## Division Summary

### Research and Training Details

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<thead>
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### Clinical Activities and Training

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## Significant Accomplishments

### Grant Funding Rises Fast

With overall grant funding rising to $9.4 million, our Division ranked first for its increase in grant funding in 2012 and 2013. We received funding from the NIH, CDC, Burroughs-Wellcome, Bill and Melinda Gates Foundation, NASA, and industry, which supported research projects exploring the pathogenesis of CMV, HSV, norovirus/calicivirus, and Candida infections; vaccine response; macrophage biology; and normal and aberrant immune responses in pregnancy.

### Transplant Infectious Diseases Program Expands

High demand for expertise from our transplant infectious diseases program, launched in 2012 under the direction of Lara Danziger-Isakov, MD, MPH, led to plans to expand the service in August. The division recruited a new faculty member, Grant Paulsen, MD, a med/peds fellow trained in both pediatric and adult infectious diseases at the University of Alabama-Birmingham. Other support to the service will be supplied by a nurse practitioner.

### Antimicrobial Stewardship Program Provides Expert Consulting

Our Antimicrobial Stewardship program is directed by David Haslam, MD, who was recruited in September 2013 from Washington University in St. Louis. The other partner in program is Joshua Courter, PharmD, from the Division of Pharmacy. With the use of VigiLanz software to monitor adverse drug events, antimicrobial usage, and targeted infections, the team has provided expert consultation to a number of services, including...
Vaccine Technology and Genetic Discovery Take Steps Forward
Division Faculty members Jason Jiang, PhD, and Ming Tan, PhD, have licensed the technology for the norovirus P particle as a vaccine platform. Meanwhile, the Hostetter laboratory worked with the Center for Technology and Commercialization to submit a provisional patent application for genes contributing to disseminated staphylococcal infection after osteomyelitis.

Vaccine and Treatment Evaluation Unit Renewed
Under the direction of David Bernstein, MD, MA, Cincinnati Children's successfully renewed the VTEU contract, a seven-year award with a cumulative budget of more than $35 million. Our medical center has been a VTEU site for nearly 20 years. The contract also provides access to cutting edge vaccines and treatments for various infectious diseases with recent pathogens including novel H1N1 influenza and anthrax. The ongoing work of Bernstein and his group has brought significant recognition to Cincinnati Children's as a leader in infectious disease research.

Research Highlights
Margaret K. Hostetter, MD
Research in the Hostetter laboratory has expanded into three main areas. 1) Heparin binding motifs in *Candida albicans* and their role in biofilm. After publishing the 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. 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.

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 two 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 NIH, DMID-sponsored clinical trial that assessed the immunogenicity of the 13-valent pneumococcal vaccine in elderly adults. Dr. Brady also served as co-investigator for many clinical studies performed at the Gamble Program for Clinical Studies, Cincinnati Children’s Infectious Diseases Division. She assumed the position of Medical Director of the Ohio American Academy of Pediatrics Maximizing Office Based Immunization Program. She also became the contributing section editor for Infectious Diseases, American Academy of Pediatrics Grand Rounds publication.

Rhonda D. Cardin, PhD
The Cardin lab focuses on Cytomegalovirus (CMV) latency and pathogenesis of CMV infection. We previously showed that the viral chemokine receptor M33 encoded by murine CMV (MCMV) is required for long term latent infection. With our collaborators, Dr. Helen Farrell in Australia and Dr. Marie-Dominique Filippi at Cincinnati Children’s, we have 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. We have 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 in our division and as part of the NIH antiviral program, we are 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. As part of the antiviral program, we are characterizing several promising new anti-CMV drugs in the MCMV model since there is a continued need for less toxic anti-CMV drugs. Lastly, we are currently evaluating 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. Dr. Connelly led the institutional initiative to bring hand hygiene to the forefront of all clinical activities of the institution. This translates into efforts to change the culture of Cincinnati Children’s and make the performance of hand hygiene the default for all clinical activities. Other areas of focus for Dr. Connelly included collaborations with hematology/oncology to understand and reduce mucosal barrier related blood infections and collaborations with surgical subspecialties to reduce surgical site infections. Collaborative work to understand the opportunities for preventive strategies along the surgical continuum of care in orthopaedic, cardiovascular and neurosurgery are ongoing. The year was punctuated by pertussis and mycormycosis. During a period of moderate community pertussis activity, a
patient in the cardiac intensive care unit developed pertussis that went unrecognized for more than a week. Epidemiologic investigation uncovered five CICU staff members with confirmed pertussis. Beyond the index patient, patient cases and additional staff cases were averted through timely chemoprophylaxis. Invasive mucormycosis occurred in multiple immunocompromised patients over a four month period, an uncommon event in our patients. An extensive investigation failed to identify a source but raised concern regarding adequacy of construction containment operations. Dr. Connelly worked closely with staff to evaluate strategic risk-assessments, surveillance activities and mitigation strategies to minimize potential risk of the introduction of environmental pathogens into our patient care areas. The result is a new enhanced surveillance program and enhanced collaborative efforts with 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 funded by the National Institute of Allergy and Infectious Diseases. 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. In addition, in collaboration with the VTEU and the solid organ transplant teams, a study to evaluate HPV vaccination in adolescents after SOT is proposed. A focus on quality improvement has led to the development of Evidence-Based Guidelines for the prevention of cytomegalovirus at CCHMC and to significant improvements in pre-transplant infectious disease risk assessment.

