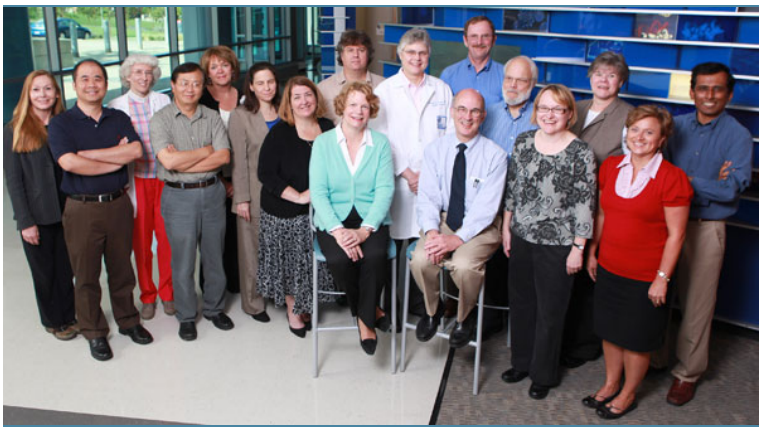
Infectious Diseases

Division Photo



Seated: Margaret K. Hostetter (incoming ID Director), Michael Gerber

Standing left to right: Nancy Sawtell, Ming Tan, Rebecca Brady, Jason Jiang, Nancy Hutchinson, Jane Strasser, Mary Staat, Tibor Farkas, Beverly Connelly, Robert Frenck, Mark Steinhoff, Rhonda Cardin, Monica McNeal, Michelle Dickey, Ramu Subbramaninan

Not Pictured: David I. Bernstein (Director), Richard Ward

Division Data Summary

Research and Training Details	
Number of Faculty	19
Number of Joint Appointment Faculty	2
Number of Research Fellows	4
Number of Support Personnel	97
Direct Annual Grant Support	$2,197,716
Direct Annual Industry Support	$2,552,663
Peer Reviewed Publications	40
Clinical Activities and Training	
Number of Clinical Staff	6
Number of Clinical Fellows	4
Inpatient Encounters	1410
Outpatient Encounters	1,361

Significant Publications

Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW Jr, Palmer AL, Ahmed A, Michaels MG, Sánchez PJ, Bernstein DI, Britt WJ, Fowler KB. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA. 2010 Apr 14;303(14):1375-82. PubMed PMID: 20388893.

Cytomegalovirus (CMV) is the most common cause of congenital infections around the world. Infection of the pregnant women can lead to infection of the fetus who may appear healthy at birth but later develop significant hearing loss. Therefore there has been considerable interest in developing a newborn screening test for CMV.

Because dried blood spots (DBS) are routinely collected from newborns to screen for metabolic disease it has been proposed as the best screening source for congenital CMV. As part of an NIH funded contract, over 20,000 infants born at 7 US medical centers had saliva and DBS collected and tested for CMV. Congenital CMV infection was confirmed in 92 infants (0.45%). Unfortunately, although the specificity of the DBS assay using real-time PCR was good the sensitivity was only between 28.3 and 34.4% compared to saliva. We therefore concluded that CMV testing with DBS real-timePCR compared with saliva rapid culture had limited value as a screening test. Effortsare now concentrating on using saliva and real-time PCR assays to test for congenital CMV.

Bernstein DI, Reap EA, Katen K, Watson A, Smith K, Norberg P, Olmsted RA, Hoeper A, Morris J, Negri S, Maughan MF, Chulay JD. Randomized, double-blind, Phase 1 trial of an alphavirus replicon vaccine for cytomegalovirus in CMV seronegative adult volunteers. Vaccine. 2009 Dec 11;28(2):484-93. Epub 2009 Oct 24. PubMed PMID: 19857446

Cytomegalovirus (CMV) infections are common and can produce significant health problems in the immunocompromised and as a congenital infection. Therefore there has been a great interest in developing a CMV vaccine. In this report we evaluated, for the first time, an alphavirus replicon vaccine that expresses three of the most important CMV immunogens gB, pp65 and IE1. We enrolled 40 healthy CMV seronegative adults in a randomized, double-blind Phase 1 clinical trial. Subjects received either a lower dose (LD) or higher dose (HD) of vaccine or placebo by intramuscular or subcutaneous injection at Weeks 0, 8 and 24. The vaccine was well tolerated, with mild to moderate local reactogenicity, minimal systemic reactogenicity, and no clinically important changes in laboratory parameters. All vaccine recipients developed both T cell responses to CMV antigens as measured by γ interferon ELISPOT assays as well as neutralizing antibodies. Polyfunctional CD4(+) and CD8(+) T cell responses including γ interferon, TNF alpha and IL-2 were detected by polychromatic flow cytometry. This alphavirus replicon particle vaccine was safe and induced neutralizing antibody and multifunctional T cell responses against three CMV antigens that are important targets for protective immunity. Continued evaluation of this novel approach to vaccination is warranted.

