Infectious Diseases

Division Photo

Seated: N. Hutchinson, B. Connelly

Standing: M. Dickey, R. Ward, M. Staat, T. Farkas, N. Sawtell, M. Steinhoff, R. Frenck, D. Bernstein - Director, R. Subbramanian, M. Tan, M. McNeal, J. Strasser, R. Cardin, J. Jiang

Not pictured: S. Black, R. Brady, M. Gerber

Division Data Summary

Research and Training Details	
Number of Faculty	21
Number of Joint Appointment Faculty	3
Number of Research Fellows	3
Number of Support Personnel	83
Direct Annual Grant Support	$4,982,159
Direct Annual Industry Support	$3,126,458
Peer Reviewed Publications	60
Clinical Activities and Training	
Number of Clinical Staff	6
Number of Clinical Fellows	3
Number of Clinical Students	9
Inpatient Encounters	1614
Outpatient Encounters	1126

Significant Publications

Bernstein DI, Cardin RD, Bravo FJ, Strasser JE, Farley N, Chalk C, Lay M, Fairman J. Potent adjuvant activity of cationic liposome-DNA complexes for genital herpes vaccines. Clin Vaccine Immunol. 2009 May;16(5):699-705. Epub 2009 Mar 11. PubMed PMID: 19279167; PubMed Central PMCID: PMC2681593.

Herpes simplex virus (HSV) infections are common and lead to substantial morbidity but no vaccines are currently available. It appears that HSV vaccines will require more potent adjuvants than are currently available for human use. We evaluated cationic liposome-DNA complexes (CLDC) in our well characterized mouse model of genital herpes and showed the vaccine enhanced antibody and T cell mediated immune responses to the vaccine compared to other adjuvants. Most importantly, CLDC increased survival, reduced symptoms, and decreased vaginal virus replication compared to vaccine alone or vaccine administered with monophosphoryl lipid A (MPL). Thus,

CLDC appears to be a potent adjuvant for HSV vaccines and should be evaluated further.

Tan, M, Xia, M, Chen, YT, Bu, WM, Huang, PW, Hegde, R, Li, WM, and Jiang, X, (2009), Conservation of Receptor Binding Interfaces, Evidence of Human HBGA selection in Norovirus Evolution, PLoS One, e5058.

The persistence and predominance of a single genotype (GII-4) of noroviruses (NVs) in recent years has raised questions about the epidemiology and evolution of NVs. One hypothesis suggests that the GII-4 viruses have undergone an epochal evolution selected by herd immunity with continual emergence of antigenic variants that are accompanied by changes of histo-blood group antigen (HBGA) binding pattern. Our investigations published recent found that the receptor binding interfaces of noroviruses are highly conserved among strains within but not between the two major genogroups (GI and GII). This suggests that the human HBGAs play an important role in noroviruses evolution. The segregation of the two genogroups further indicates a typical convergent evolution and the importance of HBGAs in the persistence of noroviruses. The epidemiology and transmission patterns of noroviruses differ from that of influenza viruses and do not support the epochal evolution of noroviruses. The well documented short term immunity seen in patients following norovirus infection also does not support herd immunity as a driving force for GII-4 epidemics. Thus, our study suggests a different explanation on the important issue of norovirus evolution. We expect this publication to stimulate further studies to resolve the conflict.

Wierzba TF, Abdel-Messih IA, Gharib B, Baqar S, Hendaui A, Khalil I, Omar TA, Khayat HE, Putnam SD, Sanders JW, Ng L, Price LJ, Scott DA, Frenck RW. (2008) Campylobacter Infection as a Trigger for Guillain-Barre´ Syndrome in Egypt. PLoS One 3:e3674

Campylobacter is a common cause of diarrhea in the developing world, both among people native to the area as well as travelers. A rare but serious complication associated with Campylobacter infection is the Guillain-Barre Syndrome (GBS), an ascending paralysis that may lead to permanent disability and even death. Means to control the infection have focused largely on development of a protective vaccine. However, vaccine development has been slowed by the concern of vaccine recipients developing GBS as a result of exposure to components of Campylobacter in the vaccine. The current study was undertaken to describe if GBS is associated with Campylobacter in Egypt, an area of the world known to be at high risk for repeated infections with the organism. Using a case-control methodology, we demonstrated that patients with GBS had higher anti-IgM antibodies against Campylobacter as well as anti-ganglioside antibodies suggesting the infection was associated with the development of GBS. We also noted the epidemiology of GBS to differ in Egypt vs. the United States in that the age of cases in the current study was an average of 4 years old as compared to adulthood in the United States. We expect this paper to further support the need to understand the components of Campylobacter associated with development of GBS and to produce vaccines free of these products.

