Infectious Diseases

Division Photo

Front Row: *J. Jiang, N. Sawtell, R. Cardin, L. Stadler, J. Strasser, M. Staat, M. Gerber;* ***Second Row:*** *N. Hutchinson, D. Bernstein, R. Brady, M. Steinhoff, S. Black, M. McNeal, T. Farkas;* ***Third Row:*** *B. Connelly, R. Subbramanian, R. Frenck*

Division Data Summary

Research and Training Details

Number of Faculty	20
Number of Joint Appointment Faculty	3
Number of Support Personnel	77
Direct Annual Grant Support	$3,872,625
Direct Annual Industry Support	$3,150,336
Peer Reviewed Publications	36

Clinical Activities and Training

Number of Clinical Fellows	3
Number of Other Students	1
Inpatient Encounters	1485
Outpatient Encounters	982

Faculty Members

David 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*

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 Staat, MD, MPH, Associate Professor Clinical ; *Director, International Adoption Center*
Research Interests: Rotavirus, epidemiology, international adoption

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

Trainees

- **Matthew Linam, MD,** PGY-VII, University of Tennessee, Memphis, TN
- **April Kilgore, MD,** PGY-IV, Marshall University School of Medicine, Huntington, WVA
- **Navjyot Vidwan, MD,** PGY-IV, University College of Dublin, Dublin, Ireland
- **Yang Yang, ,** Graduate St, China Agricultural University, China

Significant Accomplishments in FY08

Rotavirus

The major accomplishment of the division remains the development of a rotavirus vaccine, Rotarix™, now marketed by

Glaxo SmithKline. Rotavirus is the most common cause of diarrhea and vomiting in young children in the USA and around the world. Every year over 100 children are admitted to CCHMC for rotavirus gastroenteritis. The vaccine is now available in over 100 countries including the European Union, Latin America, Australia and several countries in Asia; many with universal recommendations for its use. The vaccine is also the only rotavirus vaccine that has been pre-qualified by the WHO for use in developing nations. In April of 2008, the vaccine was approved by the FDA and has since been recommended by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics for administration to infants in the USA. In August it became available to physicians in the USA. The use of the vaccine should prevent the vast majority of the 60-70,000 hospitalizations in the USA for rotavirus gastroenteritis and could prevent many of the 600,000 annual deaths in the world if it can be made available to the poorer nations of the world.

Norovirus

Noroviruses are an important cause of acute gastroenteritis, affecting people of all ages and in both developed and developing countries. The division's norovirus research team has made important contributions to the field in the past two decades. Our current work is focused on the molecular virology, immunology, epidemiology, host pathogen interaction and development of strategies to control and prevent norovirus gastroenteritis. We were among the first to identify human histo-blood group antigens as receptors for noroviruses, which could lead to the development of antivirals agents to treat or prevent these common infections. Our recent ability to resolve the crystal structures of the receptor binding interfaces of noroviruses will also aid our ability to screen and rationally design these drugs. Another area of intense effort is the development of vaccines. Recently we have discovered a subviral particle of noroviruses, the P particle, which has many advantages over other candidate norovirus vaccines. The use of these particles has attracted interests in the vaccine industry, and we will sublicense this approach shortly. Interestingly, the P particle may also be useful as a vector to deliver vaccines for other infectious diseases by insertion of antigens from these pathogens into the surface loops of the P particle. In addition, our group has collaborated with several laboratories in the USA and Mexico to characterize the elements in human breast milk that protect infants from viral gastroenteritis. One major element of protection is milk glycans that appear to be effective decoys that block enteric pathogens from binding to their receptors. The characterization of the protective factors in human milk should result in the discovery of potential highly efficient antimicrobial reagents.

