Cincinnati Children's

2015 Research Annual Report

Infectious Diseases

RESEARCH AND TRAINING DETAILS

Click to view members

Faculty	19
Joint Appointment Faculty	6
Research Fellows	2
Research Students	4
Support Personnel	82
Direct Annual Grant Support	$8,950,114
Direct Annual Industry Support	$1,748,213
Peer Reviewed Publications	59

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	6
Clinical Fellows	4
Other Students	1
Inpatient Encounters	4,158
Outpatient Encounters	2,029

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Research Highlights

Robert W. Frenck, MD

Dr. Frenck, along with Dr. David Bernstein, successfully re-competed the Vaccine and Treatment Evaluations Unit (VTEU) contract which will continue through 2024 at an estimated value of $951 million. Dr. Frenck completed an National Institutes of Health (NIH) funded phase I study to evaluate a vaccine against Shigella sonnei. Immunogenicity testing is underway to determine the dose and vaccine to proceed into a challenge study.

Dr. Frenck has been awarded an NIH-funded contract to conduct a study to determine the dose response curve of infection with norovirus. The project will enroll the first cohort by the end of the calendar year.

Dr. Frenck has been awarded a DoD-sponsored grant to develop a challenge model of Shigella sonnei. The model is a first step in a program to test vaccines to prevent S. sonnei infections, a major cause of shigellosis in industrialized nations.

Dr. Frenck continues to maintain a research focus on clinical trials with special interest in enteric diseases.

David I. Bernstein, MD, MA

This year saw the conclusion of three important clinical trials led by Dr. Bernstein. Congenital cytomegalovirus (CMV) is the most common congenital virus infection around the world. A glycoprotein B subunit CMV vaccine with the adjuvant MF 59 was evaluated in healthy adolescent girls, a possible target for eventual immunization. Over 400 girls were enrolled, vaccinated and followed for 2 years at five sites across the USA. The vaccine was safe, highly immunogenic and showed a trend towards protection from CMV infection.

In another multicenter efficacy trial, healthy men and women were vaccinated with a bivalent norovirus vaccine composed of two virus like particles (VLP) and then challenged with our GII.4 strain of norovirus. Norovirus is the most common cause of gastroenteritis and the GII.4 genotype is the most common genotype. The vaccine was shown to be safe and immunogenic and decreased the severity of vomiting and diarrhea. Therefore the vaccine will progress to field efficacy studies. This is the first successful bivalent norovirus vaccine and the best evidence that a systemic vaccine can protect against norovirus

Lastly, because strategies for post exposure prophylaxis (PEP) in case of an anthrax bioterror event are needed, we evaluated four dosing schedules of an anthrax vaccine that could reduce antigen need. The schedules that included a dose at day 14 induced antibody earlier but the peak titers and duration were less than other schedules. Reducing the amount of antigen per dose of vaccine was less effective than full dose regimens.

Dr. Bernstein participated in a clinical trial of a herpes simplex type 2 (HSV-2) vaccine. This vaccine, originally shown by our group to reduce recurrences and recurrent virus shedding in animal models, was also able to reduce clinical recurrences and recurrent asymptomatic shedding in patients with recurrent genital herpes. This is the first time a vaccine was shown to reduce recurrent HSV-2 shedding, the most common source for the spread of this virus. Work also continued on our pre-clinical evaluation of other vaccines and therapeutics for both HSV-2 and CMV in animal models developed by us.

Rebecca C. Brady, MD

Dr. Brady was the Cincinnati Children's lead investigator for a National Institutes of Health (NIH), Division of Microbiology and Infectious Diseases (DMID) sponsored clinical trial that assessed the immunogenicity of the 13-valent pneumococcal vaccine in elderly adults that was completed in 2014. Dr. Brady also served as co-investigator for many clinical studies performed at the Gamble Program for Clinical Studies, Cincinnati Children's Division of Infectious Diseases. She continues as the medical director of the Ohio American Academy of Pediatrics' Maximizing Office Based Immunization Program. This

program has been expanded to include specialized modules and quality improvement activities. She continues as the contributing section editor for *Infectious Diseases*, an American Academy of Pediatrics Grand Rounds publication. She is leading the Division of Infectious Diseases in a quality improvement project to improve review of immunization records for all new patients seen in the infectious diseases clinics. This project will provide American Board of Pediatrics Maintenance of Certification Part IV credit. Together with Jennifer Huggins in the Division of Rheumatology, she received grant funding from Pfizer for the project *Connecting the Silos: A Partnership to Improve Immunization Rates among Adolescents with High-Risk Chronic and Immunocompromising Conditions*.

Rhonda D. Cardin, PhD

The Cardin Lab, led by Rhonda Cardin focuses on cytomegalovirus (CMV) latency and pathogenesis of CMV infection. The lab previously showed that the viral chemokine receptor M33 encoded by murine CMV (MCMV) is required for long term latent infection. With collaborators, Dr. Helen Farrell in Australia, and Dr. Marie-Dominique Filippi at Cincinnati Children's, the Cardin Lab recently identified several cell populations in the bone marrow and spleen of latently-infected mice which harbor latent virus. Current efforts are aimed at characterizing M33 mutant viruses in these cell types to determine the function of M33 during CMV latency. Research has also shown that the human CMV (HCMV) chemokine receptors, US28 and UL33, function similar to M33, which is very exciting since mechanisms important for HCMV latent infection in humans may be identified. In collaboration with Dr. David Bernstein, the division, and as part of the National Institutes of Health (NIH) antiviral program, is currently evaluating whether several novel vaccines protect against transmission of virus across the placenta during pregnancy in the GPCMV congenital model. If effective, a similar vaccine strategy in humans to protect the developing fetus and long term deleterious consequences of congenital HCMV infection such as mental deficits and hearing loss can be developed. Part of the antiviral program is characterizing several promising new anti-CMV drugs in the MCMV model since there is a continued need for less toxic anti-CMV drugs. Lastly, current evaluations of several promising vaccines against HSV-2 in the guinea pig model of genital herpes (both through NIH and industry contract studies). These studies provide preclinical evaluation that could lead to testing in human clinical trials.

Beverly L. Connelly, MD

The collaborative efforts of the infection control program, directed by Dr. Connelly, aligned with the institutional strategic goals to reduce healthcare associated infections (HAIs). Hand hygiene activities focused on family engagement and moved the program to very close to our institutional goal of 95% compliance. Changes to the 2015 CDC’s National Health Safety Network definitions for HAIs created challenges for staff. With these definition changes came increased reporting in central line associated bloodstream infections (CLABSIs). The program partnered with clinical care improvement groups to identify opportunities for simplification of protocols and standardization of care. The complexity of patient care, especially in oncology and bone marrow transplant patient populations, make these areas a focus for CLABSI prevention learning in FY2016. With successful implementation of the catheter associated urinary tract infection (CAUTI) prevention bundle, the HAI approached zero. Collaborative efforts to reduce surgical site infections (SSIs) gained traction in FY15 with standardization of processes in cardiothoracic surgery, orthopaedic spine surgery, and in neurosurgery and reduced numbers of deep infections in each. Spread of standard processes in FY16 across all surgical arenas is expected to have a favorable impact on SSIs. The infection control program was a partner in the development of Cincinnati Children's policies, practices and protocols to identify and safely manage a patient who might present with ebola virus disease. These activities capitalized on collaborative relationships already in existence and fostered new ones to enable the institution to meet previously unanticipated challenges. Because of staff experiences with fungal HAIs in the context of unprecedented construction and renovation activities in FY14, the infection control program developed enhanced surveillance activities in this area. Collaborative relationships with Plant Engineering and Construction services have resulted in state-of-the-art prevention programs with our construction contractors.

