

# Division of Infectious Diseases

DIVISION PROFILE	
Number of Faculty	17
Number of Fellows	
Clinical Fellows	2
Number of Graduate Students	1
Number of Other Students (full and part-time)	4
Number of Support Personnel	80
Annual Total Grant Support (direct)	\$5,581,488
Annual Total Industry Contracts (direct)	\$2,150,609
Number of Peer Reviewed Publications	45
Patient Encounters	
Outpatient	806
Inpatient	716

## FACULTY LISTING

David I. Bernstein, MD, MA, Albert Sabin Professor of Pediatrics, Director, Div. of Infectious Diseases  
Rebecca Brady, MD, Assistant Professor  
Rhonda Cardin, PhD, Assistant Professor  
Beverly Connelly, MD, Professor of Pediatrics, Director, Infectious Disease Fellowship Program; Director, Infection Control Program  
Michelle Dickey, MS, CRNP, Field Instructor  
Tibor Farkas, PhD, DVM, Instructor  
Robert W. Frenck, MD, Professor of Pediatrics, Chairman, Institutional Review Board  
Michael Gerber, MD, Professor of Pediatrics  
Nancy Hutchinson, RN, MSN, CIC, Field Service Instructor  
Jason Jiang, PhD, Professor  
Nancy Sawtell, PhD, Associate Professor  
Gilbert M. Schiff, MD, Emeritus Professor  
Mary Allen Staat, MD, MPH, Associate Professor, Director, International Adoption Center  
Jane Strasser, PhD, Assistant Professor  
Ramu Subbramanian, PhD, Assistant Professor  
Ming Tan, PhD, Instructor  
Richard Ward, PhD, Professor

## OVERVIEW

The goals of the Division of Infectious Diseases are: to improve the health of children and adults, through excellence and innovation in research and patient care services; to promote scholarly activity in infectious diseases, through basic and clinical research; to provide training, through teaching and mentorship, for future pediatric scientists and clinicians; and to provide leadership, both at the local and national level, in pediatric medicine and research.

Research interests in the division include the pathogenesis of infectious agents, the epidemiology of infectious diseases, and preclinical and clinical vaccine and antiviral development and evaluation. The scope of basic science research includes studies of herpes virus latency and vaccines, structure-function relationships of noroviruses, the immunobiology of rotavirus infection, the immune response to influenza and the molecular pathogenesis of cytomegalovirus infection. Translational research studies, conducted in mouse, guinea pig, and primate models, provide an assessment of the potential efficacy of vaccines and antiviral therapies for a number of pathogens, and serve as a bridge between basic science and clinical investigation.



*Left to Right: (1<sup>st</sup> row) M. Gerber, R. Cardin, M. Staat, D. Bernstein, J. Jiang  
(2<sup>nd</sup> row) B. Connelly, R. Brady, N. Hutchinson, M. Tan (3<sup>rd</sup> row) J. Strasser,  
R. Frenck, T. Farkas (4<sup>th</sup> row) N. Sawtell, R. Subbramanian*

Clinical research trials evaluating vaccine and antiviral strategies in humans are conducted through our NIH funded Vaccine and Treatment Evaluation Unit (VTEU) and industrial agreements. Additional research funding is from the NIH, CDC, National Vaccine Program Office, DOD, and industry sponsors. An active collaboration with the Center of Epidemiology and Biostatistics (NIH funded Human Milk Program Project) examines the relationship of breastfeeding to a number of clinically important pediatric infectious diseases.

Educational and mentorship programs of the division include research and clinical training for undergraduates, medical students, graduate students, residents, fellows and junior faculty within and outside the division. Through adjunct appointments in the Molecular and Developmental Biology and Immunobiology training programs, faculty participates in training and mentorship of future biomedical researchers. Mentorship of clinical fellows in Pediatric Infectious Diseases, conducted through our accredited fellowship training program, continues to be an important aspect of our mission, and research opportunities have also been utilized by clinical and basic research fellows in other CCHMC divisions. Clinical care programs include a physician telephone advice service, inpatient and outpatient infectious diseases consultation services, leadership of the Hospital Infection Control and Continuing Medical Education Programs, and a multidisciplinary International Adoption Center. Academic leadership of the division includes representation at local and national levels helping to shape policy for child health, research, and training, including service on NIH study sections and representation to the American Academy of Pediatrics.