Michelle P. Dickey, MS, CRNP

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.

Tibor Farkas, PhD, DVM

In 2013, Dr. Farkas and his lab continued their studies on the recovirus/macaque cell culture and animal model development for human norovirus gastroenteritis. They demonstrated that the recovirus model is able to represent not only the biological features of the human noroviruses but it is the only current model with human norovirus-like biological diversity. An extreme serotypic diversity of enteric caliciviruses has been demonstrated for the first time that certainly will be a major challenge for vaccine design (J Gen Virol., 2014). Significantly higher rate of recovirus neutralizing antibodies against three different serotypes were detected in zookeepers than in the general population, further indicating the zoonotic potential and possible public health importance of recoviruses (J Clin Microbiol., 2014). As part of a collaborative project a comprehensive comparison of cultivable norovirus surrogates in response to different inactivation and disinfection treatments was reported, showing that Tulane virus and MNV are the best candidates to study public health outcomes of norovirus infections (Appl Environ Microbiol. 2014). In collaboration, the recovirus surrogate model was also evaluated in oyster bioaccumulation studies, resulting very similar bioaccumulation patterns to human noroviruses. All these, further indicates the extreme potential of our model as a human norovirus surrogate.
system. In addition we also participated in a study developing a novel human astrovirus sub-classification system (Arch Virol. 2014).

Robert W. Frenck, MD

Dr. Frenck, along with Dr. David Bernstein, successfully re-competed the VTEU contract which will continue through 2024 at an estimated value of $951 million. Dr. Frenck initiated a Phase I study funded by DMID to evaluate a vaccine against Shigella sonnei. The study has completed four of the planned five cohorts with the remaining cohort on schedule to be finished by late 2014.

Dr. Frenck has been asked by DMID to develop the protocol and conduct a study to evaluate the dose response curve of infection with norovirus. The protocol has been completed with a target to enroll the first cohort by the end of the calendar year.

Dr. Frenck was the lead investigator for a Phase II S. aureus vaccine. The results of the trial were presented by Dr. Frenck at the European Congress of Microbiology and Infectious Diseases (ECMID).

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

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.

Nancy 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. They 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 HGBA and sialic acids in attempt to cultivate NVs in vitro. For rotavirus, they have expended 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. In addition, they are actively
involved in development and evaluation of a vaccine against NVs and RVs. Specifically they have participated in a vaccine trial on a divalent recombinant VLP vaccine against NVs using the human volunteer challenge model developed in our group. They also demonstrated that their P particle based vaccine is effective in inducing immune response and protection against viral challenge in a gnotobiotic pig model in collaboration with Virginia Tech. Finally, their collaboration with OSU on evaluation of influenza (M2e) vaccine is going well.

Monica M. McNeal, MS

Ms. McNeal is the associate director for the Laboratory for Specialized Clinical Studies which provides lab support for a large number of clinical studies involving vaccine trials and vaccine development. Influenza virus vaccines and rotavirus vaccines continue to be important for overall health of children in the US and around the world. The lab is committed to help establish clinical labs in India and China to support rotavirus vaccine trials in those countries. In addition, the lab consults with other labs around the world to provide training and support for establishing quality assays to support vaccine trials. Additional projects include using animal models to investigate the effects of malnutrition on oral rotavirus vaccines, establish assays to detect Pneumococcal pneumonia and assays to quantitate norovirus shedding in immunocompromised patients.

