

Pediatrics 2017 Annual Report – Division Highlights

Infectious Disease

DIVISION DESCRIPTION

The Division of Infectious Diseases cares for children with common, complex or potentially life-threatening infectious diseases and illnesses.

Research interests include international health, immunization efficacy, vaccine preventable disease epidemiology and policy, respiratory tract infections, urinary tract infections, arbovirus infections and fungal infections.

2017 HIGHLIGHTS

- **James Conway, MD, FAAP**, received a Citation of Commendation from the State of Wisconsin, with bipartisan support, co-sponsored by Senators Stephen Nass and Fred Risser and Representatives Melissa Sargent and Terese Berceau, in recognition of being named Delta Chi Fraternity 2017 Man of the Year, and for his “inspiring work in the medical field.” He was honored with a ceremony at the Wisconsin State Legislature in October 2017.
- **Bruce Klein, MD**, received a 2-year, \$408,030 R21 grant from the National Institutes of Health/ National Institute of Allergy and Infectious Diseases (NIH/NIAID) for his project, “Hybrid Histidine Kinase: A Drug Target and Path to Anti-Fungal Drug Development,” which aims to discover the mode of action of anti-fungal drugs that require group III hybrid histidine kinases (HHKs).

In addition, James Gern, MD, and **Bruce Klein, MD**, are part of a team of investigators led by PI Cameron Currie, PhD, on a new, two-year UW2020 grant, “[The Human Microbiome in Health and Disease](https://research.wisc.edu/funding/uw2020/round-3-projects/the-human-microbiome-in-health-and-disease/)” (<https://research.wisc.edu/funding/uw2020/round-3-projects/the-human-microbiome-in-health-and-disease/>). The award leverages the Children’s Respiratory Research and Environment Workgroup (CREW), led by Dr. Gern, and the Wisconsin Longitudinal Study (WLS), one of the longest-running investigations of human health.

Finally, two learners in **Dr. Klein’s** laboratory received research fellowships. Postdoctoral fellow J. Scott Fites, PhD, received a two-year, \$102,550 Midwest Affiliate Postdoctoral Fellowship from the American Heart Association for his project, “Harnessing a Long-Lived Neutrophil to Fight Systemic Fungal Infections,” Graduate student Richard Merkhofer, received a four-year, \$161,276 Ruth L. Kirschstein National Research Service Award Individual Predoctoral Fellowship for MD/PhD and Other Dual Degrees from the National Institutes of Health, National Institute on Minority Health and Health Disparities for his project, “Pathogenesis of Fungal Infectious Disease in the Hmong Population.”

- Fellow **Emma Mohr, MD, PhD**, received the 2017-2019 Pediatric Infectious Diseases Society’s Stanley and Susan Plotkin and Sanofi Pasteur Fellowship Award for her project, “Development of a Macaque Congenital Zika Syndrome Model: Fetal Zika Virus Tissue Distribution and Pathology.” Dr. Mohr was also a co-author on *PLoS Pathogens* articles on [maternal-fetal Zika virus transmission in pregnant rhesus macaques](https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5444831) (<https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5444831>) and the mechanisms of [Pegivirus in a macaque model of HIV infection](https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5675458) (<https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5675458>).

Fellow **Joseph McBride, MD**, was a co-author with Dr. Klein on a *Clinical Chest Medicine* article [reviewing the clinical manifestations and treatment of blastomycosis](https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5657236) (<https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC5657236>).

- **Marcel Wüethrich, PhD**, together with **Dr. Klein** as co-investigator, received a four-year, \$2.2 million grant renewal from the National Institutes of Health–National Institute of Allergy and Infectious Diseases for their project, "Regulation of Vaccine-Induced Anti-Fungal Th17 Cells." The renewal supports years 6-9 of this project, which will investigate a novel adjuvant that elicits cellular immune responses needed for better vaccines.