Lara Danziger-Isakov, MD, MPH

Dr. Lara Danziger-Isakov continues her role as protocol chair for two studies in the Clinical Trials in Organ Transplantation in Children (CTOT-C) funded by the National Institute of Allergy and Infectious Diseases (NIAID). One study evaluates the interaction between respiratory viral infections and the development of allo – and autoimmunity after pediatric lung transplantation. The second study assesses perceived barriers to adherence after pediatric solid organ transplantation. She was recently re-appointed to the Steering Committee to CTOTC and was named as co-chair of the Adherence, Growth & Development and QOL Subcommittee. Further, Dr. Danziger-Isakov will be the protocol chair for a new study under development to assess the impact of B-cell induction on the development of allo- and autoimmunity and early graft dysfunction that was recently funded.

Dr. Danziger-Isakov has expanded her work in solid organ transplantation (SOT) in collaboration with the Studies in Pediatric Liver Transplantation (SPLIT) to evaluate current practices for cytomegalovirus prevention. A focus on quality improvement has led to the development of evidence-based guidelines for the prevention of cytomegalovirus at Cincinnati Children's and to significant improvements in pre-transplant infectious disease risk assessment.

Michelle P. Dickey, MS, CRN

Ms. Dickey's interest is in the area of clinical vaccine trials in infants, children, adolescents, adults, elderly, pregnant and breast-feeding populations. Additional interests in clinical research include the areas of informed consent and quality management. With collaborators, Ms. Dickey has undertaken an innovative approach to simplified informed consent and assent.

David B. Haslam, MD

Dr. Haslam joined the Division of Infectious Diseases in the summer of 2013 as the medical director of the Antimicrobial Stewardship Program. Along with Josh Courter, PharmD, the stewardship program has implemented VigiLanz Clinical Decision Support software which performs real-time monitoring of antimicrobial use and resistance, facilitating audit and feedback of antimicrobial use at Cincinnati Children's Hospital Medical Center. Dr. Haslam's research laboratory is investigating the mechanisms of defense against Clostridium difficile infection. In particular, the laboratory is investigating how normal intestinal bacteria (the 'microbiome') prevent C. difficile disease. Additionally, the laboratory is performing whole genome sequencing to investigate relatedness and potential transmission of bacterial strains isolated from distinct patient populations.

Margaret K. Hostetter, MD

Research in the Hostetter Laboratory, led by Margaret Hostetter, has expanded into three main areas. 1) Heparin binding motifs in Candida albicans and their role in biofilm. After publishing a paper on the effects of an antibody against heparin binding motifs in inhibiting Candida albicans biofilm production (*Journal of Infectious Diseases,* 2013; 208:1695-1704), the laboratory is now testing the efficacy of the antibody to inhibit biofilms formed by other organisms. 2) Role of candidal vaginal colonization in preterm birth. The laboratory has shown that colonization with Candida albicans skews the cytokines response of vaginal epithelial cells by augmenting the release of pro-inflammatory cytokines that are damaging to pregnancy and by inhibiting the release of cytokines that preserve pregnancy. The in vitro data have sparked a clinical study of pregnant women in Bangladesh, also funded by the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS), an arm of the Bill & Melinda Gates Foundation. 3) Genetics of disseminated staphylococcal infection after osteomyelitis. Exome sequencing of parent/child trios identified de novo mutations implicating two novel pathways for susceptibility to disseminated staphylococcal disease. In vitro experiments to identify the functional correlates of these mutations are underway.

Nancy M. Hutchinson, RN, MSN, CIC

Ms. Hutchinson's interests are in the area of prevention of healthcare-acquired infections with an emphasis on device-

associated infections. Ms. Hutchinson is an active participant in a national collaborative on strategies for prevention of central line-associated bloodstream infections in pediatric hematology/oncology patients and bone marrow transplant recipients. In addition, she has presented regionally and nationally on infection prevention and control practices.

Jason Jiang, PhD

Dr. Jiang's laboratory continued working on norovirus (NV) and rotavirus (RV) research, mainly focusing on the virus-host interaction related to human histo-blood group antigen (HBGAs) as receptors. The lab found that, in addition to HBGAs, NVs may recognize another carbohydrate ligand, the sialic acid related glycans, as potential receptors or co-receptors. This finding pointed to a new research direction on NVs for a potential solution to develop a cell culture system for NVs. They propose to further validate this finding using the Tulane virus as a model and search for permissive cell lines with potential double positive phenotypes of HBGA and sialic acids in attempt to cultivate NVs *in vitro*. For rotavirus, they have expanded their understanding on the diversity of RVs recognizing different HBGAs by variable *in vitro* binding/blocking, hemagglutination and cell culture based assays. They also generated a large amount of information on potential host ligands for a number of animal RVs by collaboration with glycobiology experts in the US and the UK. Further study to elucidate the precise carbohydrate structures recognized by these animal RVs is planned which may lead to important understanding on the host range, evolution and zoonotic of RVs which will impact the understanding of the epidemiology and vaccine development against RVs. In addition, they are actively involved in development and evaluation of vaccines against NVs and RVs.

Monica M. McNeal, MS

Ms. McNeal is the associate director for the Laboratory for Specialized Clinical Studies (LSCS), in the Division of Infectious Diseases, which provides lab support for clinical studies involving vaccine trials and vaccine development and surveillance studies. The lab has been, and continues to be, the central lab supporting the development of all past and present live oral rotavirus vaccines. Rotavirus vaccines continue to be an important aspect in improving child health worldwide. Ms. McNeal has continued to support rotavirus vaccine trials conducted in numerous countries around the world in association with nonprofit organizations and industrial sponsors. Some of those studies involve determining how to improve efficacy of rotavirus vaccines in developing countries in Asia and Africa. One of the important outcomes from several of these studies it that breast feeding does not interfere with live oral rotavirus vaccines. This has important implications for countries that rely heavily on breast feeding. The lab continues to support the development of non-living rotavirus vaccines by developing and validating assays for clinical trials. The first ever human vaccine trial using a non-living rotavirus vaccine in children and infants is being conducted in Africa, and the LSCS is analyzing all samples from this trial. She is also directly involved in supporting and establishing clinical labs in India and China to support rotavirus vaccine trials in those countries.

The lab is also involved in supporting influenza vaccines, analyzing samples from clinical trials conducted in the US and Nepal in pregnant women. Additional projects include using animal models to investigate the effects of malnutrition on oral rotavirus vaccines, detecting the pathogens causing community acquired pneumonia presenting to the ED, rotavirus vaccine effectiveness in conjunction with the Centers for Disease Control (CDC) and establishing assays to quantitate norovirus shedding in immunocompromised patients. Ms. McNeal continues to support the clinical trials run by the Gamble Program by establishing new assays and providing laboratory support.

Grant C. Paulsen, MD

Dr. Paulsen joined the Division of Infectious Diseases in the summer of 2014 with a focus in transplant infectious diseases. Dr. Paulsen maintains a research focus on clinical research with special interest in prevention of post-transplant infections, vaccination following organ transplant and treatment and prevention of viral infections in immunocompromised patients. Research in pre-transplant methicillin-resistant Staphylococcus aureus (MRSA) screening is aimed at determining the effect of screening and use of targeted peri-operative prophylactic antibiotics on early post-transplant infections. He is also

investigating the safety and efficacy of live viral vaccines, such as varicella and MMR, following liver transplantation with a proposed collaboration with the Vaccine and Treatment Evaluation Units (VTEU). Dr. Paulsen also serves as sub-investigator for a number of ongoing clinical studies in immunocompromised patients.