Shaheen HI, Abdel Messih IA, Klena JD, Mansour A. El-Wakkeel Z, Wierzba TF, Sanders JW, Khalil SB, Rockabrand DM, Monteville MR, Rozmajzl PJ, Svennerholm AM, Frenck RW. (2008) Phenotypic and genotypic analysis of enterotoxigenic Escherichia coli in samples obtained from Egyptian children presenting to referral hospitals. J. Clin Microbiol. 47(1):189-97

In Egypt, several community-based studies have reported on the burden of enterotoxigenic Escherichia coli (ETEC) infection in native children and foreign travelers. To complement these studies, a hospital based surveillance was initiated in September 2000 to determine the etiology of severe diarrhea in children less than 5 years of age in two referral hospitals located in the Nile River Delta of Egypt. Year-to-year variations in ETEC isolates expressing enterotoxins and the colonization factors (CF) types over a 3- year period, beginning in September 2000 were described. Over fifteen-hundred cases of diarrhea were evaluated and ETEC was recovered from 21% (320/1,540) of study children. ETEC isolates expressing a known CF were
identified in 151/320 (47%) samples, consistent with the isolation rates in previous studies. Over 75% of the CFs expressed by ETEC isolates were from only 4 CF types.
The genome plasticity demonstrated in the ETEC isolates collected in this work suggests an additional challenge to the development of a globally effective vaccine for ETEC.

Trehan I, Meinzen-Derr JK, Jamison L, Staat MA. Tuberculosis screening in internationally adopted children: the need for initial and repeat testing. Pediatrics 2008; 122(1):e7-14

Because most internationally adopted children come from areas of high tuberculosis prevalence, an initial tuberculin skin test is recommended after arrival to the United States. We evaluated whether repeat testing of children >3 months after arrival to the United States would identify additional children with latent tuberculosis infection. Internationally adopted children who were seen at our International Adoption Center and had a tuberculin skin test within 2 months of arrival to the United States were eligible for the study. Children not diagnosed with tuberculosis with initial testing were retested at least 3 months later. The prevalence of tuberculosis on arrival and after repeat testing was determined and potential risk factors for infection were examined. Of the 527 internationally adopted

children with an initial tuberculin skin test completed, 111 (21%) had evidence of latent tuberculosis infection. Repeat tuberculosis testing was complete for 191 internationally adopted children (46.9% of those who had an initially negative tuberculin skin test). Latent tuberculosis infection was found in 20% of those who were retested. No children were found to have active tuberculosis disease. Children with an initially positive tuberculin skin test result were better nourished at their initial clinic visit, whereas those whose tuberculin skin test result was positive after repeat testing were slightly more malnourished. Latent tuberculosis infection was found to be very common in internationally adopted children. A high proportion of internationally adopted children had an initially false negative tuberculin skin test. Repeat tuberculosis testing of all internationally adopted children with an initially negative tuberculin skin test should be the standard of care for identifying tuberculosis infection and preventing tuberculosis disease in this high-risk population.

Division Highlights

David I. Bernstein, MD, MA and Rhonda Cardin, PhD

Congenital cytomegalovirus (CMV) is the most common congenital infection in the USA but current therapies are less than optimal. During the past year we evaluated a new antiviral against CMV in our animal models of congenital CMV infection. CMX-001 is a new lipid ester analog of Cidofovir which exhibits potent antiviral activity against CMV without the kidney toxicity associated with Cidofovir. We demonstrated that CMX-001 is highly protective against transmission of guinea pig CMV across the placenta to the developing fetus in our guinea pig model of congenital CMV transmission. In a second model of neonatal CMV infection, CMX-001 protected neonatal guinea pigs and significantly reduced viral replication in a number of tissues, including the brains of infected animals. This new antiviral is a promising new candidate for treatment of congenital and neonatal CMV infection.

Rebecca Brady, MD

During this annual report period, Dr. Rebecca Brady assumed the following new roles: Director of Adult Clinical Studies, Division of Infectious Diseases at CCHMC, Chair, Drug Use and Evaluation Subcommittee of the CCHMC Pharmacy and Therapeutics Committee, Infectious diseases division representative for the Education Curriculum Committee of the CCHMC Pediatrics residency program and Chair of the Louise Rauh Scholarship Committee for fourth year medical students, CCHMC Women's Faculty Association.