Ms. McNeal has continued to support rotavirus vaccine trials conducted in numerous countries around the world in association with nonprofit organizations and industrial sponsors. The lab continues to support the development of non-living rotavirus vaccines by developing and validating assays for the clinical trials. Ms. McNeal continues to support the clinical trials run by the Gamble program by establishing new assays and providing laboratory support.

Joseph E. Qualls, PhD

Research in the Qualls laboratory 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 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 \textit{M. bovis} BCG and \textit{M. tuberculosis} infection \textit{in vivo}. 1) One project under review for NIH-R01 funding 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 \textit{in vitro} and \textit{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 \textit{in vitro}, the contribution of L-citrulline on T cell function \textit{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 \textit{in vivo} are underway.

Nancy M. Sawtell, PhD

Most of the human population world-wide has been infected by herpes simplex viruses. 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. A new project recently funded by NASA seeks to determine the effect of deep space (cosmic) radiation on damage induced in the brain by latent HSV. These studies will define risks to astronauts and may model HSV induced CNS damage (potentially increasing dementia risks) occurring in the aging population.

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 vaccines compared to pneumococcal controls for at least six months postpartum. She also demonstrated that greater exclusivity of breastfeeding in the first six 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 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 of Cellular and Molecular Immunology 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 immunologic responses to immunization in breast milk with Cincinnati Children’s Vaccine and Treatment Evaluation Unit (VTEU).

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 last year included the effectiveness of rotavirus vaccines, pre- and post-licensure costs of rotavirus disease, epidemiology of norovirus infections in children and the epidemiology and disease burden of RSV.

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. This past year, the first study in this area was published in collaboration with researchers from the Neuroimaging Center and the Division of Physical Medicine and Pediatric Rehabilitation. This study examined functional magnetic resonance imaging and language function in Eastern European and Chinese adoptees.

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. A number of papers have been published in the past year. His research outcomes provide valuable data and strategies for future development of vaccine and antivirals against norovirus and other infectious pathogens.

Sing Sing Way, MD PhD
Dr. Way's group has continued ongoing investigation on the immune pathogenesis of perinatal and persistent infections. Results from publications in the past year 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. In turn, this physiological active immune suppression within newborn infants also makes them susceptible to disseminated infection with perinatal pathogens including Listeria monocytogenes and Escherichia coli. Other related publications address fundamental 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**

Dr. Sean Moore from the Division of Gastroenterology, together with Infectious Disease colleagues Monica McNeal and Dr. David Bernstein, showed that protein malnutrition alters IgA responses to rotavirus

Dr. Lara Danziger-Isakov, and colleagues from the international CMV consensus group, presented updated international consensus guidelines on the management of cytomegalovirus in solid organ transplantations.


Michelle Dickey and Dr. Mary Staat published an innovative clinical review of infectious complications of intrathecal baclofen pump devices in a pediatric population.


Dr. Elizabeth Schlaudecker, along with senior colleagues Dr. Mark Steinhoff and Monica McNeal, published a study of IgA and neutralizing antibodies to influenza A virus in human milk: A randomized trial of antenatal influenza.


Dr. Sing Sing Way was the senior author on a highly quoted publication "Immunosuppressive CD71+ erythroid cells compromise neonatal host defence against infection". The paper was published in *Nature* and was highlighted in more than 200 radio, television, and newspaper announcements.

Division Publications

14. Ertelt JM, Buyukbasaran EZ, Jiang TT, Rowe JH, Xin L, Way SS. *B7-1/B7-2 blockade overrides the activation of protective CD8 T cells stimulated in the absence of Foxp3+ regulatory T cells.* *J Leukoc Biol.* 2013; 94:367-76.
regulatory T cells, bona fide memory or maintenance by antigenic reminder from fetal cell microchimerism?. Chimerism. 2014; 5:16-9.