OPAT

Over the past few years, the ID division noted that use of a home care system to provide intravenous (IV) antibiotics in the outpatient setting was becoming more common. In fact, there are now almost 100 new patients on home IV antibiotic therapy every month at CCHMC. While the administration of antibiotics at home is beneficial to families, the practice also requires that patients be monitored frequently for response to therapy, for adverse effects of the medications, and to make sure that the delivery system is functioning properly. Lack of appropriate monitoring could lead to patient errors and risk management issues for CCHMC. Therefore, the ID division developed the Outpatient Antibiotic Therapy (OPAT) clinic. This service provides families a continuity of care during the time of outpatient therapy. The goals of the OPAT clinic are to improve safety and clinical outcomes as well as to increase patient, family and staff satisfaction. During the first 6 months of the OPAT service, led by Dr. Michael Gerber and staffed by a full time nurse practitioner, Jennifer Kelley, CNP, 81 children have been enrolled allowing them to safely and effectively complete antibiotic therapy at home. The OPAT service has been enthusiastically received by physicians and patients and use of the clinic continues to grow each month. The OPAT clinic is open Mon/ 1-4:30, Tues. and Thurs. 8:30-12:00. We expect the clinic to expand dramatically in the coming years and are excited about our ability to fill a void in the delivery of home care to our patients.

Significant Publications in FY08

Bernstein DI, Edwards KM, Dekker CL, Belshe R, Talbot HK, Graham IL, Noah DL, He F, Hill H. Effects of adjuvants on the safety and immunogenicity of an avian influenza H5N1 vaccine in adults. J Infect Dis. 2008 Mar 1;197(5):667-75

Influenza A H5N1 viruses (bird flu) pose a significant threat to human health. Therefore there is considerable effort to identify a vaccine and stock pile it for future use. We conducted a multicenter, randomized, double-blind study in 394 healthy adults to determine a safe and effective dose of vaccine and to determine if the addition of an adjuvant would improve the immune response and/or allow the use of reduced doses. Subjects were randomly assigned to receive 2 doses of influenza A/Vietnam/1203/2004(H5N1) vaccine alone at different doses or combined with MF59 or with aluminum hydroxide. The vaccine formulations were well tolerated but local adverse effects were common and were increased by the addition of adjuvants. The addition of MF59 increased the antibody response, whereas the addition of aluminum hydroxide did not. In the group that received 15 microg of vaccine with MF59, 63% of subjects

achieved what is expected to be protective responses compared with 29% in the group that received the highest dose (45 microg per dose) of vaccine alone. It thus appears that MF59 will be a useful addition to bird flu vaccines whereas alum does not appear to be beneficial. The addition of MF59 could allow for the use of lower doses of vaccine thereby increasing the number of people that could be vaccinated with the stockpiled vaccines.

Bernstein DI, Goyette N, Cardin R, Kern ER, Boivin G, Ireland J, Juteau JM,Vaillant A. Amphipathic DNA polymers exhibit antiherpetic activity in vitro and in vivo. Antimicrob Agents Chemother. 2008 Aug; 52(8):2727-33. Epub 2008 May 27

There is a need for improved therapies for herpes virus infections as well as a world wide need for microbicides; substances that can be used topically to reduce the spread of sexually transmitted diseases like HSV and HIV. Phosphorothioated oligonucleotides have a sequence-independent antiviral activity as amphipathic polymers (APs). The activity of these agents against herpesvirus infections in vitro and in vivo was investigated in this publication. The previously established sequence-independent, phosphorothioation-dependent antiviral activity of APs was confirmed in this report. In addition, the APs demonstrated in vitro activity against a broad spectrum of other herpesviruses including HSV-2, human cytomegalovirus, varicella zoster virus, Epstein-Barr virus and human herpesvirus types 6A/B. The murine microbicide model of genital HSV-2 was then used to evaluate in vivo activity. Protection from infection and disease was seen in 75-85% of animals. These experiments suggest that APs have microbicidal activity and potential as broad-spectrum antiherpetic agents and represent a novel class of agents that should be studied further.

Farkas T, Sestak K, Wei C, Jiang X. Characterization of a rhesus monkey calicivirus representing a new genus of Caliciviridae. J Virol. 2008 Jun;82(11):5408-16.