Joseph E. Qualls, PhD

Research in the Qualls Laboratory, led by Joseph Qualls, has focused on the contribution of intracellular L-arginine synthesis on immune cell function. L-arginine is a semi-essential amino acid, meaning it cannot be synthesized to sufficient amounts in our bodies during “stressful” conditions – including infection and other disease states. In addition to serving as a building block for protein synthesis, this amino acid is required for microbicidal NO production by macrophages and for T lymphocyte proliferation. When L-arginine is limiting, these cells rely on L-arginine synthesis from L-citrulline, to sustain their respective functions. Mice that cannot convert L-citrulline to L-arginine in immune cells of hematopoietic lineage are impaired at clearing M. bovis BCG and M. tuberculosis infection in vivo. 1) One project funded by the American Heart Association aims to define the metabolic consequences of L-citrulline in mycobacteria-infected macrophages. Preliminary data suggest harnessing the L-arginine synthesis pathway, by supplementing L-citrulline *in vitro* and *in vivo*, is protective against mycobacterial infection, and experiments defining the mechanism of this protection are underway. 2) A doctoral candidate in the laboratory, Shannon Rapovy, is studying the necessity of L-citrulline metabolism during T cell function. Although previous studies have shown that L-citrulline can rescue T cell proliferation in L-arginine scarce environments *in vitro*, the contribution of L-citrulline on T cell function *in vivo* has not been addressed. Shannon has recently established a novel mouse model to probe the necessity and mechanism of L-citrulline metabolism in T cells, and experiments testing this during homeostasis and disease in vivo are underway. This project is partially funded by the American Association of Immunologists, which is supporting Ms. Rapovy’s stipend for 2015-2016.

Nancy M. Sawtell, PhD

Most of the human population world-wide has been infected by herpes simplex viruses (HSVs). Following the initial lytic infection, HSVs establish permanent latent infections within neurons in both the peripheral and central nervous systems. Reactivation of latent virus not only results in viral disease (new infections, blindness and encephalitis) but also contributes to HIV infection, diabetes, cardiovascular and neurodegenerative diseases.

No effective vaccine is available, and no therapy eliminates latency or prevents reactivation. The long-term goal of ongoing research in the Sawtell Lab is to find interventions for recurrent HSV episodes by defining mechanisms that control establishment and reactivation of HSV-1 latency. The gene expression cascade during HSV-1 lytic infection begins with activation of immediate-early (IE) gene transcription by the virion protein VP16 with host factors Oct-1 and HCF-1. In contrast, the initial events in the reactivation from latency are still poorly defined. Their central hypothesis is that a specialized region of the VP16 promoter regulates its de novo expression in neurons and thereby controls the establishment of, and reactivation from latency. A second layer of stress responsive regulation entails post translational structural modification of the VP16 proteins, which influences its interaction with its binding partners HCF-1 and Oct-1. Their studies will have a major impact on vaccine and gene transfer vector design, and may lead to a new class of therapeutics. Through the use of a mouse genetic reference population they have identified a locus on mouse chromosome 16 that regulates HSV neurovirulence as well as the severity of herpetic stromal keratitis. Their studies are the first to demonstrate that the virus’ interaction with the nervous system contributes to its ability to cause corneal opacity and blindness and have led to a novel hypothesis regarding the initiation of stromal disease. In related studies they have initiated a “genomics squared” analysis to explore the interaction of both viral and host genetics in herpetic disease. In a project funded by NASA, the Sawtell Lab is conducting studies to determine the long term outcomes of latent HSV in the central nervous system and the effects of stress and exposure to galactic cosmic radiation on HSV related pathology in the brain. These studies will not only define risks to astronauts and but also model HSV induced CNS damage (potentially increasing dementia risks) occurring in the aging population. Finally, a new National Institutes of Health (NIH) funded project exploits virally encoded miRNAs to regulate HSV reactivation in vivo.

Elizabeth P. Schlaudecker, MD, MPH

Dr. Schlaudecker's research continues to focus on the immunologic responses to maternal immunization. After completing a comprehensive epidemiologic study of the etiology and seasonality of viral respiratory infections in rural Honduras, she has shifted to prevention of these infections with maternal immunization. Her recent work has demonstrated antibody persistence in mothers one year after pneumococcal immunization in pregnancy, as well as a significantly decreased antibody response to influenza immunization in pregnant women. In collaboration with Dr. Mark Steinhoff and Monica McNeal, she evaluated influenza-specific IgA levels in breast milk and demonstrated that they were significantly higher in influenza vaccinees compared to pneumococcal controls for at least six months postpartum. She also demonstrated that greater exclusivity of breastfeeding in the first 6 months of life significantly decreased the expected number of respiratory illness with fever episodes in infants of influenza-vaccinated mothers, but not in infants of pneumococcal-vaccinated mothers.

Dr. Schlaudecker continues to study the immunologic response to influenza immunization in pregnant women with the support of a K12 Child Health Research Career Development Award from the National Institutes of Health (NIH). She investigated the IgG isotype responses to influenza immunization in Dr. Sing Sing Way's laboratory with the mentorship of Dr. Fred Finkelman in the Division Immunobiology and demonstrated an altered isotype profile in pregnant women compared to non-pregnant women consistent with a decreased response to the vaccine. She is also investigating a novel respiratory syncytial virus (RSV) vaccine administered to pregnant women to prevent RSV in their infants, as well as immunologic responses to immunization in breast milk with Cincinnati Children's Vaccine and Treatment Evaluation Unit (VTEU).

Samir S. Shah, MD, MSCE

Dr. Shah's research team focuses on improving efficiency and effectiveness of care of hospitalized children with a particular emphasis on respiratory tract infections. Several ongoing studies will determine the comparative effectiveness of different antibiotic regimens for community-acquired pneumonia and identify biomarkers that predict illness severity in children with community-acquired pneumonia and bronchiolitis. Dr. Shah is also PI on a parallel group randomized trial determining the efficacy of home nursing visits in improving outcomes after hospitalization for acute illnesses such as pneumonia and bronchiolitis.

Mary A. Staat, MD, MPH

Through Dr. Staat's large epidemiology and surveillance program developed in 1997, she has been able to develop optimal methods of detecting the changes and manifestations of infectious diseases of children within Cincinnati Children's and for the population of Hamilton County, and to compare these findings to national trends. Recognizing that Cincinnati Children's captures essentially all Hamilton County children requiring hospitalization or care in the emergency department has allowed Dr. Staat to conduct studies to determine the population-based rates of Hamilton County hospitalizations and emergency department visits for many pediatric infectious diseases using unique methods such as capture-recapture methods to determine disease burden and case-cohort and case-control designs to determine the post-licensure effectiveness of rotavirus and influenza vaccines. Studies published include the effectiveness of rotavirus and influenza vaccines, pre- and post-licensure costs of rotavirus disease, epidemiology of rotavirus, norovirus and other enteric infections as well as the epidemiology and disease burden of respiratory viruses.

Dr. Staat has also utilized data from her large international adoption center to publish studies to assist in the development of evidence-based guidelines for internationally adopted children. In addition to studies in the field of infectious diseases Dr. Staat and her colleagues have begun to explore the differences in neurological function between adopted and birth children using neuroimaging and psychological testing.

Mark C. Steinhoff, MD

Dr. Steinhoff's Global Health Center group at Cincinnati Children's focuses on global immunization research, as well as on the development of improved diagnostic technologies. A Gates-funded project of maternal influenza immunization in Southern Nepal, has enrolled and immunized 3,645 mothers over a two-year period, and has completed all field activities. The research group is currently analyzing the effect of immunization on reduction of influenza disease in the mother, improved development of the fetus, and disease in the infants below six months of age. During the two-year surveillance period, influenza was present in 28 of 36 months, common for this tropical region.

The group has completed a study with colleagues in South China to show that respiratory syncytial virus (RSV) infection is the most common cause of severe respiratory admissions and leads to substantial cost for treatment. Our group carried out preliminary studies of a new RSV vaccine in pregnant women in Cincinnati as part of a multi-center trial, and will continue the evaluation of this vaccine in other sites.