Cardin RD, Schaefer GC, Allen, J R, Davis-Poynter NJ, Farrell HE. The M33 chemokine receptor homolog of murine cytomegalovirus exhibits a differential tissue-specific role during in vivo replication and latency. J Virol, 2009, 83, 7590-601.

Human Cytomegalovirus (HCMV), a b-herpesvirus, is a ubiquitous pathogen that asymptomatically infects humans but is life-threatening to immunocompromised individuals, such as neonates, AIDS patients, and transplant patients, following primary infection or reactivation from latency. Very little is known about the viral/host interactions governing the establishment and maintenance of long term latent HCMV infection. HCMV employs multiple mechanisms which contribute to HCMV persistence in the host, including four CMV-encoded CC chemokine receptor homologs (UL33, UL78, US28, and US27). We evaluated the role of M33, a viral chemokine receptor encoded by murine CMV (MCMV), during infection of mice with wild type virus and a M33 mutant virus in order to identify a role for M33 in CMV pathogenesis and latency. Our results show that M33 functions in a tissue specific manner during MCMV infection of mice and is important during primary infection and also during latency. In particular, M33 is required for virus replication in the salivary glands, spleen, and pancreas, but not the lungs. Significantly, we demonstrate that M33 is required for latent infection in the spleen, lungs, and bone marrow of infected mice. This is the first CMV gene to be identified which plays a role in long term latent infection and increases our understanding of CMV chemokine receptor mimicry during infection. Further studies may lead to the development of therapeutic strategies aimed at controlling long term latent CMV infection, especially in the immunocompromised individual.

Farkas T, Cross RW, Hargitt E 3rd, Lerche NW, Morrow AL, Sestak K. Genetic Diversity and Histo-Blood Group Antigen Interactions of Rhesus Enteric Caliciviruses. J Virol, 2010.

In this publication we reported the isolation of 58 novel caliciviruses from rhesus macaque stool samples collected from the Tulane National Primate Research Center. 57 of the isolates were recovirus and one norovirus. The recoviruses could be classified into four genetic types within two genogroups, indicating that the genetic diversity of recovirus is similar to that of human noroviruses. The rhesus norovirus isolate grouped closely to GII human noroviruses. Testing of serum samples collected from animal caretakers reveled that over 80% contained Tulane virus neutralizing antibodies. Both in vitro saliva and synthetic oligosaccharide binding assays showed that the prototype Tulane virus binds to blood type A and B structures. This was confirmed by showing that type A and B saliva samples blocked Tulane virus replication. From these results our working hypothesis is that HBGA are possibly the co-receptors and a yet unknown cell surface molecule(s) acts as entry receptor during recovirus infection. The many similarities between recoviruses and human noroviruses, suggest that these monkey viruses will be extremely useful for studying the molecular virology and immunology of human noroviruses. We are currently focusing on the development of animal and tissue culture models that will mimic the diversity (genetic, antigenic and HBGA binding) of the uncultivable human noroviruses.

Mast TC, Walter EB, Bulotsky M, Khawaja SS, DiStefano DJ, Sandquist MK, Straus WL, Staat MA. Burden of childhood rotavirus disease on health systems in the United States. Pediatr Infect Dis J, 2010, 29, e19-25

Before the widespread use of rotavirus vaccine, it was important to determine the burden and costs of medically-attended rotavirus disease. Using our active surveillance system for acute gastroenteritis (AGE) we enrolled nearly 2,000 children and found 44% to have rotavirus. The proportion of children with rotavirus varied by hospital setting; 38% of hospitalized, 60% of short-stay visits (< 24 hour hospitalization), 49% of emergency department visits and 37% seen in the outpatient clinic were found to be rotavirus positive. During the rotavirus season, the overall proportion of AGE cases due to rotavirus was even higher with rotavirus accounting for 56% of all AGE cases. The VP7 genotypes identified were G1, 79%; G2, 14%; G3, 5%; G9, 1%; and G12, 1%. For children hospitalized with rotavirus, the estimated median direct cost was $4,565, the average length of stay was 1.9 days, and parents lost 3.4 days of work. For short-stay, emergency department, and outpatient visits, the estimated median costs were $3,160, $867, and $75, respectively. We therefore concluded that before the licensure and use of rotavirus vaccines in the United States, rotavirus was prevalent among children treated in hospital-based and outpatient settings and was associated with a substantial proportion of pediatric medical visits for AGE thus incurring a significant financial burden. The introduction of rotavirus vaccines, including Rotarix, the one developed at CCHMC should have a significant impact on the health of children, also affecting the cost and utilization of health care resources.