Faculty, Staff, and Trainees

Faculty Members

**Margaret K. Hostetter, MD**, Professor

**Leadership** Director, Division of Infectious Diseases; Albert Sabin Professor of Pediatrics

**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
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, Associate Professor
Leadership Director, Transplant ID
Research Interests Transplantation, immunocompromised hosts, respiratory viruses, vaccines

Michelle P. Dickey, MS, CRN, Instructor
Leadership Manager, Gamble Program
Research Interests Clinical vaccine trials

Tibor Farkas, DVM, PhD, MBA, Assistant Professor
Research Interests Human and animal enteric viral infections

Robert W. Frenck, MD, Professor
Leadership Chairman, Institutional Review Board; Director of Clinical Medicine
Research Interests Vaccines, enteric diseases

David B. Haslam, MD, Associate Professor
Leadership Director, Antimicrobial Stewardship Program
Research Interests Clostridim 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, Instructor
Leadership Associate Director, LSCS
Research Interests Rotavirus, influenza and Shigella vaccine research

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

Way Sing Sing, 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)
Research Interests Health services research, community infections

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

Clinical Staff Members
- Samantha Blum, RN,
  ID Transplant Clinic
- Andrea Bohlen, MSW, LISW-S,
  International Adoption Center
- Cathy Boyce, RN,
  OPAT Clinic, International Adoption Center
- Kelly Hicks, RN, MSN,
  International Adoption Center
- Tisha Way, MSSA, LISW-S,
  International Adoption Center

Trainees
- Kevin Downes, MD, PL-6, University of Pennsylvania
- Andrea Hahn, MD, PL-6, Ohio State University
- Heidi Andersen, MD, PL-4, Indiana University
Division Collaboration

Collaboration in the identification of the latent CMV infected cells in the bone marrow. (Rhonda Cardin, PhD)

Experimental Hematology & Cancer Biology - Stem Cell Biology » Marie-Dominique Filippi, PhD

Collaboration in the analysis of hearing loss in the guinea pig CMV models characterized by Drs. Bernstein and Cardin (David Bernstein, MD, MS, Rhonda Cardin, PhD)

Otolaryngology » Daniel Choo, MD

Collaboration on the role of regulatory T cell in control of murine CMV infection. (Rhonda Cardin, PhD)

Immunobiology » David Hildeman, PhD and Clare Chougnet, PhD

Collaboration on a project involving chronic shedding of norovirus and the effects on shedding after treatment with breast milk. For this project we established a quantitative real-time PCR assay developed by the CDC in our lab and will quantify norovirus shedding before and after treatment. (Monica McNeal, MS)

Bone Marrow Transplantation and Immune Deficiency Division » Javier El-Bietar, MD and Stella Davies, MBBS, PhD, MRCP

Collaboration on a project that will involve determining the organisms that are responsible for community acquired pneumonia in children. (Monica McNeal, MS)

Emergency Medicine » Todd Florin, MD, MSCE

Hospital Medicine » Lilliam Ambroggio, PhD

Collaboration on a project to generate a mouse model of environmental enteropathy to study rotavirus vaccines. (Monica McNeal, MS)

Collaboration with Dr. S. Moore in the development of a malnourished mouse model for evaluation of rotavirus vaccines. (David Bernstein, MD, MA)

Gastroenterology, Hepatology and Nutrition » Sean Moore, MD

Collaboration on a project using the animal model of rotavirus induced Biliary Atresia to determine the mechanism of the disease. (Monica McNeal, MS)

Pediatric General and Thoracic Surgery » Greg Tiao, MD

Collaboration on the integrated solid organ transplant (ISOT)–performed evidence-based guideline development for the prevention of cytomegalovirus in conjunction with liver (Rohit Kohli, John Bucuvalas), kidney (Jens Goebel), heart (Chesney Castleberry), lung (Marc Schecter) and small bowel (Sam Kocoshis) teams. (Lara Danziger-Isakov, MD)

Pediatric Liver Care Center » John Bucuvalas, MD

Gastroenterology, Hepatology, and Nutrition » Rohit Kohli, MBBS, MS
Collaboration on SPLIT survey in CMV prevention in conjunction with John Bucuvalas in Liver Transplantation. (Lara Danziger-Isakov, MD)

**Pediatric Liver Care Center** » John Bucuvalas, MD

Collaboration with Dr. Setchell on small molecule mass spectrometry, Dr. Setchell is identifying and quantifying the downstream metabolites generated from imported L-citrulline in macrophages. These findings help define the utilization of L-arginine derived from L-citrulline, its contribution during anti-pathogen macrophage function, and developing L-citrulline as a potential therapeutic during mycobacterial disease. (Joseph Qualls, PhD)

**Mass Spectrometry Lab** » Ken Setchell, PhD

Collaboration with Dr. Deepe’s laboratory and is performing preliminary studies infecting mouse macrophages with *Histoplasma capsulatum* in varying L-arginine and L-citrulline environments to assist in determining the contribution of L-citrulline on macrophage-mediated protection from this fungus. (Joseph Qualls, PhD)