A retrospective evaluation of the growth of Bangladesh infants who were randomized to receive pneumococcal or haemophilus vaccines in their infancy showed that, by 24 months of age, the infants who received pneumococcal vaccine were significantly taller and heavier than the infants who received Hib vaccine. These findings suggest that pneumococcal vaccine may have broader effects than the prevention of invasive pneumococcal disease.

Dr. Steinhoff is collaborating with the Cincinnati Children's Division of Emergency Medicine in carrying out research projects in Malawi. Initial data to assess the etiology of admission for respiratory disease suggests that influenza, RSV and other viruses are common in this southern hemisphere setting.

Ming Tan, PhD

Dr. Tan's research focused on two directions: 1) development of norovirus protruding (P) domain-based vaccines and vaccine platforms, and; 2) elucidation of complex interactions between diverse noroviruses and their carbohydrate receptors or host attachment factors. For the first direction, he has shown the norovirus P particle as a potent vaccine against noroviruses and a useful vaccine platform for display of exogenous antigens. Chimeric P particles containing various foreign epitopes and antigens have been shown to be effective dual vaccine candidates. In addition, he developed other three P domain based polymers, the linear, network, and agglomerate polymers, as vaccines and vaccine platforms. Epitopes and antigens from different pathogens can be displayed by these polyvalent vaccine platforms for increased immunogenicity for multivalent vaccine development against different infectious diseases. For norovirus-host interactions, he discovered that human noroviruses interact with another group of cell surface carbohydrates, the sialic acid-containing sialoglycoconjugates, in addition to the previously known histo-blood group antigens. Further study of these new glycans as norovirus receptors or attachment factors will shed light into the complex interactions between the diverse noroviruses and polymorphic glycans. In addition, he found that GII.13 and GII.21 genotypes of noroviruses form a unique genetic lineage that interacts with glycan receptor through a completely new binding site. A number of papers have been published in the past year. His research outcomes provide valuable data to understand noroviruses and offer strategies for future development of vaccine and antivirals against norovirus and other infectious pathogens.

Sing Sing Way, MD, PhD

Dr. Way's group investigates host defense and the immune pathogenesis of infectious disease using representative models of human infection. Prenatal infection is a particular focus, infection during the early neonatal period, and maternal-fetal immunological tolerance. Results from work over the past few years have uncovered a critical need for immune suppression in the first few days following birth that protects against pathological inflammation triggered by colonization with commensal microbes. This immune suppression within newborn infants also makes them susceptible to disseminated infection. Other related publications have uncovered fundamental new aspects of T cell biology including differentiation into immune suppressive regulatory T cells and antigen-specificity each required for maintaining maternal immune tolerance to the developing fetus during pregnancy.

Significant Publications

Mulligan MJ, **Bernstein DI**, Winokur P, Rupp R, Anderson E, Rouphael N, **Dickey M**, Stapleton JT, Edupuganti S, Spearman P, Ince D, Noah DL, Hill H, Bellamy AR, Group DHNVS. Serological responses to an avian influenza A/H7N9 vaccine mixed at the point-of-use with MF59 adjuvant: a randomized clinical trial. *JAMA.* 2014 Oct 8;312(14):1409-19.

Influenza, particularly pandemic strains, continues to be a significant cause of morbidity and mortality. This article demonstrated the ability of a new vaccine to provide strong immunity against a possible pandemic strain of influenza as well as showing that adjuvants could signficantly enhance the immune response to vaccination.

Wang L, Xia M, Huang P, Fang H, Cao D, Meng XJ, **McNeal M**, **Jiang X**, Tan M. Branched-linear and agglomerate protein polymers as vaccine platforms. *Biomaterials.* 2014 Sep;35(29):8427-38.

Currently, vaccines are “built” on their own backbone. This article describes a process to use a common platform to develop multiple vaccines. Successful use of the method could significantly enhance our ability to protect against various infections.

Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, **Jiang X**, Vinje J, Gregoricus N, **Frenck RW Jr**, Moe CL, Al-Ibrahim MS, Barrett J, Ferreira J, Estes MK, Graham DY, Goodwin R, Borkowski A, Clemens R, Mendelman PM. Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults. *J Infect Dis.* 2015 Mar 15;211(6):870-8.

Norovirus now is the most common form of viral diarrhea and is a particular problem among travelers and the military. The study demonstrated the ability of the candidate vaccine to decrease infection and disease from Norovirus. If proven out in additional trials, the vaccine could significantly enhance our ability to prevent this common infection.

Currier RL, Payne DC, **Staat MA**, Selvarangan R, Shirley SH, Halasa N, Boom JA, Englund JA, Szilagyi PG, Harrison CJ, Klein EJ, Weinberg GA, Wikswo ME, Parashar U, Vinje J, Morrow AL. Innate Susceptibility to Norovirus Infections Influenced by FUT2 Genotype in a United States Pediatric Population. *Clin Infect Dis.* 2015 Jun 1;60(11):1631-8.

Norovirus is the most common cause of acute diarrhea among children in the United States. This article enhances our knowledge about the virus by demonstrating that segments of the population are at increased risk of infection due to the present of the “secretor” gene. This work can lead to the development of agents to block norovirus binding and thus provide immunity from the organism.

Danziger-Isakov L, Bucavalas J. Current prevention strategies against cytomegalovirus in the studies in pediatric liver transplantation (SPLIT) centers. *Am J Transplant.* 2014 Aug;14(8):1908-11.

Cytomegalovirus (CMV) continues to be a major pathogen among patients who have undergone liver transplant. The article discusses the state of the art for prevention of CMV in patients who have undergone liver transplant.

Division Publications

1. Ahmed SF, Shaheen HI, Abdel-Messih IA, Mostafa M, Putnam SD, Kamal KA, Sayed AN, Frenck RW, Jr., Sanders JW, Klena JD, Wierzba TF. **The epidemiological and clinical characteristics of diarrhea associated with enteropathogenic, enteroaggregative and diffuse-adherent Escherichia coli in Egyptian children**. *J Trop Pediatr*. 2014; 60:397-400.

2. Ali A, Kazi AM, Cortese MM, Fleming JA, Moon S, Parashar UD, Jiang B, McNeal MM, Steele D, Bhutta Z, Zaidi AK.

Impact of withholding breastfeeding at the time of vaccination on the immunogenicity of oral rotavirus vaccine-a randomized trial. *PLoS One*. 2015; 10:e0127622.

3. Ali SA, Kazi AM, Cortese MM, Fleming JA, Parashar UD, Jiang B, McNeal MM, Steele D, Bhutta Z, Zaidi A. **Impact of different dosing schedules on the immunogenicity of the human rotavirus vaccine in infants in Pakistan: a randomized trial**. *J Infect Dis*. 2014; 210:1772-9.

4. Bernstein DI, Atmar RL, Lyon GM, Treanor JJ, Chen WH, Jiang X, Vinje J, Gregoricus N, Frenck RW, Jr., Moe CL, Al-Ibrahim MS, Barrett J, Ferreira J, Estes MK, Graham DY, Goodwin R, Borkowski A, Clemens R, Mendelman PM. **Norovirus vaccine against experimental human GII.4 virus illness: a challenge study in healthy adults**. *J Infect Dis*. 2015; 211:870-8.

5. Bernstein DI, Jackson L, Patel SM, El Sahly HM, Spearman P, Rouphael N, Rudge TL, Jr., Hill H, Goll JB. **Immunogenicity and safety of four different dosing regimens of anthrax vaccine adsorbed for post-exposure prophylaxis for anthrax in adults**. *Vaccine*. 2014; 32:6284-93.