Dr. Wüethrich also received a one-year \$50,000 UW-Madison Technology Innovation Fund grant for his project, "BI-Eng3—An Adjuvant for Vaccine Prevention of Global Pathogens."

RECENT PUBLICATIONS

Carberry AR, Hanson K, Flannery A, Fischer M, Gehlbach J, Diamond C, **Wald ER**. Diagnostic error in pediatric cancer. *Clin Pediatr (Phila)*. 2017 May 1;9922816687325. doi: 10.1177/0009922816687325. [Epub ahead of print] PubMed PMID: 28478722. *

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 infection. *Clin Infect Dis*. 2017 Nov 7. doi: 10.1093/cid/cix941. [Epub ahead of print] PubMed PMID: 2912120. *

DeMuri GP, Sterkel AK, Kubica PA, Duster MN, Reed KD, **Wald ER**. Macrolide and clindamycin resistance in Group A streptococci isolated from children with pharyngitis. *Pediatr Infect Dis J*. 2017 Mar;36(3):342-344. doi: 10.1097/INF.0000000000001442. PubMed PMID: 27902646.

Hernández-Santos N, **Klein BS**. Through the scope darkly: The gut mycobiome comes into focus. *Cell Host Microbe*. 2017 Dec 13;22(6):728-729. doi: 10.1016/j.chom.2017.11.013. PubMed PMID: 29241038.

Kottom TJ, Hebrink DM, Jenson PE, Nandakumar V, **Wüthrich M**, Wang H, **Klein B**, Yamasaki S, Lepenies B, Limper AH. The interaction of pneumocystis with the C-type lectin receptor mincle exerts a significant role in host defense against infection. *J Immunol*. 2017 May 1;198(9):3515-3525. doi: 10.4049/jimmunol.1600744. Epub 2017 Mar 15. PubMed PMID: 28298521; PubMed Central PMCID: PMC5423441.

Lawry SM, Tebbets B, Kean I, Stewart D, Hetelle J, **Klein BS**. Fludioxonil induces Drk1, a fungal Group III hybrid histidine kinase, to dephosphorylate its downstream target, Ypd1. *Antimicrob Agents Chemother*. 2017 Jan 24;61(2). pii: e01414-16. doi: 10.1128/AAC.01414-16. Print 2017 Feb. PubMed PMID: 27872062; PubMed Central PMCID: PMC5278731.

Lorenzini J, Scott Fites J, Nett J, **Klein BS**. *Blastomyces dermatitidis* serine protease dipeptidyl peptidase IVA (DppIVA) cleaves ELR(+) CXC chemokines altering their effects on neutrophils. *Cell Microbiol*. 2017 Sep;19(9). doi: 10.1111/cmi.12741. Epub 2017 May 30. PubMed PMID: 28346820; PubMed Central PMCID: PMC5544578.

McBride JA, Gauthier GM, **Klein BS**. Clinical manifestations and treatment of blastomycosis. *Clin Chest Med*. 2017 Sep;38(3):435-449. doi: 10.1016/j.ccm.2017.04.006. Epub 2017 Jun 12. Review. PubMed PMID: 28797487; PubMed Central PMCID: PMC5657236.

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*. 2017 Oct 20. doi: 10.1111/imm.12853. [Epub ahead of print] PubMed PMID: 29055116. *

Nanjappa SG, McDermott AJ, Fites JS, Galles K, **Wüthrich M**, Deepe GS Jr, **Klein BS**. Antifungal Tc17 cells are durable and stable, persisting as long-lasting vaccine memory without plasticity towards IFN γ cells. *PLoS Pathog*. 2017 May 22;13(5):e1006356. doi: 10.1371/journal.ppat.1006356. eCollection 2017 May. PubMed PMID: 28542595; PubMed Central PMCID: PMC5456400.

Schulz LT, McCreary EK, Vanderloo JP, **Conway JH**. ID corner: It's the most wonderful time of the year. Influenza season! *J Pharm Soc Wis*. 2017 Sept/Oct:16-19.