Caliciviruses are a major cause of gastroenteritis throughout the world but research is limited by the lack of an animal model and the inability to grow the virus in tissue culture. In this study we reported on the characterization of a novel calicivirus, the Tulane virus (TV), that was isolated from a rhesus monkey. The genome of TV contains 6,714 nucleotides,that are organized into three open reading frames that encode the nonstructural polyprotein, the capsid protein and a possible minor structural protein. Phylogenetic analysis placed the TV on a branch rooted with Norovirus. The TV can be cultured in monkey kidney cells and produces typical cytopathic effects. The discovery of the Tulane virus provides a new candidate for the development of an animal model for calicivirus diarrhea. Since it can be grown in tissue culture and a reverse genetics system is available (Wei et al., JVI 2008 Sep 10. [Epub ahead of print]), it has become a valuable tool in further understanding calicivirus replication and biology. Its role as a pathogen in primate colonies and/or humans is not yet understood and is being evaluated in ongoing studies.

Stockman LJ, Staat MA, Holloway M, Bernstein DI, Kerin T, Hull J, Yee E, Gentsch J, Parashar UD. Optimum diagnostic assay and clinical specimen for routine rotavirus surveillance. J Clin Microbiol. 2008 May;46(5):1842-3.

Rotaviruses are the leading cause of severe acute gastroenteritis (AGE) in infants and young children worldwide. The most widely used method of diagnosis of rotavirus infection is antigen detection in fecal specimens using one of several commercialenzyme immunoassays (EIA). Reverse transcriptase PCR (RT-PCR) has been shown to increase the rate of detection of rotavirus in clinical specimens from patients with AGE 10 to 20% over that by EIA. In conducting surveillance and in routine clinical care, it is often difficult to obtain a bulk stool specimen, so a rectal swab is obtained. There are however limited data regarding the differences in rates of detection of rotavirus by specimen type. In order to find a balance between practicality and the most clinically meaningful rates of detection, we examined the rate of detection of rotavirus in bulk stool and rectal swab specimens from children with AGE and age- and season- matched healthy controls. The rate of detection of rotavirus in children with AGE was significantly greater with bulk stool specimens than with rectal swabs by EIA (49% versus 27%; P = 0.01). There was no significant difference by assay when bulk specimens were evaluated (49%versus 53% for EIA and RT-PCR, respectively; P=0.71). No stools from healthy controls were positive by EIA, but 18% were positive by RT-PCR. Therefore, the difference in the rate of detection of rotavirus in bulk stool specimens between children with AGE and healthy controls was greater by the EIA than by RT-PCR, although the rates were significantly different by both methods. While our results confirm that RT-PCR is more sensitive than EIA for the detection of rotavirus in fecal specimens, the results also indicate that the high sensitivity of RT-PCR limits its utility for routine rotavirus surveillance. The lower sensitivity of the EIA compared to RT-PCR may allow the EIA to distinguish between the higher level of viral shedding that likely occurs with acute rotavirus illness and the lower level of shedding from an asymptomatic infection or a resolving infection, making EIA results easier to interpret in terms of their clinical significance. In conclusion, the findings of our study support the recommendations in the WHO generic protocol for hospital- and community-based surveillance of rotavirus disease that bulk stool specimens should be obtained from

children with AGE and should be tested by EIA for purposes of routine surveillance.

Division Highlights

Nancy Sawtell, PhD

The ID division has a focused program, lead by Dr. Nancy Sawtell, that is aimed at understanding the viral/host cell interactions which regulate entry into and exit from herpes simplex virus latency in neurons in vivo. During the past year we have identified sequences within the VP16 core promoter that are uniquely required for lytic replication in ganglionic neurons. Our *working hypothesis* is that these neuronal regulatory sequences (VP16p/NRS) are required for the de novo synthesis of VP16 in sensory neurons in vivo which, in turn, coordinates entry into the productive viral lytic cycle. We have found that within the context of the virus, over expression of sequences containing putative riboregulators blocks reactivation. Preliminary in vitro data indicate that these sequences inhibit VP16 but not VP5 expression. Our working hypothesis is that these sequences function normally to maintain latency and repress reactivation. We will determine whether these sequences inhibit the production of the immediate early proteins ICP0 and ICP4 and/or VP16 proteins and whether this inhibition is a direct or indirect effect.