Division Highlights

David I. Bernstein, MD, MA

Two important clinical trials that I have participated in over the past 5-10 years reached major milestones. In May the Endpoint Committee which I served on for the HERPEVAC trial, evaluating a herpes simplex virus (HSV) vaccine in 8,000 young women, completed its evaluation while in July the CMV vaccine study I have lead completed enrollment. Also in regards to herpesviruses, we completed a trial using a new approach to vaccines, Alpha virus vectored vaccines. We showed that an alphavirus replicon vaccine for CMV induced antibody and T cell mediated immunity establishing this approach as a leading candidate for a much needed CMV vaccine. Using our animal models, significant advances for antiviral and vaccines against HSV and CMV were also made. Regarding my other interest, gastrointestinal viruses, we completed the first trial of a norovirus vaccine while the rotavirus vaccine we developed was shown for the first time to be effective in Africa, one of the places it is needed most. Further this vaccine, Rotarix, was shown to prevent deaths due to diarrhea and dehydration in Mexico.

Rhonda D. Cardin, PhD

In 2009, my lab discovered that a viral chemokine receptor called M33 encoded by murine cytomegalovirus (CMV) plays a critical role in latency or long term infection. This is the first CMV gene to be identified for playing a role in latency. Current studies underway are determining the underlying mechanisms that M33 plays in latent infection. Also, in collaboration with Dr. David Bernstein, we developed and characterized a new HSV-2 shedding model in mice. We also performed several studies to evaluate HDP-CDV, a new cidofovir analog, in protecting against congenital CMV infection in pregnant guinea pigs and also in protecting newborn guinea pigs from guinea pig CMV infection. We also are in the process of characterizing a new anti-HSV drug in our neonatal HSV-2 guinea pig model. This new drug shows promise as a treatment for the devastating effects of HSV infection of newborn infants.

Beverly Connelly, MD

Beverly L. Connelly, M.D. and Nancy Hutchinson, M.S.N, C.I.C. have lead the infection prevention and control team in collaborative efforts throughout the medical center to reduce health care associated infections. The sustained reductions in ventilator-associated pneumonias (VAPs) have lead to a new focus on ventilator associated respiratory infections (VARIs) that will include less serious infections that drive antibiotic usage. These efforts are expected to decrease the risk of multi-drug resistance among pathogens in our critical care settings. Ongoing collaborations continue to reduce central venous catheter associated blood stream infections, have made substantial improvements this year in our bone marrow transplant population. Collaborative efforts to reduce surgical site infections have extended beyond CCHMC to a statewide collaborative (Solutions for Patient Safety) to reduce risks for all pediatric surgical patients. Focused first on device related procedures (VP shunts, spinal fusions, and open heart surgery) these efforts will bring evidence based preventive strategies to all children in Ohio. Participation in other state wide collaboratives such as the Ohio Hospital Association surveillance program for Clostidium difficile contribute to a better understanding of pathogens in pediatrics.

In addition to improvement efforts, the infection prevention and control program was challenged by pandemic influenza. The IPC program partnered with Emergency Management, Health and Safety, Employee Health, Diagnostic Microbiology, Outpatient Services among others, to provide timely information to all healthcare providers at CCHMC. These efforts were a natural extension of the leadership of Dr. Connelly to prevent influenza in patients, families and staff through aggressive immunization campaigns and programs which reached out to more than 80% of our high risk patients through the "Flu Collaborative" and resulted in > 98% of CCHMC employees receiving influenza vaccine.

Tibor Farkas, PhD, DVM, MBA

We continued our research on rhesus enteric caliciviruses focusing on animal and tissue culture model development. Our ongoing research demonstrated that calicivirus infections are common in non human primates (NHP) with the

potential for interspecies transmission between humans and non-human primates (Farkas et al., JGV 2010; Farkas et al., JVI 2010). Moreover, we isolated over 60 rhesus enteric caliciviruses (recoviruses; prototype: Tulane virus) representing four different genotypes, showed antigenic relationship between recoviruses and human NoVs (cross reactive B-cell epitopes) and demonstrated that recoviruses bind to the same carbohydrate structures (histo-blood group antigens; HBGA) as human noroviruses (Farkas et al., JVI 2010). In recent NHP challenge studies with the prototype Tulane virus, challenged animals developed diarrhea and fever, seroconverted, shed the virus for 5-7 days post challenge. Tulane virus was also detectable in biopsies obtained from the small intestine. Since recoviruses can be adapted to tissue culture and are reverse genetics facile (Farkas et al., 2008; Wei et al., 2008) our present research focuses on developing recovirus tissue culture and animal models that represents the high diversity (genetic, antigenic and HBGA binding) of human noroviruses. These models will help us to address fundamental questions about immunity, host-virus interactions and virus replication strategies.

