huttenlocher A, Kernien JF, Nett JE. Emerging fungal pathogen *Candida auris* evades neutrophil attack. *MBio*. 2018 Aug 21;9(4). pii: e01403-18. doi: 10.1128/mBio.01403-18. PubMed PMID: 30131360; PubMed Central PMCID: PMC6106086.

Kalantari P, Morales Y, Miller EA, Jaramillo LD, Ponichtera HE, **Wuethrich MA**, Cheong C, Seminario MC, Russo JM, Bunnell SC, Stadecker MJ. CD209a synergizes with Dectin-2 and Mincle to drive severe Th17 cell-mediated schistosome egg-induced immunopathology. *Cell Rep*. 2018 Jan 30;22(5):1288-1300. doi:10.1016/j.celrep.2018.01.001. PubMed PMID: 29386115; PubMed Central PMCID: PMC5815841.

Kottom TJ, Hebrink DM, Jenson PE, Marsolek PL, **Wüthrich M**, Wang H, **Klein B**, Yamasaki S, Limper AH. Dectin-2 is a C-type lectin receptor that recognizes pneumocystis and participates in innate immune responses. *Am J Respir Cell Mol Biol*. 2018 Feb;58(2):232-240. doi: 10.1165/rcmb.2016-0335OC. PubMed PMID: 28886250; PubMed Central PMCID: PMC5805995.

Kujoth GC, **Sullivan TD**, Merkhofer R, Lee TJ, Wang H, **Brandhorst T**, **Wüthrich M**, **Klein BS**. CRISPR/Cas9-mediated gene disruption reveals the importance of zinc metabolism for fitness of the dimorphic fungal pathogen *Blastomyces dermatitidis*. *MBio*. 2018 Apr 3;9(2). pii: e00412-18. doi: 10.1128/mBio.00412-18. PubMed PMID: 29615501; PubMed Central PMCID: PMC5885028.

**McBride JA**, Gauthier GM, **Klein BS**. Turning on virulence: Mechanisms that underpin the morphologic transition and pathogenicity of *Blastomyces*. *Virulence*. 2018 Aug 1:1-9. doi: 10.1080/21505594.2018.1449506. [Epub ahead of print] PubMed PMID: 29532714. \*

**McBride JA**, Lepak AJ, Dhaliwal G, Saint S, Safdar N. The wrong frame of mind. *N Engl J Med*. 2018 May 3, 378:1716-21. Doi: 10.1056/NEJMcp1710814. PMID:29719187.

McDermott AJ, **Klein BS**. Helper T-cell responses and pulmonary fungal infections. *Immunology*. 2018 Oct;155(2):155-163. doi: 10.1111/imm.12953. Epub 2018 Jun 14. Review. PubMed PMID: 29781185; PubMed Central PMCID: PMC6142286.

McDermott AJ, Tumeay TA, Huang M, Hull CM, **Klein BS**. Inhaled *Cryptococcus neoformans* elicits allergic airway inflammation independent of Nuclear Factor Kappa B signalling in lung epithelial cells. *Immunology*. 2018 Apr;153(4):513-522. doi: 10.1111/imm.12853. Epub 2017 Nov 16. PubMed PMID: 29055116; PubMed Central PMCID: PMC5838417. \*\*

Misch EA, Saddler C, **Davis JM**. Skin and soft tissue infections due to nontuberculous mycobacteria. *Curr Infect Dis Rep*. 2018 Mar 19;20(4):6. doi: 10.1007/s11908-018-0611-3. Review. PubMed PMID: 29556857.

**Mohr EL**. Modeling Zika virus-associated birth defects in nonhuman primates. *J Pediatric Infect Dis Soc*. 2018 Dec 26;7(suppl\_2):S60-S66. doi: 10.1093/jpids/piy120; PubMed PMID: 30590626.

**Mohr EL**, Block LN, Newman CM, Stewart LM, Koenig M, Semler M, Breitbach ME, Teixeira LBC, Zeng X, Weiler AM, Barry GL, Thoong TH, Wiepz GJ, Dudley DM, Simmons HA, Mejia A, Morgan TK, Salamat MS, Kohn S, Antony KM, Aliota MT, Mohns MS, Hayes JM, Schultz-Darken N, Schotzko ML, Peterson E, Capuano S 3rd, Osorio JE, O'Connor SL, Friedrich TC, O'Connor DH, Golos TG. Ocular and uteroplacental pathology in a macaque pregnancy with congenital Zika virus infection. *PLoS One*. 2018 Jan 30;13(1):e0190617. doi: 10.1371/journal.pone.0190617. eCollection 2018. PMID: 29381706; PMCID: PMC5790226.