Jason Jiang, PhD, Tibor Farkas, PhD, DVM

In the past year members of the ID division, Jason Jiang, PhD and Tibor Farkas, DVM, PhD discovered a novel calicivirus, the Tulane virus (TV), that was isolated from stool samples of captive juvenile rhesus macaques (*Macaca mulatta*) of the Tulane National Primate Research Center (TNPRC). In the past year we have successfully established a cell culture system for this virus using a monkey cell line which produces typical cytolytic infection. We then cloned and sequenced the entire viral genome of TV which reveals a typical calicivirus genomic organization. Finally, we succeeded in developing a reverse genetics system by transfection of TV RNA made in vitro from the cloned cDNA. The recombinant virus exhibited similar growth kinetics to that of wild type TV. Human caliciviruses remain difficult to study due to the lack of cell culture and an efficient animal model. The discovery of the TV and the successful establishment of the reverse genetics system will provide a useful tool for studying the pathogenesis and host interaction of caliciviruses.

Ramu Subbramanian, PhD

Members of the ID divison, Dr. Subbramanian and colleagues are exploring cell mediated immunity to seasonal and avian influenza. Using samples obtained from VTEU vaccine study participants and others we have made substantial progress in defining antigenic regions within the virus that the immune system focuses upon. These studies clearly define vaccine targets within the virus that may be important in developing efficacious vaccines against pandemic influenza. One of the key highlights of Dr. Subbramanian's research is the identification of cross-protective cell mediated immune responses in naive populations against potential pandemic strains of influenza. Current studies in his laboratory are geared toward characterizing this response in detail amongst several volunteer cohorts. Results from these studies will significantly increase our ability to design a broadly reactive vaccine against pandemic influenza strains. Cutting-edge immunoassays developed in this laboratory are also helping high-throughput monitoring of cell mediated immune responses elicited by other experimental vaccines. The laboratory is currently involved in RSV and PIV vaccine studies in infants, sponsored by MedImmune.

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

The ID division has recently targeted cytomegalovirus (CMV), the leading cause of congenital infection in the USA and around the world, for its research program. Efforts are underway to screen newborn infants at Good Samaritan Hospital to better define the incidence and outcome of congenital CMV. Further, two vaccine trials are underway. One evaluates the safety and efficacy of a novel, alpha virus replicon vaccine expressing gB, IE1, and PP65 in healthy adults. The other is evaluating the safety and efficacy of a subunit gB vaccine with MF-59 adjuvant in teenage girls. Lastly, we are evaluating new antiviral treatments in an animal model of congenital CMV and have identified effective new therapies.

Division Collaboration

Collaboration with Adolescent Medicine

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

Dr. Bernstein collaborates on studies of HPV vaccine. He is also the primary mentor on Dr. Huppert's K21 Award and Dr. Widdice's BIRCWH Award.

Collaboration with Gastroenterology, Hepatology and Nutrition

Collaborating Faculty: Mitchell Cohen, MD

Dr. Bernstein collaborates on studies of vaccines to prevent gastrointestinal infections including salmonella and cholera.

Collaboration with Pediatric Surgery

Collaborating Faculty: Dr. Greg Tiao

Monica McNeal, MS and Dr. Richard Ward collaborate on a model of biliary atresia in mice induced by rotavirus.

Collaboration with UC and COM, Dept of Mol. Genetics

Collaborating Faculty: Dr. A.A. Weiss

Jane Strasser, PhD collaborates with Dr. Weiss on studies of Shiga toxin.

Collaboration with Critical Care

Collaborating Faculty: Dr. Eman Al-Kadra

Beverly Connelly, MD has collaborated with Critical Care on methicillin resistant staph aureus (MRSA) research.

Collaboration with Developmental Biology

Collaborating Faculty: Dr. Susan Wiley

Beverly Connelly, MD has worked with Dr. Wiley on cochlear implant infections.

Collaboration with Quality Improvement

Collaborating Faculty:

Beverly Connelly, MD has worked on numerous improvement strategies for CCHMC.