Rhonda Cardin, PhD

Cytomegalovirus infections are common and important in people with immunocompromised immune systems and as a cause of congenital infections. Cytomegalovirus encodes G protein-coupled receptors (GPCRs) which share homology to host chemokine receptors. We recently showed that the viral chemokine receptor, M33, encoded by murine cytomegalovirus (MCMV) plays a tissue specific role during MCMV infection of mice and is also critical for long term latent infection. In our studies, we demonstrated that M33 function is required for replication in the salivary glands, spleen, and pancreas but not the lungs. Significantly, our studies using a M33 mutant virus provides the first evidence that M33 leads to reduced latency in the spleen, lungs, and bone marrow. This is the first CMV gene to be identified that plays a role in long term latent infection and importantly, our preliminary data shows that two viral chemokine receptors encoded by human CMV (HCMV) can rescue the latency defect, thus demonstrating a conserved role for the CMV-encoded chemokine receptors in CMV latency.

Beverly Connelly, MD

The Infection Control Program, under the direction of Dr. Connelly has focused its efforts on projects that improve the quality of health care delivered at Children’s Hospital. They have been key participants in efforts that gained for the hospital the Codman Award from The Joint Commission for reducing surgical site infections. Dr. Connelly collaborates with individuals in the Center for Health Care Quality and serves as an advisor to the Ascension Health group to improve care of children in their facilities throughout the United States by reducing healthcare associated infections.

Robert Frenck, MD

Over the past year, Dr. Frenck has continued to expand his research portfolio to include additional studies on the 13-valent conjugate pneumococcal vaccine from Wyeth for which he has been the lead author on an abstract presented at the CDC conference National Vaccine Update and will be the lead author of the pending manuscript. He is also the lead author of an abstract on use of the 13-v pneumococcal vaccine in adults which will be presented at the 2009 Infectious Disease Society of America meeting. He has recently begun a study of the epidemiology of Group A Streptococcus (GAS) in children with the long term goal of leading a series of trials to determine the safety and

efficacy of a GAS vaccine. In collaboration with colleagues at the Department of Defense (DoD), Dr Frenck will be conducting a series of studies on candidate vaccines against Shigella sonnei, a common cause of diarrheal diseases in travelers. Finally, Dr. Frenck is collaborating with Dr. Jiang to study the immune response and natural defenses against norovirus through a challenge model to be conducted on the inpatient unit at CCHMC.

Dr. Frenck has continued to be an active member of the American Academy of Pediatrics Committee on Infectious Diseases (Red Book Committee) and over the past year has co-authored policy statements on influenza, RSV and rotavirus as part of his duties on the committee. Dr. Frenck has also become a recognized expert on community associated methicillin resistant Staphylococcus aureus (CA-MRSA) and has lectured at the AAP national meeting in 2008 and 2009 on the topic as well as locally at the CCHMC Outreach Lecture series.

Michael Gerber, MD

The inpatient consultation service of the Division continues to grow with a 120% increase in new consultations over the past 6 years. The outpatient consultation service of the Division also continues to grow with a 110% increase in new consultations over the same period of time. The clinical service provides an outstanding educational experience for medical students and residents, and over the past 6 years, we have seen a substantial increase in the number of residents who have taken electives in our Division. In recognition of the educational program that we are providing, for the first time in the history of our Division, we have won the annual divisional teaching award from the residents. The Division has also established a new Outpatient Antibiotic Therapy (OPAT) service. This service closely monitors patients who are receiving home IV antibiotic therapy to improve patient safety and clinical outcomes, as well as to increase family and staff satisfaction. This service is headed by a full-time APN. In the first full year of operation, the service had over 330 visits. It has been greatly appreciated by clinical services throughout CCHMC and has made a major contribution to improving the quality of care provided.