**Internal Medicine and Infectious Diseases, University of Cincinnati College of Medicine** » George Deepe, MD

Collaboration with Dr. Greis in utilizing peptide mass spectrometry. Dr. Greis is analyzing the incorporation of the L-citrulline carbon backbone into newly synthesized protein in macrophages. These findings support the potential for L-citrulline as an immune-stimulating supplement during intracellular pathogenesis. (Joseph Qualls, PhD)

**Cancer Biology at the University of Cincinnati, Proteomics and Mass Spectrometry** » Ken Greis, PhD

Continued collaboration with Drs. Black, Huggins and Mina as part of CCHMC’s membership in the CDC Clinical Immunization Safety Assessment network. (Rebecca Brady, MD)

**Rheumatology** » Jennifer Huggins, MD and Rina Mina, MD

**Global Child Health Center** » Steve Black, MD

Collaboration with Dr. Cohen MD in the conduct of a clinical trial that assessed the safety and efficacy of a candidate oral cholera vaccine. (Rebecca Brady, MD)

**Gastroenterology, Hepatology and Nutrition** » Mitchell Cohen, MD

Collaboration with Dr. Waggoner in the writing of the human subject portions of a grant to study the role of natural killer cells in the destruction of activated helper CD4 cells. This grant was funded as an Avant-Garde Award for HIV/AIDS Research from the National Institute on Drug Abuse, NIH. (Rebecca Brady, MD)

**Center for Autoimmune Genomics and Etiology (CAGE), Division of Rheumatology** » Stephen Waggoner, PhD

Collaboration with Dr. Meller to study norovirus capsid as target of antiviral drugs, funded by a joint NIH R21. (Ming Tan, PhD)

**Biomedical Informatics** » Jaroslaw Meller, PhD
Collaboration with Dr. F. Finkelman on IgG isotype and cytokine analysis after influenza immunization in pregnant women. (Elizabeth Schlaudecker, MD, MPH)

**Cellular and Molecular Biology** » Fred Finkelman, MD

Collaboration with Dr. M. Williams to determine the acute and long term outcomes of simulated deep space radiation exposure on latent viral CNV infection and CNS pathology. (Nancy Sawtell, PhD)

**Neurology** » Michael Williams, PhD

Collaboration with Dr. A. Morrow under the human milk grant. (Tibor Farkas, PhD, DVM)

**Section of Neonatology, Perinatal and Pulmonary Biology** » Ardythe Morrow, PhD

Collaboration with Dr. M. Barnes on the evaluation of recovirus zoonosis. (Tibor Farkas, PhD, DVM)

**Rheumatology** » Michael Barnes PhD

Collaboration with Dr. J. Schaffzin (Place Award – Surgical Site Infection Prevention Continuum) in the development of the care continuum. (Beverly Connelly, MD)

**Hospital Medicine** » Joshua Schaffzin, MD, PhD

Collaboration with Dr. J. Meller on studies in characterization of virus-host interaction and viral capsid assembling of human noroviruses to develop strategy to control and prevent norovirus infection. (Jason Jiang, PhD, Ming Tan, PhD)

**Environmental Health, UC** » Jarek Meller, PhD

Collaboration with Dr. A. Morrow in a study on human milk for viral ligands as potential decoy receptors for human norovirus and rotavirus as potential antivirals against these viruses. (Jason Jiang, PhD)

**Section of Neonatology, Perinatal and Pulmonary Biology** » Ardythe Morrow, PhD

Collaboration with Drs. J. Harley and K. Kaufman of CAGE to perform exome sequencing of parent/child trios for de novo mutations that contribute to disseminated staphylococcal osteomyelitis. De novo mutations identified in the first two trios implicated a new pathway for osteomyelitis susceptibility. (Margaret Hostetter, MD)

**Center for Autoimmune Genomics and Etiology (CAGE)** » John Harley, MD, PhD and Ken Kaufman, PhD

Collaboration with Dr. S. Wells on conducting in vitro studies of the biology of disseminated staphylococcal osteomyelitis. (Margaret Hostetter, MD)

**Cancer and Blood Diseases Institute** » Susanne Wells, PhD

Collaboration with Drs. J. Lu. R. Ittenbach and A. Porollo to identify heparin binding motifs in several pathologic microorganisms and their structural correlates. (Margaret Hostetter, MD)