Collaboration with UC, Intenal Medicine, Digestive Diseases

Collaborating Faculty: Dr. Tarek Shata

Ramu Subbramanian, PhD collaborates with Dr. Shata on cell mediated immunity (CMI) assays and their application to human clinical trials.

Collaboration with Adolescent Medicine

Collaborating Faculty: Dr. Jill Huppert

Dr. Subbramanian collaborates with Dr. Huppert in exploring phenotypic and functional attributes of T-cells at the vaginal interface.

Collaboration with Hematology/Oncology

Collaborating Faculty: Dr. Timothy Cripe

Nancy Sawtell, PhD has been working with Dr. Cripe on the safety of oncolytic herpes viruses.

Collaboration with Molecular Immunology

Collaborating Faculty: Dr. Christopher Karp; Dr. Julio Aliberti

Nancy Sawtell, PhD has been working with Dr. Karp on opposing biological functions of tryptophan catabolizing enzymes during intracellular infection and with Dr. Aliberti on the role of SOCS-2 in herpes simplex virus pathogenesis.

Collaboration with UC and COM, Molecular Genetics, Biochemistry, and Microbiology

Collaborating Faculty: Dr. Richard Thompson; Dr. Malik Kotb

Nancy Sawtell, PhD has been working with Dr. Thompson on molecular mechanisms regulating herepes simplex virus latency and reactivation and with Dr. Kotb on forward systems genetic approach to identify host genes and pathways that moderate HSV pathogenesis.

Collaboration with Immunobiology

Collaborating Faculty: Dr. Michael Jordan

Rhonda Cardin, PhD collaborates with Dr. Jordan on herpes virus vaccines and development of T-cell assays.

Collaboration with Molecular Immunology

Collaborating Faculty: Dr. Christopher Karp

Rhonda Cardin, PhD collaborates with Dr. Karp on immune response to herpes virus role of IL-10 in CMV infections.

Collaboration with UC and COM Internal Medicine

Collaborating Faculty: Dr. Tarek Shata

Rhonda Cardin, PhD collaborates with Dr. Shata on developing Elispot assays for guinea pigs.

Collaboration with UC and COM Neurobiology (Vontz)

Collaborating Faculty: Dr. Aaron Johnson; Dr. Istvan Pirko

Rhonda Cardin, PhD collaborates with Drs. Johnson and Pirko on the effects of MCMV on Multiple Sclerosis infection in a mouse model.

Mentions in Consumer Media

- FDA Approves GlaxoSmithKline (GSK)'s ROTARIX(R) Rotavirus Vaccine Biospace , Web Site
- FDA Approves Rotarix The First Vaccine Licensed To Complete The Rotavirus Immunisation Series By Four Months Of Age Medical News Today , Web Site
- AlphaVax Announces Initial Analysis Of Data From CMV Phase 1 Clinical Trial Medical News Today , Web Site
- FDA Approves Rotarix The First Vaccine Licensed To Complete The Rotavirus Immunisation Series By Four Months Of Age Medical News Today , Web Site
- Young Children Hospitalized For Flu Associated With Higher Costs And Higher Risk Illness Medical News Today , Web Site
- U.S. Health Authorities Report Reduction In Rotavirus Disease After The Introduction Of Pentavalent Rotavirus Vaccine RotaTeq(R) Medical News today , Web Site
- Chickenpox Protection: Get That Booster WCAX , Television
- Corticosteroids of Little Use Against Childhood Meningitis WCAX , Television
- 1 in 4 U.S. Toddlers Improperly Vaccinated WOODTV , Television
- CDC: 1 in 4 US Children Not Protected Against Preventable Disease Wake Up America , Web Site
- How to keep kids healthy in the summer CNN , Television
- Summer Health Smarts Parenting , Magazine