Jason Jiang, PhD

In the past year we continued our norovirus research program focusing on examining the norovirus/host interaction as it relates to human histo-blood group antigen receptors and antigenic types of noroviruses in different genotypes and genogroups. We have determined the receptor binding interface of an additional strain following our first co-crystallization study on the prototype VA387. We also further elucidated the structures of the receptor binding interfaces using mutagenesis analysis and crystallography studies. We have focused on GII-4 strains because they are currently dominant in many countries. These studies may also help us understand the evolution of noroviruses and address the important issue on the epochal evolution of the GII-4 viruses. Following the crystallography studies, we performed genetic analysis and found that the receptor binding interfaces of noroviruses are highly conserved within but not between the two major genogroups. Our work indicates that the human histo blood group antigens play an important role in norovirus evolution. We now believe that the human HBGAs play a major role in the evolution of noroviruses and the predominance of GII-4 viruses is due to their relative broader host range determined by their spectrum of binding to human HBGAs. We will continue this line of investigation using our large collection of GII-4 strains to address this question. If our hypothesis is correct, a unique vaccine approach may be needed for noroviruses. During this year we also made significant progress in studies using P particles of norovirus as a candidate vaccine and were licensed the technology to a vaccine company (LigoCyte) for further development of the vaccine.

Nancy Sawtell, PhD

Susceptibility and outcomes for the overwhelming majority of human diseases is influenced by complex interactions of traits that vary according to the genetic context of the host. Inbred mouse models have been used for years to better understand human disease. While these models have provided useful information, classic inbred mice, unlike the human population have a very limited genetic variability. It follows that many phenotypes that are seen in individuals may not be reflected in these inbred strains. On the other hand, advanced Recombinant Inbred (ARI) strains are large populations of genetically diverse yet fully inbred mouse strains. Generation of C57/Blk6xDBA/2 (BxD) ARI lines are at the core of this powerful approach for identifying the combinations of genetic variation that together contribute to differences in disease susceptibility and severity. Ultimately any phenotype or disease state that is influenced by genetics can be converted into a set of associated gene loci called quantitative trait loci (QTLs). Mapping QTLs associated with measurably distinct phenotypic manifestations of disease will reveal insight into the mechanisms underlying the disease processes. Because this strategy relies upon parsing the identified QTL into pathways and elucidating disease modulating networks (which are undoubtedly conserved among mammalian organisms), findings can be expected to be relevant to human disease mechanisms. The large and growing database of information generated within these ARI lines can be mined utilizing extant bioinformatic approaches to detect unknown correlations between infections with diverse agents, or other unanticipated phenotypes. Using this approach to advance our

knowledge of herpes simplex virus infections Nancy Sawtell PhD in collaboration with two UC investigators scored a 2 percentile on their Challenge Grant Application.

Mary Allen Staat, MD, MPH

The International Adoption Center (IAC), began in 1999, has assisted more nearly 3000 families with pre-adoptive services and has cared for nearly 2000 children through our post-adoption services. While most internationally adopted children transition well to their new families, some children because of the loss and trauma they have encountered prior to being adopted have more difficulties and could benefit from mental health services for attachment and behavioral issues that are unique to adopted children. In addition, a number of factors from pre-natal exposures, malnutrition and lack of stimulation from institutionalization place these children at a higher risk for attention and learning issues. A long term vision for the IAC has been to develop a comprehensive program to address the Attention, Behavioral, Learning and Educational (ABLE) issues of internationally adopted children and their families. We are pleased that we now are able to offer these services to our families through collaboration with the Division of Psychology. The team is comprised of a licensed independent social worker, a psychologist and a neuropsychologist who evaluates children with more complex issues. This year, an educational specialist/school advocate will join our team in order to help families navigate the school system. The growth of our clinical services has also expanded our research program to include studies evaluating transitional and learning issues in internationally adopted children through collaborations with the Division of Pediatric Rehabilitation and Radiology. We have completed studies examining transitional issues in children and functional MRI testing to identify whether there are differences in brain function in internationally adopted children who have been institutionalized compared to non-institutionalized controls. Through this research program we hope to learn more about the neurologic and mental health issues in internationally adopted children so that we can improve our services for these children.

Ramu Subbramanian, PhD

The recent emergence of a novel pandemic H1N1 influenza underscores the need for reliable immunological markers that correlate with protection from influenza disease in humans. The Subbramanian laboratory has contributed substantially to developing assays and immunological approaches amenable to the study influenza immunity in humans and is one of the few laboratories that specialize in cell mediated immunity to influenza in humans. These assays are particularly geared toward use in clinical studies including vaccine trials and naturally exposed individuals. The lab has applied polychromatic flowcytometry methodology and high-throughput ELISPOT approaches to elucidate T cell immunity to influenza antigens derived from both seasonal and pandemic influenza strains. These approaches paint a complex picture of influenza immunity in humans. An important observation from the laboratory has been the lack of correlation between the cellular and humoral arms of the immune system toward the viral hemagglutinin (HA) protein, which provides a rational to explore T cell based vaccines as a possible alternate to control the virus. The laboratory has also deficits in the magnitude and diversity of influenza specific T cell in the elderly; a group who bear the brunt of influenza related mortality. These observations and ongoing studies on pandemic influenza strains have immediate ramifications to the design of future universal influenza vaccines and our understanding of influenza immunity in humans in general.