6. Brady RC. **Pertactin-Negative B pertussis and Vaccine Effectiveness**. *AAP Grand Rounds*. 2015; 33:37.

7. Brady RC. **Alternative Vaccination Schedules and Up-to-date Status**. *AAP Grand Rounds*. 2015; 33:13.

8. Brady RC. **Clinical Practice Guidelines for Skin and Soft Tissue Infections**. *AAP Grand Rounds*. 2015; 33:24.

9. Brady RC. **Frequency of Acute Respiratory Illnesses in Households**. *AAP Grand Rounds*. 2015; 33:33.

10. Brady RC. **Influenza Vaccine: Nasal Spray or Intramuscular Shot?**. *AAP Grand Rounds*. 2015; 33:49.

11. Brady RC. **Clostridium Difficile Infection Among US Children**. *AAP Grand Rounds*. 2014; 32:20.

12. Brady RC. **Urinary Tract Infection in Febrile Neonates**. *AAP Grand Rounds*. 2014; 32:14.

13. Brady RC. **Updated Guidance for Palivizumab Prophylaxis**. *AAP Grand Rounds*. 2014; 32:62.

14. Brady RC. **Is Metronidazole Beneficial For Dientamoeba Fragilis Infection?**. *AAP Grand Rounds*. 2014; 32:40.

15. Brady RC. **Influenza Infection Facilitates Pneumococcal Acquisition**. *AAP Grand Rounds*. 2014; 32:32.

16. Brady RC, Hu W, Houchin VG, Eder FS, Jackson KC, Hartel GF, Sawlwin DC, Albano FR, Greenberg M. **Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children**. *Vaccine*. 2014; 32:7141-7.

17. Callahan ST, Wolff M, Hill HR, Edwards KM, Vaccine N, Treatment Evaluation Unit Pandemic HNVSG. **Impact of body mass index on immunogenicity of pandemic H1N1 vaccine in children and adults**. *J Infect Dis*. 2014; 210:1270-4.

18. Chaturvedi V, Ertelt JM, Jiang TT, Kinder JM, Xin L, Owens KJ, Jones HN, Way SS. **CXCR3 blockade protects against Listeria monocytogenes infection-induced fetal wastage**. *J Clin Invest*. 2015; 125:1713-25.

19. Chen WH, Garza J, Choquette M, Hawkins J, Hoeper A, Bernstein DI, Cohen MB. **Safety and immunogenicity of escalating dosages of a single oral administration of peru-15 pCTB, a candidate live, attenuated vaccine against enterotoxigenic Escherichia coli and Vibrio cholerae**. *Clin Vaccine Immunol*. 2015; 22:129-35.

20. Clark A, Hemmelgarn T, Danziger-Isakov L, Teusink A. **Intravenous pentamidine for Pneumocystis carinii/jiroveci pneumonia prophylaxis in pediatric transplant patients**. *Pediatr Transplant*. 2015; 19:326-31.

21. Clark DR, Chaturvedi V, Kinder JM, Jiang TT, Xin L, Ertelt JM, Way SS. **Perinatal Listeria monocytogenes**

susceptibility despite preconceptual priming and maintenance of pathogen-specific CD8(+) T cells during pregnancy. *Cell Mol Immunol*. 2014; 11:595-605.

22. Cornfield DN, Lane R, Rosenblum ND, Hostetter M, Jobe A, Albertine K, Aschner J, Abman SH. **Patching the pipeline: creation and retention of the next generation of physician-scientists for child health research**. *J Pediatr*. 2014; 165:882-4 e1.

23. Currier RL, Payne DC, Staat MA, Selvarangan R, Shirley SH, Halasa N, Boom JA, Englund JA, Szilagyi PG, Harrison CJ, Klein EJ, Weinberg GA, Wikswo ME, Parashar U, Vinje J, Morrow AL. **Innate Susceptibility to Norovirus Infections Influenced by FUT2 Genotype in a United States Pediatric Population**. *Clin Infect Dis*. 2015; 60:1631-8.

24. Dai YC, Zhang XF, Xia M, Tan M, Quigley C, Lei W, Fang H, Zhong W, Lee B, Pang X, Nie J, Jiang X. **Antigenic Relatedness of Norovirus GII.4 Variants Determined by Human Challenge Sera**. *PLoS One*. 2015; 10:e0124945.

25. Danziger-Isakov L, Bucavalas J. **Current prevention strategies against cytomegalovirus in the studies in pediatric liver transplantation (SPLIT) centers**. *Am J Transplant*. 2014; 14:1908-11.

26. Danziger-Isakov L, Evans HM, Green M, McCulloch M, Michaels MG, Posfay-Barbe KM, Verma A, Allen U, IPTA ICCf. **Capacity building in pediatric transplant infectious diseases: an international perspective**. *Pediatr Transplant*. 2014; 18:790-3.

27. Danziger-Isakov L, Sabella C. **Zoonosis**. In: RP Usatine, C Sabella, eds. *Color Atlas of Pediatrics*. New York: McGraw Hill Education; 2015:1099-1111.

28. Drummond RA, Wallace C, Reid DM, Way SS, Kaplan DH, Brown GD. **Cutting edge: Failure of antigen-specific CD4+ T cell recruitment to the kidney during systemic candidiasis**. *J Immunol*. 2014; 193:5381-5.

29. El Feghaly RE, Bangar H, Haslam DB. **The molecular basis of Clostridium difficile disease and host response**. *Curr Opin Gastroenterol*. 2015; 31:24-9.

30. Frey SE, Bernstein DI, Brady RC, Keitel WA, El Sahly H, Rouphael NG, Mulligan MJ, Atmar RL, Edupuganti S, Patel SM, Dickey M, Graham I, Anderson EL, Noah DL, Hill H, Wolff M, Belshe RB. **Phase II trial in adults of concurrent or sequential 2009 pandemic H1N1 and 2009-2010 seasonal trivalent influenza vaccinations**. *Vaccine*. 2015; 33:163-73.

31. Hahn A, Frenck RW, Jr., Zou Y, Vinks AA. **Validation of a pediatric population pharmacokinetic model for vancomycin**. *Ther Drug Monit*. 2015; 37:413-6.

32. Han L, Kitova EN, Tan M, Jiang X, Pluvinage B, Boraston AB, Klassen JS. **Affinities of human histo-blood group antigens for norovirus capsid protein complexes**. *Glycobiology*. 2015; 25:170-80.

33. Han L, Tan M, Xia M, Kitova EN, Jiang X, Klassen JS. **Gangliosides are ligands for human noroviruses**. *J Am Chem Soc*. 2014; 136:12631-7.

34. Hao N, Chen Y, Xia M, Tan M, Liu W, Guan X, Jiang X, Li X, Rao Z. **Crystal structures of GI.8 Boxer virus P dimers in complex with HBGAs, a novel evolutionary path selected by the Lewis epitope**. *Protein Cell*. 2015; 6:101-16.

35. Hill JM, Quenelle DC, Cardin RD, Vogel JL, Clement C, Bravo FJ, Foster TP, Bosch-Marce M, Raja P, Lee JS, Bernstein DI, Krause PR, Knipe DM, Kristie TM. **Inhibition of LSD1 reduces herpesvirus infection, shedding, and recurrence by promoting epigenetic suppression of viral genomes**. *Sci Transl Med*. 2014; 6:265ra169.

36. Hoeper A, Dickey M. **Building A Quality Management Plan into Your Clinical Research Program**. *Clinical Researcher*. 2014; August:15-19.

37. Huprikar S, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, Koval C, Lease ED, Pillai A, Doucette KE, Levitsky J, Morris MI, Lu K, McDermott JK, Mone T, Orlowski JP, Dadhania DM, Abbott K, Horslen S, Laskin BL, Mougdil A, Venkat VL, Korenblat K, Kumar V, Grossi P, Bloom RD, Brown K, Kotton CN, Kumar D. **Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management**. *Am J Transplant*. 2015; 15:1162-72.

38. Ison MG, Danziger-Isakov L. **Severe respiratory illness associated with enterovirus 68: implications for solid organ transplantation**. *Transplantation*. 2014; 98:1253-4.

39. Jiang X, Wu Y, Marsolo K, Ohno-Machado L. **Development of a web service for analysis in a distributed network**. *EGEMS (Wash DC)*. 2014; 2:1053.