Division Publications

1. Bernstein DI, Edwards KM, Dekker CL, Belshe R, Talbot HK, Graham IL, Noah DL, He F, Hill H. Effects of adjuvants on the safety and immunogenicity of an avian influenza H5N1 vaccine in adults. *J Infect Dis.* 2008; 197: 667-75.
2. Kahn JA, Rosenthal SL, Tissot AM, Bernstein DI, Wetzel C, Zimet GD. Factors influencing pediatricians' intention to recommend human papillomavirus vaccines. *Ambul Pediatr.* 2007; 7: 367-73.
3. Nolan T, Bernstein DI, Block SL, Hilty M, Keyserling HL, Marchant C, Marshall H, Richmond P, Yogev R, Cordova J, Cho I, Mendelman PM. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Pediatrics.* 2008; 121: 508-16.
4. Rupp R, Bernstein DI. The potential impact of a prophylactic herpes simplex vaccine. *Expert Opin Emerg Drugs.* 2008; 13: 41-52.
5. Tissot AM, Zimet GD, Rosenthal SL, Bernstein DI, Wetzel C, Kahn JA. Effective strategies for HPV vaccine delivery: the views of pediatricians. *J Adolesc Health.* 2007; 41: 119-25.
6. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, Sigurdardottir B, Hoeper A, Graham IL, Edelman R, He F, Nino D, Capellan J, Ruben FL. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine.* 2007; 25: 7656-63.
7. Bravo FJ, Cardin RD, Bernstein DI. A model of human cytomegalovirus infection in severe combined immunodeficient mice. *Antiviral Res.* 2007; 76: 104-10.
8. Farkas T, Sestak K, Wei C, Jiang X. Characterization of a rhesus monkey calicivirus representing a new genus of Caliciviridae. *J Virol.* 2008; 82: 5408-16.
9. Frenck RW. Prevention of influenza: recommendations for influenza immunization of children, 2007-2008. *Pediatrics.* 2008; 121: e1016-31.
10. Sanders JW, Frenck RW, Putnam SD, Riddle MS, Johnston JR, Ulukan S, Rockabrand DM, Monteville MR, Tribble DR. Azithromycin and loperamide are comparable to levofloxacin and loperamide for the treatment of traveler's diarrhea in United States military personnel in Turkey. *Clin Infect Dis.* 2007; 45: 294-301.
11. Gerber MA. **"Group A streptococcus."** Philadelphia: Saunders/Elsevier; 2007: 1135-1145.
12. Gerber MA. **"Non-group A or B streptococcus."** Philadelphia: Saunders/Elsevier; 2007: 1150-1151.
13. Gerber MA. **"Pharyngitis."** Philadelphia: Churchill Livingston/Elsevier; 2007: 206-213.
14. Gerber MA. **"Streptococcus pyogenes (Group A Streptococcus)."** Philadelphia, PA: Churchill Livingston/Elsevier; 2007: 700-711.