Michael A. Gerber, MD

Dr. Gerber was the local PI of an NIH-supported, multicenter, randomized Phase II study of an inactivated influenza H1N1 virus vaccine in infants, toddlers, children and adolescents. The study was designed to investigate the safety, reactogenicity, and immunogenicity of this vaccine when given concurrently with seasonal influenza vaccine or sequentially with (before or after) seasonal influenza vaccine. The 108 subjects enrolled at CCHMC represented over 20% of the total national enrollment.

Dr. Gerber is the overall PI of an NIH-supported study of the safety and immunogenicity of a full dose of trivalent inactivated influenza vaccine for children 6-36 months of age. This study was scheduled to begin in the fall of 2009. However, because of the novel H1N1 vaccine studies, work on this study was deferred. The plan is to begin this study in the late summer or early fall of 2010.

Dr. Gerber is the local PI of a Hoffmann-La Roche-sponsored that was scheduled to begin in early spring of 2010 but has been delayed until the fall.nThis study is a randomized, partially blinded, multi-center trial of the safety of Intravenous Oseltamivir for the treatment of influenza in patients aged >13 years.

Dr. Gerber is the overall PI of an NIH-supported investigation of Penicillin G Benzathine. The purpose of this study is to address the proper dose and frequency of administration of penicillin G benzathine needed to provide an adequate concentration of penicillin for strep prophylaxis in children and adolescents. The study is currently being reviewed by the FDA, and initiation is planned for later this year.

Jason Jiang, PhD

In the past year we have made significant advancements in understanding the epidemiology and evolution of human noroviruses (NVs) associated with the human histo-blood group antigen (HBGA) and herd immunity to NVs. This is a hot topic because of the increasing activity of a single genotype (GII-4) of NVs in the past decade. A number of studies suggested that host herd immunity plays an important role in NV evolution, resulting in immune evasion similar to influenza virus. Limited studies also showed that the antigenic variation may accompany HBGA receptor binding changes, leading to GII-4 variants with new receptor binding patterns. Our sequence analysis, however, showed that the receptor binding interfaces of NVs are highly conserved, indicating that the host HBGAs play an important role in NV evolution. To further address the questions, we performed a genetic and phenotypic characterization of GII-4 viruses circulating in the past two decades. We found that the HBGA receptor binding interfaces of all GII-4 NVs are also highly conserved and the binding patterns of GII-4 variants did not significantly change in the past decade. Significant levels of cross-reactive antigens among GII-4 viruses were detected by EIA, Western blot, and receptor binding/blocking assays. Genetic analysis did not identify a clear chronological order or ancestor/progeny relationships among different GII-4 variants. Our conclusions are that 1) The GII-4 may remain in colonial expansion stages, with multi-variants co-circulating in the same year or same epidemic seasons, 2) The increased epidemics of GII-4 may be a random fluctuation and 3) the ability of GII-4 recognizing all A, B and O secretor HBGAs may be the major reason for their predominance. We also believe that host immunity also plays a role in NV evolution but it was restricted by the HBGAs (a convergent factor in evolution) which allow only limited variation in adjacent regions to the HBGA receptor binding sites. This type of counter-selection theory is novel and will impact future studies on the epidemiology and evolution as well as vaccine development against NVs.

Monica M. McNeal, MS

The Laboratory for Specialized Clinical Studies, in conjunction with the VTEU sites, participated in the huge NIH effort to evaluate pandemic H1N1 vaccines. The lab was responsible for analyzing over 6000 serum specimens for influenza antibody. The lab was further involved in ongoing clinical evaluations of rotavirus and CMV vaccines. In addition, the lab has been very active in supporting clinical studies for Dr. Mark Steinhoff and Dr. Mary Staat in conjunction with the CDC and PATH.

New funding was awarded from three different NIH grants in collaboration with Dr. Carol de la Motte at the Cleveland Clinic, investigating Hyaluronan oligosaccharide regulation of microbial host defense of the intestine, with Allison Weiss and Dr Suri LIyer at the University of Cincinnati looking at Glycan receptor mimics for rapid detection, typing, and susceptibility testing of Influenza and with Dr. Jason Jiang at Cincinnati Children's investigating a novel vaccine against Norovirus.