Division Collaboration

Collaboration with Adolescent Medicine

Collaborating Faculty: Lea Widdice, MD; Jessica Kahn, MD

Dr. David Bernstein collaborates with Drs. Widdice and Kahn to determine the effects of altered HPV immunization schedules on safety and immunogenicity.

Collaboration with Adolescent Medicne

Collaborating Faculty: Jessica Kahn, MD

Dr. David Bernstein is a co-investigator on the RO-1 grant of Dr. Kahn evaluating the virologic and behavioral impact of HPV vaccine.

Collaboration with Gastroenterology, Hepatitis & Nutrition

Collaborating Faculty: Mitchell Cohen, MD

Dr. David Bernstein is a co-investigator on a project evaluating a combined cholera and ETEC vaccine.

Collaboration with Pediatric Otolaryngology

Collaborating Faculty: Daniel Choo, MD

Drs. Bernstein and Cardin collaborate with Dr. Choo to investigate congenital CMV and hearing loss.

Collaboration with Experimental Hematology

Collaborating Faculty: Marie-Dominique Filippi, PhD

Dr. Rhonda Cardin works with Dr. Filippi on identification of myeloid lineage cells for MCMV latency.

Collaboration with Dept. of Neurology, UCCOM

Collaborating Faculty: Aaron Johnson, PhD

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

Collaboration with Molecular Genetics

Collaborating Faculty: Alison Weiss, PhD; Thomas Lamkin, PhD

Dr. Jane Strasser works with Dr. Weiss on a U01 identifying glycoconjugates that can be used as diagnostic and/or therapeutic agents for intoxication and on a RO1 on characterization of factors influencing Shiga toxin production and toxicity in E coli O157:H7 infection.

She also works with Dr. Lamkin on identifying genetic factors influencing disease susceptibility in biowarfare agents.

Collaboration with UC Internal Medicine

Collaborating Faculty: Tarek Shata, MD, PhD

Dr. Ramu Subbramanian works with Dr. Shata on ELISPOT technologies to monitor T cell responses following vaccination and infection.

Collaboration with Molecular Genetics UCCOM

Collaborating Faculty: Malek Kotb, PhD; Richard Thompson, PhD

Dr. Nancy Sawtell works with Malek Kotb, PhD on forward Genetics approach to identify host genes and pathways involved in susceptibility and resistance to HSV disease outcomes.

She also works with Richard Thompson, PhD on molecular mechanisms underlying HSV latency and reactivation.

Collaboration with Pediatric Surgery

Collaborating Faculty: Greg Tiao, MD

Monica McNeal, MS collaborates with Dr. Tiao on Rotavirus induced model of Biliary Atresia in neonatal mice: This model uses different rotavirus strains to induce biliary atresia in neonatal mice. Research involves looking at receptor differences, effects of different rotaviruses to induce the model and cell signaling pathways.

Collaboration with Pulmonary Biology

Collaborating Faculty: Ardythe Morrow, PhD

Dr. Jason Jiang and his lab work on a collaboration in a study on the role of human milk in infant nutrition and health, which is funded by a NIH P01 grant.

Collaboration with Center for Epidemiology and Biostatistics; ;

Collaborating Faculty: Ardythe Morrow, PhD; Mekibib Altaye, PhD; Sheila Salisbury, PhD

Dr. Mary Saat works with Epidemiology on epidemiologic research on vaccine preventable idiseases.

Collaboration with Pediatric Neuroimaging

Collaborating Faculty: Scott Holland, MD

Dr. Staat collaborates on the neuroimaging of internationally adopted children.