15. Halasa NB, Gerber MA, Chen Q, Wright PF, Edwards KM. Safety and immunogenicity of trivalent inactivated influenza vaccine in infants. *J Infect Dis.* 2008; 197: 1448-54.
16. Linam WM, Gerber MA. Changing epidemiology and prevention of Salmonella infections. *Pediatr Infect Dis J.* 2007; 26: 747-8.
17. Tian P, Engelbrektson AL, Jiang X, Zhong W, Mandrell RE. Norovirus recognizes histo-blood group antigens on gastrointestinal cells of clams, mussels, and oysters: a possible mechanism of bioaccumulation. *J Food Prot.* 2007; 70: 2140-7.
18. Tian P, Jiang X, Zhong W, Jensen HM, Brandl M, Bates AH, Engelbrektson AL, Mandrell R. Binding of recombinant norovirus like particle to histo-blood group antigen on cells in the lumen of pig duodenum. *Res Vet Sci.* 2007; 83: 410-8.
19. Jafri M, Donnelly B, McNeal M, Ward R, Tiao G. MAPK signaling contributes to rotaviral-induced cholangiocyte injury and viral replication. *Surgery.* 2007; 142: 192-201.
20. McNeal MM, Basu M, Bean JA, Clements JD, Choi AH, Ward RL. Identification of an immunodominant CD4+ T cell epitope in the VP6 protein of rotavirus following intranasal immunization of BALB/c mice. *Virology.* 2007; 363: 410-8.
21. McNeal MM, Basu M, Bean JA, Clements JD, Lycke NY, Ramne A, Lowenadler B, Choi AH, Ward RL. Intrarectal immunization of mice with VP6 and either LT(R192G) or CTA1-DD as adjuvant protects against fecal rotavirus shedding after EDIM challenge. *Vaccine.* 2007; 25: 6224-31.
22. McNeal MM, Stone SC, Basu M, Clements JD, Choi AH, Ward RL. **IFNy is the only anti-rotavirus cytokine found after in vitro stimulation of memory CD4+ T cells from mice immunized with a chimeric VP6 protein.** *Virol Immunol.* 2007; 20: 571-584.
23. Shivakumar P, Sabla G, Mohanty S, McNeal M, Ward R, Stringer K, Caldwell C, Chougnet C, Bezerra JA. Effector role of neonatal hepatic CD8+ lymphocytes in epithelial injury and autoimmunity in experimental biliary atresia. *Gastroenterology.* 2007; 133: 268-77.
24. Currier MA, Gillespie RA, Sawtell NM, Mahller YY, Stroup G, Collins MH, Kambara H, Chiocca EA, Cripe TP. Efficacy and safety of the oncolytic herpes simplex virus rRp450 alone and combined with cyclophosphamide. *Mol Ther.* 2008; 16: 879-85.
25. Fairbrother G, Broder K, Staat MA, Schwartz B, Heubi C, Hiratzka S, Walker FJ, Morrow AL. Pediatricians' adherence to pneumococcal conjugate vaccine shortage recommendations in 2 national shortages. *Pediatrics.* 2007; 120: e401-9.
26. Miller EK, Griffin MR, Edwards KM, Weinberg GA, Szilagyi PG, Staat MA, Iwane MK, Zhu Y, Hall CB, Fairbrother G, Seither R, Erdman D, Lu P, Poehling KA. Influenza burden for children with asthma. *Pediatrics.* 2008; 121: 1-8.
27. Stockman LJ, Staat MA, Holloway M, Bernstein DI, Kerin T, Hull J, Yee E, Gentsch J, Parashar UD. Optimum diagnostic assay and clinical specimen for routine rotavirus surveillance. *J Clin Microbiol.* 2008; 46: 1842-3.
28. Gessner BD, Sedyaningsih ER, Griffiths UK, Sutanto A, Linehan M, Mercer D, Mulholland EK, Walker DG, Steinhoff M, Nadjib M. Vaccine-preventable haemophilus influenza type B disease burden and cost-effectiveness of infant vaccination in Indonesia. *Pediatr Infect Dis J.* 2008; 27: 438-43.
29. Kerdpanich A, Hutagalung Y, Watanaveeradej V, Bock HL, Steinhoff M. **The immunological response of Thai infants to haemophilus influenzae type B polysaccharide-tetanus conjugate vaccine co-administered in the same syringe with locally produced doptheria-tetanus-pertussis vaccine.** *J Med Assoc Thai.* 2007; 90: 1330-1336.
30. Chu CF, Meador MG, Young CG, Strasser JE, Bourne N, Milligan GN. Antibody-mediated protection against genital herpes simplex virus type 2 disease in mice by Fc gamma receptor-dependent and -independent mechanisms. *J Reprod Immunol.* 2008; 78: 58-67.
31. Sen P, Charini WA, Subbramanian RA, Manuel ER, Kuroda MJ, Autissier PA, Letvin NL. Clonal focusing of epitope-specific CD8+ T lymphocytes in rhesus monkeys following vaccination and simian-human immunodeficiency virus challenge. *J Virol.* 2008; 82: 805-16.
32. Bu W, Mamedova A, Tan M, Xia M, Jiang X, Hegde RS. Structural basis for the receptor binding specificity of Norwalk virus. *J Virol.* 2008; 82: 5340-7.
33. Tan M, Jiang X. Norovirus gastroenteritis, increased understanding and future antiviral options. *Curr Opin Investig Drugs.* 2008; 9: 146-51.
34. Ward RL. Rotavirus vaccines: how they work or don't work. *Expert Rev Mol Med.* 2008; 10: e5.
35. Ward RL, McNeal MM, Steele AD. Why does the world need another rotavirus vaccine? *Ther Clin Risk Manag.* 2008; 4: 49-63.
36. Clark HF, Offit PA, Parashar U, Ward RL. **"Rotavirus vaccines."** Philadelphia, PA: Elsevier Press; 2008: 715-734.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
Bernstein, D		
Animal Models of Human Viral Infections for Evaluation National Institutes of Health N01 AI 15438	05/01/01 - 04/30/09	$345,043 / $2,179,143
Phase III Vaccine Trial in Sero-Negative Women National Institutes of Health (St. Louis University) N01 AI 45250	11/01/02 - 08/31/08	$4,716 / $1,380,600
The Natural History of CMV-Related Hearing Loss National Institutes of Health (University of Alabama at Birmingham)	06/01/05 - 05/31/12	$236,846 / $1,079,552
Vaccine and Treatment Evaluation Units National Institutes of Health HHSN272200800006C	11/01/07 - 10/31/14	$2,099,051 / $16,899,332
Brady, R		
CASG Subcontract National Institutes of Health (University of Alabama at Birmingham) N01 AI 30025	08/01/03 - 07/31/10	$1,889 / $13,224
Cardin, R		
Role of HCMV Chemokine Receptors in Atherosclerosis American Heart Association - Ohio 0665211B	07/01/06 - 06/30/08	$55,000 / $110,000
Farkas, T		
Enteric Viral Infections of Captive Rhesus Macaques National Institutes of Health (Tulane University) R21 RR 002487	04/01/08 - 03/31/10	$39,894 / $75,773
Jiang, X		
The Third International Calicivirus Conference National Institutes of Health R13 AI 077221	09/01/07 - 08/31/08	$25,210 / $25,210
Norwalk-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 Category B Pathogens National Institutes of Health (Massachusetts General Hospital) U01 AI 075563	09/01/07 - 08/31/13	$12,125 / $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
Staat, M		
Enhanced Surveillance for New Vaccine Preventable Diseases Centers for Disease Control and Prevention U01 IP 000147	09/01/07 - 08/31/09	$524,403 / $1,074,546
Strasser, J		
Shiga Toxin Production and Role in Pathogenesis of E coli National Institutes of Health (University of Cincinnati) R01 AI 064893	03/01/07 - 02/28/12	$42,932 / $232,872