40. Jin M, Tan M, Xia M, Wei C, Huang P, Wang L, Zhong W, Duan Z, Jiang X. **Strain-specific interaction of a GII.10 Norovirus with HBGAs**. *Virology*. 2015; 476:386-94.

41. Kim SH, Chen S, Jiang X, Green KY, Samal SK. **Newcastle disease virus vector producing human norovirus-like particles induces serum, cellular, and mucosal immune responses in mice**. *J Virol*. 2014; 88:9718-27.

42. Kocher J, Bui T, Giri-Rachman E, Wen K, Li G, Yang X, Liu F, Tan M, Xia M, Zhong W, Jiang X, Yuan L. **Intranasal P particle vaccine provided partial cross-variant protection against human GII.4 norovirus diarrhea in gnotobiotic pigs**. *J Virol*. 2014; 88:9728-43.

43. Ledgerwood JE, Bellamy AR, Belshe R, Bernstein DI, Edupuganti S, Patel SM, Renehan P, Zajdowicz T, Schwartz R, Koup R, Bailer RT, Yamshchikov GV, Enama ME, Sarwar U, Larkin B, Graham BS, team VRCs. **DNA priming for seasonal influenza vaccine: a phase 1b double-blind randomized clinical trial**. *PLoS One*. 2015; 10:e0125914.

44. Makari D, Staat MA, Henrickson KJ, Wu X, Ambrose CS. **The Underrecognized Burden of Respiratory Syncytial Virus Among Infants Presenting to US Emergency Departments**. *Clin Pediatr (Phila)*. 2015; 54:594-7.

45. Mansour A, Shaheen HI, Amine M, Hassan K, Sanders JW, Riddle MS, Armstrong AW, Svennerholm AM, Sebeny PJ, Klena JD, Young SY, Frenck RW. **Diarrhea burden due to natural infection with enterotoxigenic Escherichia coli in a birth cohort in a rural Egyptian community**. *J Clin Microbiol*. 2014; 52:2595-603.

46. McNeal M, Bernstein DI. **Rotaviruses**. In: RA Kaslow, LR Stanberry, JW Le Duc, eds. *Viral Infections of Humans: Epidemiology and Control*. New York: Springer; 2014:713-732.

47. Mulligan MJ, Bernstein DI, Frey S, Winokur P, Rouphael N, Dickey M, Edupuganti S, Spearman P, Anderson E, Graham I, Noah DL, Mangal B, Kim S, Hill H, Whitaker J, Emery W, Beck A, Stephens K, Hartwell B, Ogilvie M, Rimann N, Osinski E, Destefano E, Gajadhar T, Strudwick A, Pierce K, Lai L, Yue L, Wang D, Ying C, Cline A, Foltz T, Wagner N, Dull G, Pacatte T, Taggart B, Johnson V, Haller L, Looney C, Li S, May M, Myers B, May R, Parker L, Cochran N, Bowen D, Bell M, Scoggins J, Burns A, Stablein C, Wolff M, Jolles B, Leung B, Lambert L, Shorer S, Buchanan W, Murray S, Chang S, Gorman R. **Point-of-Use Mixing of Influenza H5N1 Vaccine and MF59 Adjuvant for Pandemic Vaccination Preparedness: Antibody Responses and Safety. A Phase 1 Clinical Trial**. *Open Forum Infect Dis*. 2014; 1:ofu102.

48. Mulligan MJ, Bernstein DI, Winokur P, Rupp R, Anderson E, Rouphael N, Dickey M, Stapleton JT, Edupuganti S, Spearman P, Ince D, Noah DL, Hill H, Bellamy AR, Group DHNVS. **Serological responses to an avian influenza A/H7N9 vaccine mixed at the point-of-use with MF59 adjuvant: a randomized clinical trial**. *JAMA*. 2014; 312:1409-19.

49. Nanton MR, Lee SJ, Atif SM, Nuccio SP, Taylor JJ, Baumler AJ, Way SS, McSorley SJ. **Direct visualization of**

endogenous Salmonella-specific B cells reveals a marked delay in clonal expansion and germinal center development. *Eur J Immunol*. 2015; 45:428-41.

50. Oliveira DB, Iwane MK, Prill MM, Weinberg GA, Williams JV, Griffin MR, Szilagyi PG, Edwards KM, Staat MA, Hall CB, Durigon EL, Erdman DD. **Molecular characterization of respiratory syncytial viruses infecting children reported to have received palivizumab immunoprophylaxis**. *J Clin Virol*. 2015; 65:26-31.

51. Pinninti SG, Ross SA, Shimamura M, Novak Z, Palmer AL, Ahmed A, Tolan RW, Jr., Bernstein DI, Michaels MG, Sanchez PJ, Fowler KB, Boppana SB, National Institute on D, Other Communication Disorders CMV, Hearing Multicenter Screening S. **Comparison of saliva PCR assay versus rapid culture for detection of congenital cytomegalovirus infection**. *Pediatr Infect Dis J*. 2015; 34:536-7.

52. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, Fisher S, Golos T, Matzuk M, McCune JM, Mor G, Schulz L, Soares M, Spencer T, Strominger J, Way SS, Yoshinaga K. **Immune mechanisms at the maternal-fetal interface: perspectives and challenges**. *Nat Immunol*. 2015; 16:328-34.

53. Ross SA, Ahmed A, Palmer AL, Michaels MG, Sanchez PJ, Bernstein DI, Tolan RW, Jr., Novak Z, Chowdhury N, Fowler KB, Boppana SB, National Institute on D, Other Communication Disorders CS. **Detection of congenital cytomegalovirus infection by real-time polymerase chain reaction analysis of saliva or urine specimens**. *J Infect Dis*. 2014; 210:1415-8.

54. Schlaudecker EP, Heck JP, MacIntyre ET, Martinez R, Dodd CN, McNeal MM, Staat MA, Heck JE, Steinhoff MC. **Comparison of a new transport medium with universal transport medium at a tropical field site**. *Diagn Microbiol Infect Dis*. 2014; 80:107-10.

55. Vander Schaaf E, Potisek NM, Puri K, Schlaudecker EP, Newman NC, Notario PM, Nagpal R. **Index of suspicion**. *Pediatr Rev*. 2014; 35:487-92.

56. Wang L, Xia M, Huang P, Fang H, Cao D, Meng XJ, McNeal M, Jiang X, Tan M. **Branched-linear and agglomerate protein polymers as vaccine platforms**. *Biomaterials*. 2014; 35:8427-38.

57. Xin L, Jiang TT, Chaturvedi V, Kinder JM, Ertelt JM, Rowe JH, Steinbrecher KA, Way SS. **Commensal microbes drive intestinal inflammation by IL-17-producing CD4+ T cells through ICOSL and OX40L costimulation in the absence of B7-1 and B7-2**. *Proc Natl Acad Sci U S A*. 2014; 111:10672-7.

58. Yu G, Vago F, Zhang D, Snyder JE, Yan R, Zhang C, Benjamin C, Jiang X, Kuhn RJ, Serwer P, Thompson DH, Jiang W. **Single-step antibody-based affinity cryo-electron microscopy for imaging and structural analysis of macromolecular assemblies**. *J Struct Biol*. 2014; 187:1-9.

59. Zhang D, Huang P, Zou L, Lowary TL, Tan M, Jiang X. **Tulane virus recognizes the A type 3 and B histo-blood group antigens**. *J Virol*. 2015; 89:1419-27.

Faculty, Staff, and Trainees

Faculty Members

Robert W. Frenck, MD, Professor

Leadership Interim Director, Division of Infectious Diseases; Chairman, Institutional Review Board

Research Interests Vaccines; enteric diseases.