Collaboration with Pediatric Rehabilitation

Collaborating Faculty: Shari Wade, PhD

Dr. Staat collaborates with Dr. Wade examining the adaptation of internationally adopted children after arriving here and on neuroimagining of internationally adopted children

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, Professor Clinical ; *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*

Larry Pickering, MD, Adjunct Professor

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

Laura Stadler, MD, MA, Assistant Professor Clinical
Research Interests: Cytomegalovirus

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

Mark Steinhoff, MD, Professor
Center for Global Child Health

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

Laura Stadler, MD, MA, Assistant Professor
Infectious Diseases/Hematology/Oncology

Clinical Staff Members

- **Jennifer Kelley, APN**
- **Tracy Byrne, RN**
- **Ann Malinowski, MSN, CNP**
- **Matthew Linam, MD**
- **Kelly Hicks, RN, MSN**
- **Carrie Moore, LISW, MSW**

Trainees

- **April Kilgore, MD,** PGY-V, Marshall University School of Medicine, Huntington, WVA
- **Navjyot Vidwan, MD,** PGY-V, University College of Dublin, Dublin, Ireland
- **Elizabeth Schlaudecker, MD,** PGY-V, University of Cincinnati College of Medicine
- **Yang Yang, ,** 2, Beijing Aqricultural University, Beijing, China
- **Diana Koch, ,** 2, Molecular Genetics UCCOM
- **Kasey Leach, ,** 2, Vanderbilt University
- **Dustin Poole, ,** 1, Harvard University
- **Ron Kloska, ,** 1, University of Kentucky
- **Rebecca Sebastian, ,** 3, University of Kentucky
- **Elizabeth Toebbe, ,** 3, University of Kentucky
- **Sarah Leyman, ,** 2, Amherst College in MA
- **Staci Hazenfeld, ,** 4, Mt. St. Joseph

Significant Accomplishments

Rotarix Vaccine

The Rotarix vaccine, originally developed by Richard Ward and David Bernstein to prevent rotavirus disease, and licensed to GlaxoSmithKline, reached a major milestone in April of 2009 when it was recommended by the World Health Organization for universal vaccination of all the world's children. The vaccine had been originally licensed in Mexico in 2004, and since has been licensed in over 110 countries worldwide, but universal recommendations for its usage had been limited to developed and less-developed countries. Although rotavirus causes a few deaths and high morbidity in the former and thousands of deaths in the latter each year, the vast majority of the estimated 600,000 deaths due to rotavirus annually occur in the world's poorest countries. No successful studies with any rotavirus vaccine had been completed in any of these poorest (developing) countries so a recommendation from the WHO for any rotavirus vaccine in these countries had not been granted. However, an efficacy trial of Rotarix was completed in Malawi and South Africa in 2008 and showed that the vaccine prevented >60% of severe rotavirus illnesses in these developing country settings, sufficient to save many lives each year. Thus, in 2009 the WHO provided the universal recommendation. This recommendation makes way for the release of funding to support Rotarix usage in these nations by GAVI and UNICEF, global donor agencies responsible for initiating and paying for vaccine usage in the world's poorest countries.

Effectiveness of Rotavirus Vaccine

Two recently approved rotavirus vaccines showed excellent efficacy in pre licensure trials but they had not been tested for effectiveness under field conditions. We therefore sought to assess the impact of the pentavalent rotavirus vaccine (RV5), recommended since 2006, on rotavirus disease burden through our rotavirus active surveillance program. Using the Centers for Disease Control and Prevention's New Vaccine Surveillance Network, we conducted active surveillance in three US counties from January 2006 through June 2008 to identify children <3 years of age hospitalized or seen in the emergency department (ED) with rotavirus acute gastroenteritis (AGE). Rates of laboratory-confirmed rotavirus hospitalization and ED visits were calculated before and after licensure of RV5 and RV5 vaccine effectiveness (VE) was calculated by comparing vaccination rates in rotavirus positive cases and rotavirus-negative AGE or acute respiratory infection (ARI) controls. Compared with the 2006 and 2007 seasons we found a >80% decline in rates of rotavirus hospitalizations (22.5, 26.8 and 3.7/10,000 respectively) and ED visits (281, 301 and 44.2/10,000 respectively). In 2008, rates declined >75% in <12, 12-23 and 24-35 month olds compared to earlier years. RV5 coverage with >1 dose for those age groups was 67%, 54% and 19% respectively. We found the effectiveness of RV5 for 1, 2 and 3 doses to be 71%, 72% and 88%. We found RV5 to be highly effective in preventing rotavirus disease, even after a partial series of less than three doses. Rotavirus rates in 2008 declined far greater than expected based on vaccine coverage, suggesting indirect benefits for non-vaccinated children.