Glycoconjugate Based Diagnostics for Biodefense Toxins
National Institutes of Health (University of Cincinnati)
U01 AI 075498 08/01/07 - 07/31/12 $90,058 / $487,783

Ward, R

Advancing Rotavirus Vaccine Development
PATH Vaccine Solutions
11/15/07 - 08/01/08 $88,171 / $88,171

Current Year Direct **$3,872,625**

Industry Contracts

Bernstein, D	
AlphaVax Human Vaccines, Inc.	$ 304,057
Apollon	$ 8,959
Clinical Trials SPF	$ 219,466
GlaxoSmithKline	$ 20,597
MedImmune Inc.	$ 24,450
Brady, R	
GlaxoSmithKline	$ 44,332
Cardin, R	
Inhibitex Inc.	$ 12,292
REPLICor, Inc.	$ 50,261
Frenck, R	
Novartis Pharmaceuticals	$ 20,867
Wyeth Pharmaceuticals	$ 245,946
Gerber, M	
Aventis Pasteur	$ 84,196
Novartis Pharmaceuticals	$ 240,335
Staat, M	
GlaxoSmithKline	$ 77,000
MedImmune Inc.	$ 368,060
Strasser, J	
AMCOL	$ 15,621
Ward, R	
Merck & Company, Inc.	$ 705,813
Protein Sciences Corporation	$ 208,962
Sanofi Sythelabo	$ 83,285
Virus Research Inst.	$ 415,837

Current Year Direct Receipts **$3,150,336**

Total $7,022,961