Margaret K. Hostetter, MD, Professor

Leadership BK Rachford Professor and Chair; Director, Pediatric Research

Research Interests Candida albicans - heparin binding motifs and biofilm; Candida albicans - role of vaginal colonization in preterm birth; genetics of disseminated Staphylococcus aureus infection.

David I. Bernstein, MD, MA, Professor

Leadership Director, Gamble Program for Clinical Studies; Director, VTEU

Research Interests Vaccines; rotavirus; herpes simplex; cytomegalovirus.

Rebecca C. Brady, MD, Associate Professor

Leadership Director of Adult Clinical Studies; Director of the Drug Use Evaluation Committee

Research Interests Vaccines for adults; influenza.

Rhonda D. Cardin, PhD, Associate Professor

Research Interests Cytomegalovirus; herpes simplex type 2; antivirals; vaccines.

Beverly L. Connelly, MD, Professor

Leadership Director, Pediatric Infectious Diseases Fellowship Training Program; Director, Infection Control Program

Research Interests Understanding and preventing healthcare associated infections.

Lara Danziger-Isakov, MD, MPH, Professor

Leadership Director, Transplant ID

Research Interests Transplantation, immunocompromised hosts; respiratory viruses; vaccines.

Michelle P. Dickey, MS, CRNP, Instructor

Leadership Manager, Gamble Program

Research Interests Clinical vaccine trials.

David B. Haslam, MD, Associate Professor

Leadership Director, Antimicrobial Stewardship Program

Research Interests Clostridium difficile infection; microbiome; whole genome sequencing; antimicrobial resistance.

Nancy M. Hutchinson, RN, MSN, CIC, Instructor

Leadership Infection Control Program

Research Interests Prevention of device-associated infections.

Xi Jason Jiang, PhD, Professor

Research Interests Caliciviruses; rotavirus; vaccines.

Monica M. McNeal, MS, Assistant Professor

Leadership Associate Director, LSCS

Research Interests Rotavirus; influenza and Shigella vaccine research.

Grant C. Paulsen, MD, Assistant Professor

Leadership Associate Director, Pediatric Infectious Diseases Fellowship Training Program

Research Interests Transplantation; immunocompromised hosts; vaccines.

Joseph E. Qualls, PhD, Assistant Professor

Research Interests Macrophage biology; macrophage/T cell interactions; intracellular pathogenesis; amino acid metabolism and immune function.

Nancy M. Sawtell, PhD, Professor

Research Interests Herpes simplex virus: a) molecular mechanisms regulating viral latency and reactivation and recurrence; b) host gene variants and molecular pathways affecting the outcome of infection; c) regulation of disease severity by the intersection of viral and host genetics; d) short- and long-term consequences of simulated

deep space radiation on latent herpes simplex virus infection of the central nervous system.

Elizabeth P. Schlaudecker, MD, MPH, Assistant Professor
Research Interests Immunologic responses to maternal immunization in serum and breast milk.

Mary A. Staat, MD, MPH, Professor
Leadership Director, International Adoption Center
Research Interests Rotavirus, epidemiology, international adoption; vaccine preventable diseases.

Jane E. Strasser, PhD, Assistant Professor
Leadership UC Associate Vice President of Research
Research Interests Shiga-like toxins; genetics of susceptibility and resistance.

Ming Tan, PhD, Assistant Professor
Research Interests Calicivirus; rotavirus; multivalent vaccine development.

Sing Sing Way, MD, PhD, Associate Professor
Leadership Pauline and Lawson Reed Chair
Research Interests Immunity to microbes; immune pathogenesis of perinatal infection; maternal fetal tolerance.

Joint Appointment Faculty Members

Steve Black, MD, Adjunct (Global Health Center)
Research Interests Vaccine safety.

Samir Shah, MD, MSCE, Professor (Hospital Medicine, Director)
Research Interests Pneumonia; meningitis; improving efficiency and effectiveness of hospital care using quality improvement and comparative effectiveness research methods.

Mark C. Steinhoff, MD, Professor (Global Health Center, Director)
Research Interests Global vaccines; vaccine in pregnancy.

Andrew B. Herr, PhD, Associate Professor (Immunobiology)

David M. Hartley, PhD, MPH, Associate Professor (James M. Anderson Center)

Clinical Staff Members

- **Samantha Blum, RN**, ID Transplant Clinic
- **Brookana Bonezza, RN, APN**, ID/Transplant Nurse
- **Andrea Bohlen, MSW, LISW-S**, International Adoption Center
- **Cathy Boyce, RN**, OPAT Clinic Nurse
- **Kelly Hicks, RN, MSN**, International Adoption Center
- **Tisha Way, MSSA, LISW-S**, International Adoption Center

Trainees

- **Heidi Andersen, MD**, PL5, Indiana Univeristy
- **Kathleen Ryan, MD**, PL5, University of Wisconsin
- **Matthew Washam, MD**, PL4, Ohio State University
- **Jon Woltmann, MD**, PL4, North East Ohio Medical University

- **Shannon Rapovy,** , PG3, University of Cincinnati
- **Jeremy Kinder,** , PG3, University of Cincinnati
- **Tony Jiang,** , University of Cincinnati

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct

Bernstein, D

Vaccine and Treatment Evaluation Units (VTEU)

National Institutes of Health

HHSN272200800006C	11/1/2007-7/31/2017	$1,749,257

Vaccine and Treatment Evaluation Units (VTEU)

National Institutes of Health

HHSN272201300016I	9/16/2013-9/15/2023	$1,180,271

Mouse and Guinea Pig Models for Herpesviruses

National Institutes of Health

HHSN272201000008I	9/27/2010-9/26/2015	$417,872

Brady, R

Connecting the Silos: A Partnership to Improve Immunization Rates among Adolescents with High-Risk (Chronic and Immunocompromising) Conditions

Pfizer

	11/1/2014-10/31/2016	$358,199

Cardin, R

Role of Viral Chemokine Receptors in Cytomegalovirus Latency

National Institutes of Health

R01 AI087683	7/5/2012-6/30/2016	$257,045

Danziger-Isakov, L

B-Cell Targeted Induction to Improve Outcomes in Pediatric Lung Transplantation

National Institutes of Health(Washington University)

U01 AI077810	3/1/14-2/28/2015	$60,093

Multi-center Studies to Improve Diagnosis and Treatment of Pediatric Candidiasis

National Institutes of Health(Duke University)

R01 AI103315	1/1/2014-12/31/2017	$1,540

Haslam, D

CFF Research Development Program - P&F

Cystic Fibrosis Foundation

	3/1/2012-6/30/2015	$65,000

Hostetter, M

Pediatric Scientist Development Program (PSDP)

National Institutes of Health

K12 HD000850	7/3/2012-6/30/2017	$1,486,739

Hostetter, M

Pediatric Scientist Development Program (PSDP)

American Academy of Pediatrics

	9/1/2010-6/30/2017	$162,810

Pediatric Scientist Development Program

American Pediatric Society

	9/1/2010-6/30/2017	$162,810

Pediatric Scientist Development Program

March of Dimes

#4-FY14-504	10/1/2014-9/30/2017	$210,870

Pediatric Scientist Development Program (PSDP)

March of Dimes

#4-FY13-530	7/1/2013-6/30/2015	$108,540

Balance of Th17 Cells and Regulatory T Cells in Candidal Colonization in Humans Vaginal Tlssue and Pregnant Macaques.