Reactivation of Herpes Simplex Virus

The human herpes virus family, includes several important pathogens. This family of viruses sets up life long infection in the host by creating a reservoir of latently infected cells from which infectious virus is periodically released. Reactivation of one of these viruses, herpes simplex virus (HSV), is a leading cause of sporadic fatal viral encephalitis while recurrent herpetic keratitis is the most important infectious cause of blindness. The molecular mechanisms underlying the complex biology of reactivation has remained ill-defined. How does the virus replicate but also enter the latent program and establish a long term latent infection in the same cell type? Investigators from CCHMC ID and UCCOM MolGen have

recently uncovered a critical piece of the latency/reactivation regulatory puzzle. Their research shows that HSV has evolved an elegant regulatory strategy that exploits not only the neuronal molecular environment but also its unique anatomy. Replication in epithelial cells at the body surface releases virions which are transported into neurons in the nervous system. Although these neurons are fully permissive for the replicative cycle the latent transcriptional pathway is engaged in these neurons because a key viral tegument protein is left behind as the virus travels up the axon. This protein, VP16 is a strong transactivator which normally starts the viral lytic cycle. Reactivation from latency occurs when stressful stimuli cause the stochastic derepression of the VP16 gene, which is modulated by a specialized region in the VP16 promoter such that a very small percentage of latently infected neurons (0.1%) express VP16 de novo. VP16 then initiates the productive lytic cycle by turning on the viral immediate early genes from the latent viral genome. These findings present a rational basis for the development of new antiviral therapeutic and vaccine strategies.

Division Publications

1. Brady RC, Bernstein DI, Fine KS. "Infectious disease." *Blueprints pediatrics.* Baltimore: Lippincott, Williams & Wilkins; 2009: 158-184.
2. Chacko M, Wood C, Staat M. "Genital Infections." *Textbook of pediatric infectious diseases.* Philadelphia, PA: Saunders; 2009: 575-616.
3. Kaplan EL, Gerber MA. "Group A, group C and group G beta-hemolytic streptococcal infections." *Textbook of pediatric infectious diseases.* Philadelphia, PA: Saunders; 2009: 1225-1239.
4. McCormack PL, Keam SJ, Bernstein DI, Grimwood K, Linhares AC, Madhi SA, Nakagomi O, Vesikari T. Rotavirus vaccine RIX4414 (Rotarix): a review of its use in the prevention of rotavirus gastroenteritis. *Paediatr Drugs.* 2009; 11: 75-88.
5. McNeal M, Bernstein DI. "Rotavirus vaccines." *Vaccines for biodefense and emerging and neglected diseases.* Amsterdam; Boston: Academic Press; 2009: 645-669.
6. Tan M, Farkas T, Jiang X. "Molecular pathogenesis of human norovirus." *RNA viruses: host gene responses to infection.* New Jersey, London and Singapore: World Scientific; 2009: 575-600.
7. Tan M, Xia M, Chen Y, Bu W, Hegde RS, Meller J, Li X, Jiang X. Conservation of carbohydrate binding interfaces: evidence of human HBGA selection in norovirus evolution. *PLoS One.* 2009; 4: e5058.
8. Ward RL, Staat MA, Bernstein DI. "Rotaviruses." *Textbook of pediatric infectious diseaes.* Philadelphia, PA: Saunders; 2009: 2245-2270.
9. De Vos B, Han HH, Bouckenooghe A, Debrus S, Gillard P, Ward R, Cheuvart B. Live attenuated human rotavirus vaccine, RIX4414, provides clinical protection in infants against rotavirus strains with and without shared G and P genotypes: integrated analysis of randomized controlled trials. *Pediatr Infect Dis J.* 2009; 28: 261-6.
10. Dickey M, Jamison L, Michaud L, Care M, Bernstein DI, Staat MA. Rotavirus meningoencephalitis in a previously healthy child and a review of the literature. *Pediatr Infect Dis J.* 2009; 28: 318-21.
11. Ryckman FC, Schoettker PJ, Hays KR, Connelly BL, Blacklidge RL, Bedinghaus CA, Sorter ML, Friend LC, Kotagal UR. Reducing surgical site infections at a pediatric academic medical center. *Jt Comm J Qual Patient Saf.* 2009; 35: 192-8.
12. Sundberg JP, Silva KA, Zhang W, Sundberg BA, Edwards K, King LE, Davis RL, Black S. Recombinant human hepatitis B vaccine initiating alopecia areata: testing the hypothesis using the C3H/HeJ mouse model. *Vet Dermatol.* 2009; 20: 99-104.
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Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