**Biomedical Informatics** » Jason Lu, PhD and Richard Ittenbach, PhD

**Center for Autoimmune Genetics and Etiology** » Alexey Porollo, PhD

Collaboration with Dr. K. Greis to identify proteins released from the surface of *Candida albicans* after treatment with heparin. (Margaret Hostetter, MD)

**Proteomics and Mass Spectroscopy,** » Ken Greis, PhD
Collaboration with Dr. R. Ittenbach on the development of protocols researching understanding of informed consent and assent in clinical research. (Michelle Dickey, MS, CRNP)

**Biostatistics and Epidemiology** » Richard Ittenbach, PhD

Collaboration with Dr. L. Widdice on two NIH VTEU projects; HPV and Bacterial Vaginosis. (Michelle Dickey, MS, CRNP)

**Adolescent and Transition Medicine** » Lea Widdice, MD

Co-investigator with Dr. Widdice on a VTEU project to assess the impact of off schedule HPV vaccination. (David I. Bernstein, MD, MA)

**Adolescent and Transition Medicine** » Lea Widdice, MD

Co-investigator successfully recompeted Dr. Kahn's R0-1 evaluating the effect of HPV vaccination on circulating strains of HPV: Behavioral and Virologic Impact of HPV Immunization. (David I. Bernstein, MD, MA)

**Adolescent and Transition Medicine** » Jessica Khan, MD

Collaboration with Dr. M. Cohen on developing a cholera vaccine study. (Michelle Dickey, MS, CRNP)

**Gastroenterology, Hepatology and Nutrition** » Mitchell B. Cohen, MD

Collaboration with Dr. S. R Geraghty on the recruitment of pediatric participants from the CCHMC Pediatric clinics for inclusion in clinical vaccine trials. (Michelle Dickey, MS, CRNP)

**General and Community Pediatrics** » Sheela Rath Geraghty, MD, MS, IBCLC, FAAP

Collaboration with Dr. D. Kinnett on a research study examining the infectious complications of intrathecal baclofen pump devices in pediatrics. (Michelle Dickey, MS, CRNP)

**Physical Medicine and Rehabilitation** » Douglas G. Kinnett, MD

Collaboration with Dr. J. Heubi on the development of protocols researching understanding of informed consent and assent in clinical research. (Michelle Dickey, MS, CRNP)

**Center for Clinical and Translational Science and Training (CCTST)** » James Heubi, MD

Collaboration with Rebecca Harper, RN, MSN on the development of a Research Participant Advisory Group for CCHMC. (Michelle Dickey, MS, CRNP)

**Center for Clinical and Translational Science and Training (CCTST)** » Rebecca Harper, RN, MSN

Collaboration with Michael Zender and Todd Timney on the development of protocols researching understanding of informed consent and assent in clinical research. (Michelle Dickey, MS, CRNP)