Nancy M. Sawtell, PhD

Our continued efforts toward understanding the molecular mechanisms of herpes simplex virus latency and reactivation have led to a major new insight into this process. The practical significance of our findings is the identification of a novel drug target which, if exploited, has the potential to block viral reactivation at the earliest stages. This is important because many of the long term human health issues associated with HSV infection result from chronic inflammatory damage, for example to the eye, leading to blindness. We have also determined that latent HSV in the CNS is linked to significant CNS pathology which accrues over time and that the severity of this pathology is strongly influenced by host genetics. We are developing high throughput assays to screen for small molecule inhibitors of this target and Julianne Green, an ID fellow with a PhD in Organic Chemistry is collaborating on this project.

Mary A. Staat, MD, MPH

The International Adoption Center continues to conduct research to provide data to develop evidence-based guidelines for caring for internationally adopted children. The areas under study include examining the prevalence of acute and past hepatitis A infection, hepatitis B infection, hepatitis C infection, immunization verification and screening for tuberculosis and intestinal parasites. These studies provide important data to help policy-makers with decision-making about recommendations that will improve the standard of care for internationally adopted children.

The Epidemiology and Surveillance program has continued to monitor trends in vaccine preventable diseases such as rotavirus and influenza. Population-based surveillance has been conducted for each of these pathogens. For rotavirus, we are also conducting vaccine effectiveness studies to examine the impact of both rotavirus vaccines post-licensure.

Ming Tan, PhD

Dr. Tan's research focused on: 1) the development of norovirus (NV) P particles as a vaccine platform and 2) further elucidation of NV-host interactions. For the first goal, we have successfully constructed chimeric P particles containing rotavirus (RV) VP8 antigens. Animal trials showed that the P particle-VP8 chimeras had induced increased neutralizing antibody and protection against RV infection after immunization in mice compared to the free VP8 antigens. In addition, the vaccine induced blocking antibody against the NV-receptor interaction. These data demonstrated that the P particle is able to increase the immunogenicity of antigens and thus is an excellent platform for novel vaccine development against different pathogens. A manuscript and a patent application based these results have been submitted. For the second aim the histo-blood group antigen (HBGA) binding sites of a nonsecretor binding NV (VA207, GII.9) has been studied by crystallography. This study elucidated the crystal structure of the HBGA-binding site of a Lewis antigen binder and indicated that a nonsecretor-binding NV interacts with the HBGA receptor through the Lewis epitope (α-1,4, fucose) as the major interaction. This is unlike a secretor-binding norovirus (such as VA387, GII.4) that uses the H epitope (α-1,2, fucose) as the major interaction sugar. Our data provide valuable information that will lead to strategies for the development of vaccines and antivirals against norovirus and other infectious diseases.

Division Collaboration

Collaboration with Biostatistics and Epidemiology

Collaborating Faculty: Ardythe Morrow, PhD

Dr. Jiang is the PI of the Molecular Core and Viral Gastroenteritis project of the PO1 grant on the role of milk in infants' nutrition and health. He is also co-investigator of the NIH NEC grant of Dr. Morrow.

Collaboration with Neonatology

Collaborating Faculty: Kurt Schibler, MD

Dr. Jiang is collaborating on the NEC study.

Collaboration with Gastroenterology

Collaborating Faculty: Lee A. Denson, MD

Dr. Jiang is collaborating on a study related with human histo-blood group antigen expression in the intestinal tract.

Collaboration with UC, Environmental Health

Collaborating Faculty: Jarek Meller, PhD

Dr. Jiang is collarborating in structural and bioinformatic analysis of human norovirus capsid associated with HBGA recognition.

Collaboration with Neonatology and Pulmonary Biology

Collaborating Faculty: Kurt Schibler, MD

Dr. Bernstein is collaborating with Dr. Kurt Schibler in the study to determine the prevalence of congenital CMV and the burden of this disease on child health.

Collaboration with Pediatric Otolaryngology

Collaborating Faculty: Daniel Choo, MD

Drs. Bernstein and Cardin are working with Dr. Choo to develop an animal model of hearing loss due to congenital cytomegalovirus.

Collaboration with Adolescent Medicine

Collaborating Faculty: Lea Widdice, MD

Dr. Bernstein is collaborating with Dr. Widdice to determine the effects of delaying completion of the immunization schedule for HPV.