Children's Hospital & Regional Medical Center-Seattle

12002	10/5/2012-9/30/2015	$259,199

Jiang, T

Antifungal Immunity Controlled by Commensal Intestinal Bacteria

National Institutes of Health

F30 DK107199	5/1/2015-4/30/2020	$37,088

Jiang, X

HBGA Receptors in Host Cell Entry and Infection of Norovirus

National Institutes of Health(Purdue University)

R01 AI111095	12/1/2014-11/30/2019	$163,124

Inactivation of Enteric Foodborne Viruses in High Risk Foods by Non-Thermal Processing Technologies

US Department of Agriculture(University of Delaware)

2011-68003-30005	2/1/2011-1/1/2016	$126,589

Universal Flu Vaccine by a Norovirus P Particle Platform

US Department of Agriculture(Ohio State University)

2013-67015-20476	2/1/2013-1/31/2018	$139,843

Qualls, J

L-citrulline and Host Defenses to Mycobacteria

American Heart Association

15SDG21550007	1/1/2015-12/31/2017	$70,000

Sawtell, N

Acute and Long Term Outcomes of Simulated Deep Space Radiation Exposure on Latent Viral CNS Infection and CNS Pathology

National Aeronautics and Space Administration

NNX13A047G	1/1/2014-12/31/2016	$236,091

HSV Latency and Reactivation and the Novel Neuronal Regulation of VP16 In Vivo

National Institutes of Health

R01 AI093614	7/1/2012-6/30/2017	$416,371

Staat, M

Enhanced Surveillance for New Vaccine Preventable Disease

Centers for Disease Control and Prevention

U01 IP000458	8/1/2011-7/31/2016	$318,180

Tan, M

Norovirus Capsid: A Novel Drug Target

National Institutes of Health(University of Cincinnati)

R21 AI097936	8/6/2013-7/31/2015	$63,320

Way, S

Investigators in the Pathogenesis of Infectious Disease Award

Burroughs Wellcome Foundation(University of Cincinnati)

1011031	10/1/2012-9/30/2017	$100,000

Pregnancy Induced Maternal Regulatory T Cells

March of Dimes

6-FY15-254	6/1/2015-5/31/2018	$350,000

The Immune Pathogenesis of Prenatal Listeria Monocytogenes Infection

National Institutes of Health

R01 AI100934	9/6/2012-6/30/2017	$299,263

CD4 T Cells with Specificity to Noninherited Maternal Antigen.

National Institutes of Health

R21 AI112186	1/20/2014-12/31/2015	$150,000

	Current Year Direct	**$8,950,114**

Industry Contracts

Bernstein, D

Genocea Biosciences, Inc	$352,218
Pfizer, Inc	$6,385
Sanofi Pasteur Biologics, LLC	$62,827
Takeda Global Res & Development Ctr, Inc	$164,157
Vaxart Inc	$52,160

Cardin, R

Genocea Biosciences, Inc	$86,280

Danziger-Isakov, L

Alberta Health Services	$5,390
Ansun Biopharma Inc.	$14,000

Frenck, R

GlaxoSmithKline	$8,655
Pfizer, Inc	$32,879

Haslam, D

Astellas Pharma Us Inc.	$15,639

McNeal, M

GlaxoSmithKline	$6,218
Sanofi Sythelabo	$26,595
Merck & Company, Inc	$914,810

Current Year Direct Receipts	**$1,748,213**
Total	**$10,698,327**

Mother's Own Immune System May Cause Pregnancy Complications

Sing Sing Way, MD, PhD

Vandana Chaturvedi, PhD

RESEARCH AND TRAINING DETAILS

Faculty	19
Joint Appointment Faculty	6
Research Fellows	2
Research Students	4
Support Personnel	82
Direct Annual Grant Support	$8.9M
Direct Annual Industry Support	$1,748,213
Peer Reviewed Publications	59

Chaturvedi V, Ertelt JM, Jiang TT, Kinder JM, Xin L, Owens KJ, Jones HN, Way SS. CXCR3 blockade protects against Listeria monocytogenes infection-induced fetal wastage. *J Clin Invest.* 2015;125(4):1713-1725.

PUBLISHED MARCH 9, 2015
The Journal of Clinical Investigation

Redirecting an expectant mother's immune cells to prevent them from attacking the fetus might reduce complications such as stillbirth and prematurity, according to a study that identifies a cell traffic pathway that plays a critical role in the process.

The causes of premature birth and many other pregnancy complications are not completely known, but maternal infection is an important contributor, says senior author Sing Sing Way, MD, PhD, Division of Infectious Diseases. When infection strikes, maternal immune cells can "overreact" and attack the placenta as if it were a foreign invader.

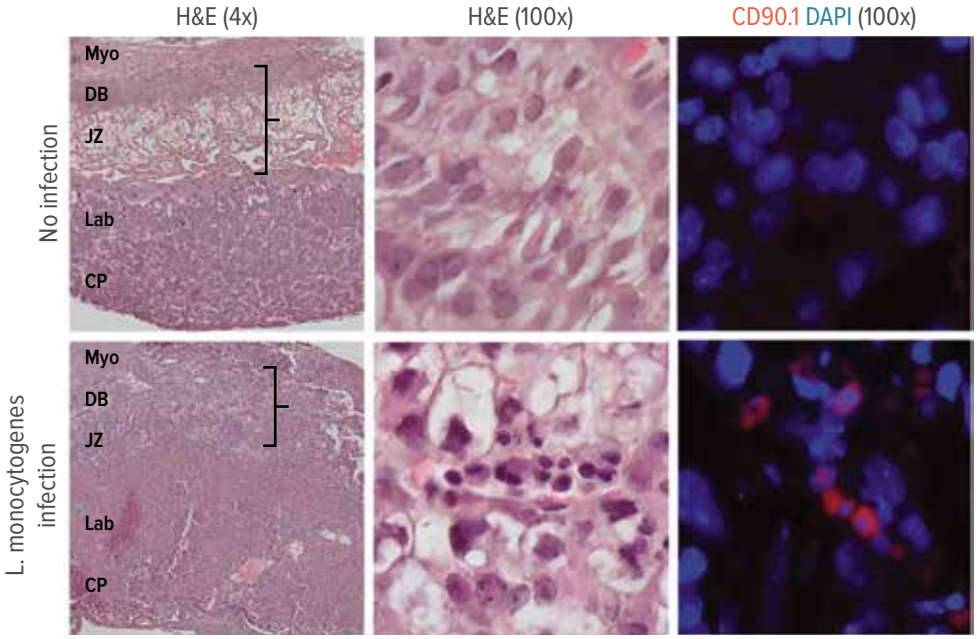
Way's study, published March 9, 2015, in *The Journal of Clinical Investigation*, identifies a pathway that could reduce these harmful overreactions.

"It might seem counterintuitive to prevent maternal immune cells from optimally penetrating into tissues," says Way. "But restricting harmful immune cells' access to developmentally delicate placental tissue represents a highly innovative therapeutic strategy."

The research team, led by Way and first author Vandana Chaturvedi, PhD, infected pregnant mice with *Listeria monocytogenes*, a bacterium commonly found in food supplies that causes invasive infection in pregnant women. It is often fatal to the fetus. Mice and human share this susceptibility.

The researchers found that specialized subsets of first-responder immune cells — neutrophils and macrophages — rapidly infiltrate the placenta, producing high levels of a chemoattractant protein, CXCL9, which attracts harmful maternal T cells to attack genetically foreign placental-fetal tissue.

The finding is significant because placental cells are not programmed to express chemoattractant proteins like CXCL9. The team found neutralizing CXCL9 activity by blocking its receptor on T cells efficiently protects against fetal injury after prenatal *Listeria* infections.



Histological analysis of the placentas recovered from female mice during allogeneic pregnancies sired by ovalbumin expressing transgenic male mice showing no infection control compared with *L. monocytogenes* infection after H&E staining, along with anti-CD90.1 staining for ovalbumin specific CD8+ T cells (red) and DAPI nuclear immunofluorescence staining (blue). High-magnification fields show placental tissue intersecting the decidua basalis (DB) and junctional zone (JZ). Brackets in the low-magnification fields indicate the source of decidual tissue harvested for analysis by flow cytometry. Myo = myometrium; Lab = labyrinth; CP = chorionic plate.

"Restricting harmful immune cells' access to developmentally delicate placental tissue represents a highly innovative therapeutic strategy."