BERNSTEIN, D

Phase III Vaccine Trial in Sero-Negative Women
National Institutes of Health (St. Louis University)
N01 AI 045250 — 11/01/02 - 08/31/09 — $4,716 / $1,380,600

Animal Models of Human Viral Infections for Evaluation
National Institutes of Health
N01 AI 015438 05/01/01 - 04/30/10 $183,333 / $2,179,143

The Natural History of CMV-Related Hearing Loss
National Institutes of Health (University of Alabama at Birmingham)
HHSN26020050008C 06/01/05 - 05/31/12 $202,780 / $1,079,552

Vaccine and Treatment Evaluation Units
National Institutes of Health
HHSN272200800006C 11/01/07 - 10/31/14 $3,379,995 / $16,899,332

FARKAS, T

Enteric Viral Infections of Captive Rhesus Macaques
National Institutes of Health (Tulane University)
R21 RR 002487 04/01/08 - 03/31/10 $35,911 / $75,773

JIANG, X

Norway-Like Viruses and Their Receptors
National Institutes of Health
R01 AI 055649 08/01/05 - 01/31/10 $209,287 / $1,012,500

Novel Broad Spectrum Therapeutic Glycans Against Cancer
National Institutes of Health (Massachusetts General Hospital)
U01 AI 075563 09/01/07 - 08/31/13 $12,249 / $256,076

SAWTELL, N

Ocular HSV Infection Latency and Pathogenesis
National Institutes of Health (University of Cincinnati)
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 12/01/08 - 11/30/10 $150,000 / $275,000

Forward "Systems Genetics" Approach to Identify Host Genes and Pathways that Moderate HSV Pathogenesis
University of Cincinnati
07/01/08 - 12/31/09 $25,000 / $25,000

STAAT, M

Enhanced Surveillance for Newly Vaccine Preventable Diseases
Centers for Disease Control and Prevention
U01 IP 000147 08/31/07 - 08/30/09 $636,530 / $1,074,546

WARD, R

PATH sub GAT.1334-07574
PATH Vaccine Solutions
11/15/07 - 12/31/09 $44,358 / $143,529

Current Year Direct **$4,982,159**

Industry Contracts

Bernstein, D

AlphaVax Human Vaccines, Inc.	$ 15,370
LigoCyte Pharmaceuticals, Inc	$ 100,967
MedImmune Inc.	$ 97,861

Brady, R

Covance, Inc	$ 72,583

Cardin

Genocea Biosciences, Inc.	$ 54,518

Frenck, R	
Merck & Company, Inc.	$ 2,156
Wyeth Pharmaceuticals	$ 260,280
Gerber	
Aventis Pasteur	$ 30,960
Novartis Pharmaceuticals	$ 122,255
Jiang	
Meridian Bioscience, Inc	$ 2,310
R-Biopharm Inc.	$ 53,116
McNeal	
Novavax Inc	$ 41,156
Staat, M	
GlaxoSmithKline	$ 539,000
MedImmune Inc.	$ 123,200
R-Biopharm Inc.	$ 123,160
Subbramanian	
MedImmune Inc.	$ 27,268
Ward	
Merck & Company, Inc.	$ 853,433
Protein Sciences Corporation	$ 160,845
Sanofi Sythelabo	$ 78,475
Virus Research Inst.	$ 367,545
Current Year Direct Receipts	**$ 3,126,458**

Funded Collaborative Efforts

BERNSTEIN, D

Behavioral and Virologic Impact of HPV Immunization
National Institutes of Health
Kahn, J — 01/15/08 - 01/14/13 — 5 %

A Randomized, Double-Blind, Placebo-Contolled Dose Esculation,Inpatient Phase I Study to Determine the Safety and Immunogenicity of a Single Oral Dose of a Combined Enterotoxigenic Escherichia coli (ETEC)-Cholera Vaccine (Peru-15-pCTB) in Healthy Adult Subjects
National Institutes of Health
Cohen, M — 05/01/08 - 11/30/10 — 5 %

Jiang, X

Novel Genetic and Salivary Glycan Biomarkers for Risk of NEC in ELBW Infants
National Institutes of Health
Morrow, A — 01/15/09 - 12/31/13 — 10 %

Total	**$ 8,108,167**