Collaboration with Adolescent Medicine

Collaborating Faculty: Jessica Kahn, MD

Dr. Bernstein is collaborating with Dr. Kahn to examine how the introduction of the HPV vasccine is effecting the epidemiology of HPV

Collaboration with Pediatric Surgery

Collaborating Faculty: Greg Tiao, MD

Monica McNeal, MS collaborates with Dr. Tiao using Rotavirus to induce a mouse model of Biliary Atresia. Research involves looking at receptor differences, effects of different rotaviruses to induce the model and cell signaling pathways.

Collaboration with Molecular Genetics and Chemistry

Collaborating Faculty: Alison Weiss, PhD ; Suri Saranathan Iyer, PhD

Monica McNeal, MS collaborates with Drs. Weiss and Iyer on developing receptor mimics for rapid dection, typing and susceptibility testing of Influenza.

Collaboration with UC Molecular Genetics, Biochemistry and Microbiology

Collaborating Faculty:

Dr. Strasser has an appointment with this division where she works with Air Force Research Laboratories on biodefense research.

Collaboration with Experimental Biology

Collaborating Faculty: Marie-Dominique Fillippi, PhD

Dr. Cardin works with Dr. Marie-Dominique Fillippi on identification of myeloid lineage cells for MCMV latency.

Collaboration with UCCOM Neurology

Collaborating Faculty: Aaron Johnson, PhD

Dr. Cardin works with Dr. Aaron Johnson on MCMV modulation of Theiler's virus-induced multiple sclerosis.

Collaboration with Univ. of Queensland, Brisbane Australia

Collaborating Faculty: Helen Farrell, PhD; Nick Davis-Poynter, PhD

Dr. Cardin works with Drs. Helen Farrell and Nick Davis-Poynter on the role of chemokine receptor homolog, M33, in muring CMV pathogenesis and latency.

Faculty Members

David I. Bernstein, MD, MA, Professor ; *Director, Division of Infectious Diseases; Albert Sabin Professor of Pediatrics; Director, Gamble Program for Clinical Studies*
Research Interests: Vaccines, rotavirus, herpes simplex, cytomegalovirus

Steven Black, MD, Adjunct Professor
Research Interests: Vaccine safety

Rebecca Brady, MD, Associate Professor ; *Director of Adult Clinical Studies*
Research Interests: Adult vaccines, influenza

Rhonda D. Cardin, PhD, Research Assistant Professor
Research Interests: Cytomegalovirus, genital herpes vaccines

Beverly L. Connelly, MD, Professor Clinical ; *Director, Pediatric Infectious Diseases Fellowhship Training Program; Director, Infection Control Program*
Research Interests: Infection control

Michelle P. Dickey, MS, CRN, Field Service Instructor ; *Manager, Gamble Program*

Tibor Farkas, PhD, Research Assistant Professor
Research Interests: Calicivirus

Robert Frenck, MD, Professor ; *Chairman, Institutional Review Board*
Research Interests: Vaccines

Michael Gerber, MD, Professor ; *Director, Clinical Care and Teaching; Medical Director, Continuing Medical Education*

Nancy Hutchinson , RN, MSN, CIC, Field Service Instructor ; *Infection Controll Program*

Xi Jason Jiang, PhD, Professor
Research Interests: Calicivirus

Monica McNeal, MS, Field Service Instructor ; *Associate Director, LSCS*

Nancy Sawtell, PhD, Associate Professor
Research Interests: Herpes simplex virus

Mary Allen Staat, MD, MPH, Professor ; *Director, International Adoption Center*
Research Interests: Rotavirus, epidemiology, international adoption, vaccine preventable diseases

Mark Steinhoff, MD, Professor ; *Director, Center for Global Child Health*
Research Interests: Global vaccines

Jane Strasser, PhD, Research Assistant Professor ; *Director, Biosafety Committee*
Research Interests: Shiga like toxins

Ramu Subbramanian, PhD, Research Assistant Professor
Research Interests: Influenza, T cell immunity

Ming Tan, PhD, Research Instructor
Research Interests: Calicivirus

Richard Ward, PhD, Research Professor ; *Director, LSCS*
Research Interests: Rotavirus

Joint Appointment Faculty Members

Steve Black, MD, Adjunct Professor
Center for Global Child Health

Mark Steinhoff, MD, Professor
Center for Global Child Health

Clinical Staff Members

- **Tracy Byrne, RN**
- **Kelly Hicks, RN, MSN**
- **Jennifer Kelley, APN**
- **Carrie Moore, LISW, MSW**
- **Susan Ruedy, MA**
- **Tisha Way, MSSA, LISW-S**