Wald ER, Conway JH. Mastoiditis. In: Long SS, Prober CG. Principles and Practice of Pediatric Infectious Disease, 5th ed. Philadelphia: Elsevier; 2017: 225-229.

Wald ER, DeMuri GP. Sinusitis. In: Long SS, Prober CG. Principles and Practice of Pediatric Infectious Disease, 5th ed. Philadelphia: Elsevier; 2017: 230-233.

Wald ER, Ewing LJ, Moyer SCL, Eickhoff JC. An interactive web-based intervention to achieve healthy weight in young children. *Clin Pediatr (Phila)*. 2017 Oct 1:9922817733703. doi: 10.1177/0009922817733703. [Epub ahead of print] PubMed PMID: 29067819. *

Wald ER. Preseptal and orbital infections. In: Long SS, Prober CG. Principles and Practice of Pediatric Infectious Disease, 5th ed. Philadelphia: Elsevier; 2017: 517-521.

Walker JL, **Conway JH**, Svenson JE. Zika: information in the nick of time. *J Glob Health*. 2017 Jun;7(1):010305. doi: 10.7189/jogh.07.010305. Review. PubMed PMID: 28400948; PubMed Central PMCID: PMC5370213.

Wang H, Lee TJ, Fites SJ, Merkhofer R, Zarnowski R, **Brandhorst T**, Galles K, **Klein B, Wüthrich M**. Ligation of Dectin-2 with a novel microbial ligand promotes adjuvant activity for vaccination. *PLoS Pathog*. 2017 Aug 9;13(8):e1006568. doi: 10.1371/journal.ppat.1006568. eCollection 2017 Aug. PubMed PMID: 28793349; PubMed Central PMCID: PMC5565193.

Wiesner DL, **Klein BS**. Lung epithelium: barrier immunity to inhaled fungi and driver of fungal-associated allergic asthma. *Curr Opin Microbiol*. 2017 Dec;40:8-13. doi: 10.1016/j.mib.2017.10.007. Epub 2017 Oct 27. Review. PubMed PMID: 29096195; PubMed Central PMCID: PMC5733720.

Wiesner DL, **Klein BS**. The balance between immunity and inflammation. *Science*. 2017 Sep 8;357(6355):973-974. doi: 10.1126/science.aao3086. PubMed PMID: 28883060; PubMed Central PMCID: PMC5735847.

Williams K, Wargowski D, Eickhoff J, **Wald E**. Disparities in health supervision for children with Down syndrome. *Clin Pediatr (Phila)*. 2017 Dec;56(14):1319-1327. doi: 10.1177/0009922816685817. Epub 2017 Jan 30. PubMed PMID: 28135877.