**Nanjappa SG**, Mudalagiriappa S, Fites JS, Suresh M, **Klein BS**. CBLB constrains inactivated vaccine-induced CD8(+) T cell responses and immunity against lethal fungal pneumonia. *J Immunol*. 2018 Sep 15;201(6):1717-1726. doi: 10.4049/jimmunol.1701241. Epub 2018 Jul 27. PubMed PMID: 30054317; PubMed Central PMCID: PMC6125178.

Nguyen JC, Rebsamen SL, Tuite MJ, **Davis JM**, Rosas HG. Imaging of *Kingella kingae* musculoskeletal infections in children: a series of 5 cases. *Emerg Radiol*. 2018 Jun 16. doi: 10.1007/s10140-018-1617-8. [Epub ahead of print] PubMed PMID: 29909593. \*

Roberts KB, **Wald ER**. The diagnosis of UTI: colony count criteria revisited. *Pediatrics*. 2018 Feb;141(2). pii: e20173239. doi: 10.1542/peds.2017-3239. Epub 2018 Jan 16. PubMed PMID: 29339563.

Rosowski EE, Knox BP, Archambault LS, Huttenlocher A, Keller NP, Wheeler RT, **Davis JM**. The zebrafish as a model host for invasive fungal infections. *J Fungi (Basel)*. 2018 Dec 13;4(4). pii: E136. doi: 10.3390/jof4040136. Review. PubMed PMID: 30551557.

Shaikh N, **Wald ER**, Jeong JH, Kurs-Lasky M, Nash D, Pichichero ME, Kearney DH, Haralam MA, Bowen A, Flom LL, Hoberman A. Development and modification of an outcome measure to follow symptoms of children with sinusitis. *J Pediatr*. 2018 Dec 10. pii: S0022-3476(18)31604-4. doi: 10.1016/j.jpeds.2018.11.016. [Epub ahead of print] PubMed PMID: 30545562. \*

Sharma A, Lawry SM, **Klein BS**, Wang X, Sherer NM, Zumwalde NA, Gumperz JE. LFA-1 Ligation by high-density ICAM-1 is sufficient to activate IFN- $\gamma$  release by innate T lymphocytes. *J Immunol*. 2018 Oct 15;201(8):2452-2461. doi: 10.4049/jimmunol.1800537. Epub 2018 Aug 31. PubMed PMID: 30171164; PubMed Central PMCID: PMC6179935.

Sui P, Wiesner DL, Xu J, Zhang Y, Lee J, Van Dyken S, Lashua A, Yu C, **Klein BS**, Locksley RM, Deutsch G, Sun X. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science*. 2018 Jun 8;360(6393). pii: eaan8546. doi: 10.1126/science.aan8546. Epub 2018 Mar 29. PubMed PMID: 29599193.

Thompson KM, Sterkel A, **[McBride JA]**, Corliss RF. The shock of strep: Rapid deaths due to group A *Streptococcus*. *Acad Forensic Pathol*. 2018 8(1): 136-149.

**Wald ER, DeMuri GP**. Antibiotic recommendations for acute otitis media and acute bacterial sinusitis: conundrum no more. *Pediatr Infect Dis J*. 2018 Dec;37(12):1255-1257. doi: 10.1097/INF.0000000000002009. PubMed PMID: 29570583; PubMed Central PMCID: PMC6151174.

**Wald ER, DeMuri GP**. Complications of acute bacterial sinusitis in children. In: Durand ML, Deschler DG, eds. *Infections of the Ears, Nose, Throat, and Sinuses*, 1<sup>st</sup> edition. North America: Springer International Publishing; 2018; 145-154.