Trainees

- **April Kilgore, MD,** PGY-VI, Marshall University School of Medicine, Huntington, WVA
- **Navjyot Vidwan, MD,** PGY-VI, University College of Dublin, Dublin, Ireland
- **Elizabeth Schlaudecker, MD,** PGY-VI, University of Cincinnati College of Medicine
- **Julianne Green, MD,** PGY-IV, University of Louisville Collete of Medicine
- **Diana Taft, Graduate Student,** 1, Dept. of Environmental Health, Division of Biostatics, University of Cincinnati
- **Diana Koch, PhD Program,** 2, University of Cincinati College of Medicine
- **Blake Frey, Sr. Undergraduate,** Xavier University
- **Kasey Leach, Student,** Jr., Vanderbilt University
- **Roohi Abdulla, Medical Student,** 4th Yr, University of Cincinnati
- **Camila Shanahan, Graduate Student,** University of Cincinnati
- **Ann McCormick, Graduate Student,** Virginia Commonweatlh University
- **Ron Kloska, Student,** Fr., University of Kentucky

Significant Accomplishments

Update on Rotarix™

The impact of Rotarix™, a rotavirus vaccine developed by Cincinnati Children's researchers Richard Ward, PhD, and David Bernstein, MD, MA, continues to be felt around the world.

Before vaccines were available, Rotavirus infections accounted for about 527,000 deaths around the world and about 500,000 hospitalizations in the United States. Rotarix has been approved for use in more than 114 nations, but widespread distribution remains a challenge.

An article published this year in the *New England Journal of Medicine*, reviewed the real-world impacts of the vaccine so far. In Mexico, the first country to license the vaccine, researchers found that within two years after introduction of the vaccine, diarrhea-related mortality fell 35 percent, from 18.1 deaths per 100,000 children to 11.8 per 100,000 children. Among infants 11 months of age or younger, diarrhea-related mortality fell from 61.5 deaths per 100,000 children to 36.0 per 100,000 children, a reduction of 41 percent.

The vaccine also was shown to be effective in Africa, an area where deaths from rotavirus are not uncommon. Although efficacy was not as great in this setting as it had been in Latin America or Europe, the vaccine still prevented about five cases of severe rotavirus gastroenteritis per 100 infants vaccinated per year. In Malawi, vaccine efficacy was lower than in South Africa, yet the vaccine still prevented more cases of severe illness (6.7 vs. 4.2 cases prevented per 100 infant-

years) primarily because Malawi experiences a higher overall rate of severe rotavirus gastroenteritis.

With the safety and efficacy of rotavirus vaccines well-established, the next hurdle is finding the means to supply the vaccine to all infants around the world.

Pandemic Influenza

The NIH-funded Vaccine Treatment Evaluation Unit (VTEU) within the Division was called upon to participate in unprecedented efforts to evaluate vaccines for the novel H1N1 virus that reached pandemic levels in 2009.

The first reports of a novel H1N1 virus strain emerged from the CDC in April 2009. A virus that originated in Mexico had quickly spread within the United States and around the world. The nation's eight VTEU sites were asked to evaluate vaccines for this new threat in adults and the elderly and, then in children of all ages.

The first questions to be addressed were whether people would need one or two immunizations, how much virus should be in the vaccines and would the vaccines require adjuvants (substances that improve vaccine response). Protocols were quickly developed to address all these questions and by August 2009, clinical trials had begun at Cincinnati Children's.

During the next several months, our unit screened more than 650 individuals and enrolled more than 300 adults and 100 children, at times doubling and even tripling the study teams' usual workload. Nearly 400 vaccines were administered, 3,000 clinic visits were performed and more than 16,000 antibody tests were collected between August and December of 2009.

The testing quickly revealed that only one immunization with the usual amount of virus was required to protect adults, but two doses were necessary for children. These efforts were applauded by the NIH and led to the availability of safe and effective influenza vaccines for the United States.

Potential Treatments for HSV and CMV

Neonatal herpes simplex (HSV) infection is a devastating illness that affects 1,500 to 4,000 newborns each year in the United States. Current therapy with acyclovir (ACV) has improved outcomes for many, but mortality and neurologic sequelae remain unacceptably high.

Similarly, cytomegalovirus (CMV) is the most common congenital infection occurring in infants, affecting up to 2 percent of all live births. Congenital CMV can lead to severe neurologic impairments and sometimes death. The most common sequelae, however, is hearing loss. Currently, there are no effective interventions against congenital CMV infection.