**ePub only; no print citation available when report was compiled*

GRANT SUPPORT

| Faculty/Role | Funding Agency | Title |
|------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Conway, James H (PI) | Infectious Diseases Society of America | J McBride IDWeek 2017 travel grant |
| Conway, James H (PI) | 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 (co-I) with Temte, Jon (PI) | DHHS, PHS, Centers for Disease Control | Oregon Child Absenteeism due to Respiratory Disease Study (ORCHARDS) |
| Henderson, Sheryl (PI) with Sosman, James (co-I) | HRSA | Ryan White Part C Early Intervention Services Program 2015-2017 |
| Klein, Bruce S (PI) | American Heart Association Greater Midwest | Harnessing a long-lived neurophil to fight systemic fungal infections |
| Klein, Bruce S (PI) | Burroughs Wellcome Fund | Role of airway epithelial cells in host defense against pulmonary fungal pathogens |
| Klein, Bruce S (PI) | DHHS, PHS, National Institutes of Health | Hybrid histidine kinase: a drug target and path to anti-fungal drug development |
| Klein, Bruce S (PI) with Wuethrich, Marcel (co-I) | DHHS, PHS, National Institutes of Health | Mechanisms of anti-fungal vaccine immunity |
| Klein, Bruce S (PI) | DHHS, PHS, National Institutes of Health | Microbes in health and disease |
| Klein, Bruce S (PI) | DHHS, PHS, National Institutes of Health | Molecular pathogenesis of blastomycosis |
| Klein, Bruce S (PI) | DHHS, PHS, National Institutes of Health | Pathogenesis of fungal infectious disease in the Hmong population |
| Klein, Bruce S (PI) | Interior, US Geological Society | Oral vaccines and delivery methods for controlling diseases in bats |
| Klein, Bruce S (PI) | Pediatric Infectious Diseases Society | Understanding fungal morphogenesis and dissemination using in vivo imaging of a larval zebrafish model |
| Klein, Bruce S (PI) | The Hartwell Foundation | Elucidating the induction of allergic asthma by the pulmonary epithelium |
| Klein, Bruce S (PI) | UWF - Wisconsin Partnership - MERC | Genetic susceptibility to infections in Wisconsin Hmong |
| Klein, Bruce S (Core D Co-PI) with Andes, David (PI) | DHHS, PHS, National Institutes of Health | Antimicrobial drug discovery from coevolved symbiotic communities. Core 3: Mode of Action Core |
| Nanjappa, Somashekarappa G (PI) | DHHS, PHS, National Institutes of Health | Role of GM-CSF+IL-17+ CD8+ T cells in respiratory fungal immunity |
| Wald, Ellen R (PI) | Astrazeneca AB | A single blind randomized trial to evaluate safety tolerability pharmacokinetics & efficacy of ceftazidime & avibactam compared with cefepime in children 3 mos to < 18 yrs w/complicated urinary tract infections (cUTIs) |
| Wald, Ellen R (PI) | Cubist Pharmaceuticals | CUBEXA-01: a multi-center, |

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| | | randomized, double-blinded comparative study to evaluate the efficacy, safety, and pharmacokinetics of Ceftaroline or Daptomycin versus active comparator in pediatric subjects with acute hematogenous osteomyelitis due to gram-po |
| Wald, Ellen R (PI) with DeMuri, Gregory (co-I) | DHHS, PHS, National Institutes of Health | Sinusitis in children and the nasopharyngeal microbiome |
| Wald, Ellen R (PI) | Glaxosmithkline | A phase IIIA, blinded, randomized, controlled, multinational consistency study to evaluate the immunogenicity and safety of GSK Biologicals' MMR vaccine (209762) compared to Merck & Co., Inc.'s MMR vaccine as a first dose, both co-administered with Variv |
| Wald, Ellen R (PI) | Glaxosmithkline | Immunogenicity and safety study of GSK Biologicals "Infanrix hexa" at 2, 4 and 6 months of age in healthy infants |
| Wald, Ellen R (PI) | 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 (PI) | Medimmune, 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 infants |
| Wald, Ellen R (PI) | Regeneron Pharmaceuticals | 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 (PI) | University of Pittsburgh | Corticosteroids for children with febrile urinary tract infections |
| Wald, Ellen R (PI) with DeMuri, Gregory (co-I) | University of Pittsburgh | Efficacy of antibiotics in children with acute sinusitis: which subgroups benefit? |
| Wald, Ellen (co-I) with Seroogy, Christine A (PI) and Baker, Mei Wang; Laffin, Jennifer; Rice, Gregory; Scott Schwoerer, Jessica (collaborators) | UWF - Wisconsin Partnership - MERC | Improved Health Care Delivery to Wisconsin Amish Infants |
| Wuethrich, Marcel (PI) with Klein, Bruce (co-I) | DHHS, PHS, National Institutes of Health | Regulation of vaccine-induced anti-fungal Th17 cells |
| Wuethrich, Marcel (PI) | Wisconsin Alumni Research | Bl-Eng3 - an adjuvant for vaccine |

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| | Foundation | prevention of global pathogens |
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