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#### GRANT SUPPORT

Principal Investigator	Sponsor	Title	Co-Investigators
Conway, James H	Sanofi Pasteur	Surveillance for rates of pertussis disease among persons birth through 59 months of age receiving pentacel or other pertussis vaccines	
Conway, James H	Pediatric Infectious Diseases Society	Travel grant	
Temte, Jonathan L (UW Department of Family Medicine and Community Health)	Centers for Disease Control & Prevention (CDC)	Oregon child absenteeism due to respiratory disease study (ORCHARDS)	Infectious Diseases: James Conway
Davis, James M	National Institutes of Health (NIH)	Fungal and host factors in initiation of cryptococcal persistence	Infectious Diseases: Bruce Klein (Co-Mentor) AIR: Anna Huttenlocher (Primary Mentor)
Sosman, James M (UW Department of Medicine)	Health Resources & Services Administration (HRSA)	Ryan White HIV/AIDS program part C HIV early intervention services program: Existing geographic service areas	Infectious Diseases: Sheryl Henderson
Klein, Bruce S	National Institutes of Health (NIH)	Microbes in health and disease	

Klein, Bruce S	National Institutes of Health (NIH)	Molecular pathogenesis of blastomycosis	
Klein, Bruce S	The Hartwell Foundation	Elucidating the induction of allergic asthma by the pulmonary epithelium	
Klein, Bruce S	Burroughs Wellcome Fund	Role of airway epithelial cells in host defense against pulmonary fungal pathogens	
Klein, Bruce S	National Institutes of Health (NIH)	Hybrid histidine kinase: a drug target and path to anti-fungal drug development	
Klein, Bruce S	American Heart Association	Harnessing a long-lived neutrophil to fight systemic fungal infections	
Klein, Bruce S	National Institutes of Health (NIH)	Pathogenesis of fungal infectious disease in the Hmong population	
Klein, Bruce S	National Institutes of Health (NIH)	Lung epithelial cell regulation of immunity to inhaled fungi	
Klein, Bruce S	Interior, US Geological Society	A novel method for assessing vaccines against White Nose Syndrome using a mouse model	
Klein, Bruce S	The Hartwell Foundation	Harnessing a long-lived neutrophil to fight systemic fungal infections	
Klein, Bruce S	Wisconsin Partnership Program	Genetic susceptibility to infections in Wisconsin Hmong	
Mohr, Emma	Pediatric Infectious Diseases Society	Development of a macaque congenital Zika syndrome model: fetal Zika virus tissue distribution and pathology	
Mohr, Emma	National Institutes of Health (NIH) & Institute for Clinical & Translational Research (UW-ICTR)	Defining maternal antibody responses in congenital Zika virus infection	

Golos, Thaddeus (UW School of Veterinary Medicine)	National Institutes of Health (NH)	Pathways of vertical Zika virus transmission in nonhuman primate pregnancy	Infectious Diseases: Emma Mohr
O'Connor, David H (UW School of Veterinary Medicine)	National Institutes of Health (NH)	Zika virus pathophysiology during pregnancy	Infectious Diseases: Emma Mohr
Wald, Ellen R	Regeneron Pharmaceuticals, Inc.	A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of a human monoclonal antibody, REGN2222, for the prevention of medically attended RSV infection in preterm infants	
Wald, Ellen R	National Institutes of Health (NIH) & University of Pittsburgh	Efficacy of antibiotics in children with acute sinusitis: which subgroups benefit	Infectious Diseases: Gregory DeMuri
Wald, Ellen R	Medlummune, Inc.	A phase 2b randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of MEDI8897, a monoclonal antibody with an extended half-life against respiratory syncytial virus, in healthy preterm infant	
Wald, Ellen R	Janssen Research & Development	A phase 2, randomized double-blind placebo-controlled study to evaluate antiviral activity, clinical outcomes, safety, tolerability, & pharmacokinetics of orally administered Lumicitabine regimens in hospitalized infants & children with RSV	

Wald, Ellen R	Janssen Research & Development	A long-term follow-up of study 64041575RSV2004 to evaluate the impact of Lumicitabine on the incidence of asthma and/or wheezing in infants and children with a history of respiratory syncytial virus infection	
Wald, Ellen R	Roche	Comparison of sensitivity and specificity of detection of Group A streptococcus from pharyngeal and lolly pop specimens	
Wald, Ellen R	Merck Sharp & Dohme Corporation	Double-blind, randomized, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of MK-1654 in pre-term and full-term infants	
Wald, Ellen R	Merck Sharp & Dohme Corporation	A phase 3, multicenter, randomized, double-blind, active comparator controlled study to evaluate the safety and tolerability of V114 in healthy infants (PNEU-LINK)	



Allen, David B	National Institutes of Health (NIH)	Childhood diabetes clinical & molecular research training program	Endocrinology: Aaron Carrel (Associate Director)  Infectious Diseases: Ellen Wald (Associate Director)
Wuethrich, Marcel	National Institutes of Health (NIH)	Regulation of vaccine-induced anti-fungal Th17 cells	Infectious Diseases: Bruce Klein