As part of our NIH funded contract, Bernstein and Rhonda Cardin, PhD, have evaluated two potential antivirals, N-MCT and CMX001, for activity against HSV and CMV. Treatment of HSV infected mice or newborn guinea pigs with N-MCT protected 100 percent of animals from death and significantly prevented disease symptoms, a significant improvement over acyclovir treatment. Meanwhile, oral treatment of CMV-infected pregnant guinea pigs with CMX001 significantly improved pup survival and reduced viral replication in the placenta, the mother, and in the newborn pups.

Both N-MCT and CMX001 appear to be well-tolerated and thus are promising new drugs for herpesvirus infections. Currently, CMX001 is in Phase II clinical trials for other indications.

In order to improve our ability to screen potential antiviral drugs we also continue to improve our models. Most recently, in collaboration with Dan Choo, MD, a new model of CMV-induced hearing loss has been developed. This model shows that CMV infects the cochlea and causes hearing loss within days after infection. This new model is being further characterized and eventually could be useful for screening antiviral drugs to prevent hearing loss.

These and other accomplishments have led to renewal of our VTEU contract with NIH; a contract we have had since 1990.

Division Publications

1. :

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

Bernstein, D

Evaluation of Control Measures Against Diseases Other Than AIDS
National Institutes of Health
AI-25459 — 05/01/02 - 8/31/10 — $0.00 / $21,739,506

Phase III Vaccine Trial in Sero-Negative Women
Saint Louis University (National Institutes of Health)
N01 AI 045250 — 11/01/02 - 08/31/11 — $4,716 / $1,404,180

Animal Models of Human Viral Infections for Evaluation of Experimental Therapies
National Institutes of Health
N01 AI 15438 05/01/01 - 08/31/10 $246,873 / $2,283,709

The Natural History of CMV-Related Hearing Loss
University of Alabama-Birmingham (National Institutes of Health)
HHSN260200500008C 07/01/05 - 06/30/12 $126,774 / $1,079,552

Jiang, J

Novel Vaccine Against Norovirus
National Institutes of Health
R01 AI 089634 05/15/10 - 04/30/15 $770,870 / $4,134,172

Characterization of Human Caliciviruses
National Institutes of Health
R01 AI 037093 09/01/09 - 08/31/11 $284,943 / $569,886

Novel Broad Spectrum Therapeutic Glycans Against Categor
Massachusetts General Hospital (National Institutes of Health)
U01 AI 075563 09/01/07 - 08/31/11 $47,659 / $72,033

McNeal, M

Hyaluronan Regulation of Microbial Host Defense of the Intestine
Cleveland Clin Lerner Col of Med of CWRU (National Institutes of Health)
R01 HD 061918 09/15/09 - 07/31/10 $29,609 / $29,609

Sawtell, N

Ocular HSV Infection-Latency and Pathogenesis
University of Cincinnati (National Institutes of Health)
R01 EY 013168 05/01/08 - 04/30/12 $98,000 / $392,000

Neuronal Regulation of HSV Lytic and Latent Infection
National Institutes of Health
R21 AI 081083 12/24/08 - 11/30/10 $123,750 / $273,750

Neuronal Regulation of HSV Lytic and Latent Infection
National Institutes of Health
R21 AI 081083 09/12/09 - 08/31/11 $111,033 / $111,033

Unbiased Forward Genetic Analysis of Virus/Host Interactions
National Institutes of Health
RC1 AI 087336 09/26/09 - 08/31/11 $348,093 / $688,089

Forward "Systems Genetics" Approach to Identify Host Gen
University of Cincinnati
07/01/08 - 12/31/09 $5,396 / $25,000

Current Year Direct **2,197,716**

Industry Contracts

Bernstein, D

LigoCyte Pharmaceuticals, Inc	$ 746,725
MedImmune Inc.	$ 37,917

Brady, R

Covance, Inc	$ 7,158
Accelovance, Inc.	$ 64,418

Cardin, R

Novartis Pharmaceuticals	$ 129,482
Replicor	$ 620
Genocea Biosciences, Inc.	$ 109,037

Frenck, R	
Merck & Company, Inc.	$ 8,006
Wyeth Pharmaceuticals	$ 334,584
GlaxoSmithKline	$ 5,775
Gerber, M	
Hoffman	$ 8,855
Jiang, J	
LigoCyte Pharmaceuticals, Inc	$ 97,925
McNeal, M	
LigoCyte Pharmaceuticals, Inc	$ 21,859
Staat, M	
GlaxoSmithKline	$ 246,400
MedImmune Inc.	$ 2,310
Ward, R	
Merck & Company, Inc.	$ 709,824
Sanofi Sythelabo	$ 21,768
Current Year Direct Receipts	**$2,552,663**
Total	**$4,750,379**