**Design, Art, Architecture and Planning Program (DAAP) – University of Cincinnati** » Michael Zender and Todd Timney

### Grants, Contracts, and Industry Agreements

**Grant and Contract Awards**

<table>
<thead>
<tr>
<th>Grant and Contract Awards</th>
<th>Annual Direct</th>
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BERNSTEIN, D
<table>
<thead>
<tr>
<th>Project Title</th>
<th>Institution</th>
<th>Start Date</th>
<th>End Date</th>
<th>Funding</th>
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<tr>
<td>The Natural History of CMV-Related Hearing Loss</td>
<td>National Institutes of Health(University of Alabama-Birmingham)</td>
<td>06/12/12</td>
<td>12/12/14</td>
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<td>Vaccine and Treatment Evaluation Units (VTEU).</td>
<td>National Institutes of Health</td>
<td>09/16/13</td>
<td>09/15/23</td>
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<td>Vaccine and Treatment Evaluation Units (VTEU):</td>
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<td>VRC701/702</td>
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<td>05/15/12</td>
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<td>CARDIN, R</td>
<td>Role of Viral Chemokine Receptors in Cytomegalovirus Latency</td>
<td>07/05/12</td>
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<td>DANZIGER, I</td>
<td>B-Cell Targeted Induction to Improve Outcomes in Pediatric Lung Transplantation</td>
<td>03/01/13</td>
<td>02/28/18</td>
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<td>DOWNES, K</td>
<td>Urinary Biomarkers for Aminoglycoside-Associated Acute Kidney Injury in Cystic Fibrosis</td>
<td>10/01/12</td>
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<td>HASLAM, D</td>
<td>Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease</td>
<td>06/01/12</td>
<td>05/31/17</td>
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<td>HOSTETTER, M</td>
<td>Balance of Th17 Cells and Regulatory T Cells in Candidal Vaginal Colonization in Pregnant Macaques and Humans</td>
<td>10/05/12</td>
<td>09/30/15</td>
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<td>Inactivation of Enteric Foodborne Viruses in High Risk Foods by Non-Thermal Processing Technologies</td>
<td>US Department of Agriculture (University of Delaware)</td>
<td>2011680033005</td>
<td>02/01/11-11/31/16</td>
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<td>Newcastle Disease Virus Vectored Vaccines for Norovirus</td>
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<td>Novel Vaccine Against Norovirus</td>
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<td>Universal Flu Vaccine by a Norovirus P Particle Platform</td>
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<td>2013-67015-20476</td>
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<td>The Role of Human Milk in Infant Nutrition and Health</td>
<td>National Institutes of Health</td>
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<td>Advancing Rotavirus Vaccine Development</td>
<td>Bill &amp; Melinda Gates Foundation (PATH Vaccine Solutions)</td>
<td>GAT.1334-06712-CRT</td>
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<td>Receptor Mimics for Rapid Detection, Typing, and Susceptibility Testing</td>
<td>National Institutes of Health (University of Cincinnati)</td>
<td>R01AI 089450</td>
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<td>Acute and Long Term Outcomes of Simulated Deep Space Radiation Exposure on Latent Viral CNS Infection and CNS Pathology</td>
<td>National Aeronautics and Space Administration</td>
<td>NNX13AO47G</td>
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<td>HSV Latency and Reactivation and the Novel Neuronal Regulation of VP16 In Vivo</td>
<td>National Institutes of Health</td>
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<td>Enhanced Surveillance for New Vaccine Preventable Disease-Patient Protection-ACA</td>
<td>Centers for Disease Control and Prevention</td>
<td>U01IP 000458</td>
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<td>Receptor Mimics for Rapid Detection, Typing, and Susceptibility Testing</td>
<td>National Institutes of Health (University of Cincinnati)</td>
<td>R01AI 089450</td>
<td>05/15/10-04/30/15</td>
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**CD4 T Cells with Specificity to Noninherited Maternal Antigen**  
National Institutes of Health  
R21 AI 112186  
01/20/14-12/31/15  
$125,000

**Investigators in the Pathogenesis of Infectious Disease Award**  
Burroughs Wellcome Foundation (University of Cincinnati)  
10/01/12-09/30/17  
$100,000

**Regulatory T Cells Dictate Immunity During Persistent Salmonella Infection**  
National Institutes of Health  
R01 AI 087830  
09/06/12-04/30/15  
$247,500

**The Immune Pathogenesis of Prenatal Listeria Monocytogenes Infection**  
National Institutes of Health  
R01 AI 00934  
09/06/12-06/30/17  
$281,307

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<td>Genocea Biosciences, Inc</td>
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<td>LigoCyte Pharmaceuticals, Inc</td>
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<tr>
<td>Pfizer, Inc</td>
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<tr>
<td>Vaxart Inc</td>
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<td>Sanofi Pasteur Biologics LLC</td>
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<td>Nanobio Corporation</td>
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<td>Pfizer, Inc</td>
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<tr>
<th><strong>HOSTETTER, M</strong></th>
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<tr>
<td>Allergen Research Corporation</td>
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<td>LigoCyte Pharmaceuticals, Inc</td>
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<tr>
<td>GlaxoSmithKline</td>
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<tr>
<td>PATH Vaccine Solutions</td>
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<td>Merck &amp; Company, Inc</td>
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<td>Sanofi Sythelabo</td>
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<td>Massachusetts General</td>
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<td>Genocea</td>
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**Current Year Direct**  
$7,632,936
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<tr>
<th>Company</th>
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<tr>
<td>Gilead Sciences, Inc</td>
<td>$231,112</td>
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<tr>
<td>Ortho-Clinical Diagnostics, Inc</td>
<td>$168,667</td>
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<tr>
<td><strong>Current Year Direct Receipts</strong></td>
<td><strong>$2,295,604</strong></td>
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<td><strong>Total</strong></td>
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