## HIGHLIGHTS

The research focus of the division continues to be on major infectious disease pathogens including rotavirus, herpes simplex virus (HSV), cytomegalovirus (CMV), influenza virus, Norovirus, and bioterrorism pathogens. A fundamental goal of ongoing research is to translate basic science and animal model findings into prevention and treatment strategies that can improve human health. Areas of research in the division include viral pathogenesis and immunology, the epidemiology of common infectious disease and clinical trials of new vaccines and treatments. Below we highlight a few of the many accomplishments of the division.

Clinical/Translational Research: This year's major highlight was the introduction of a new rotavirus vaccine, developed by Drs. Ward and Bernstein, into Latin America and Europe. The availability of this vaccine could eventually save 500,000 lives per year around the world. Evaluation of vaccines for potential bioterrorism agents and newly emerging pathogens such as avian influenza also continued. Multicenter studies of avian influenza vaccines led by Drs. Bernstein and Brady were promising. With the addition of Dr. Subbramanian, these evaluations were extended to include determination of cell mediated responses. Other studies of influenza vaccines led to the availability of an influenza vaccine from another manufacturer, thus increasing the ability to provide vaccine to all who should receive vaccines. Preclinical studies funded through our NIH contract to evaluate antivirals, led by Drs. Cardin and Bernstein, have identified promising microbicides and treatments for herpes virus infections. Epidemiologic research, led by Dr. Staat, include a CDC funded contract, which established CCHMC as a sentinel site in surveillance of common viral respiratory pathogens as well as rotavirus. These studies are helping to more accurately determine the health burden of these infections as was presented in a recent NEJM article. Research conducted through our International Adoption Center, directed by Dr. Staat, could change the way TB screening and immunization verifications are performed. Our Infection Control Program, directed by Dr. Connelly, has been part of an AHRQ funded project to reduce the number of surgical site and catheter associated infections.

Basic Research: In order to better understand herpes virus latency, Dr. Sawtell utilized viral mutants and a quantifiable mouse latency/in vivo reactivation model to determine that transactivation of the HSV protein, VP16, is indispensable for the transition from latent to lytic viral gene expression in vivo. She and her colleague, Dr. Thompson at UC, hypothesize that the VP16 promoter functioned as a key organizational platform through which host cell stress induced changes are communicated to the latent viral genome leading to the upregulation of VP16 and subsequent gene expression. These studies uncovered an important new target for blocking HSV transmission and recurrent disease. Significant progress has also been made in the most common cause of gastroenteritis epidemics, Noroviruses. The team led by Dr. Jiang and his colleagues, Drs. Farkas and Tan, found that human Noroviruses recognize human histo-blood group antigens as receptors and that different Noroviruses recognize different receptors thus identifying some people as susceptible and some resistant to outbreaks of different viruses. They continue characterizing the antigenic epitopes of the human histo-blood group antigens that are responsible for norovirus recognition and to map the capsid gene that interacts with the human histo-blood group antigens. This research is leading to the design of compounds that can block Norovirus/receptor interaction and act as antivirals against Noroviruses.

Clinical Care: Under the direction of Dr. Gerber the number of inpatient consultations reached new highs as did the number of families using our International Adoption Center, directed by Dr. Staat. We continue to be a valuable resource for local pediatricians as demonstrated by the number of Priority Link calls answered by our faculty.

The division was well-represented in important academic leadership positions in the past year, both at local and national levels. Local leadership positions include President of the CCHMC Women's Faculty Association (Dr. Sawtell), Director of CME (Dr. Gerber), Chair of the Steering Committee for AAHRPP accreditation (Dr. Bernstein), Chair of the IRB (Dr. Frenck) and Chair of the Biosafety Committee (Dr. Strasser). National leadership is reflected by extensive representation of our faculty on NIH study sections, editorial boards, and representation to academic pediatric societies including the AAP Red Book Committee, PIDS and the AAP.

## TRAINING

Matthew Linam, MD	PGYVI	University of Tennessee
Laura Stadler, MD	PGY-VII	University of Louisville
Rachel Pestridge	Student	University of West England
Danielle Kroetz	Undergraduate	Auburn University
Kristen Frommoyer	Undergraduate	University of Kentucky
Julie Thayer	Undergraduate	Ryerson
Michelle Neace	Graduate	University of Cincinnati

## GRANTS, CONTRACTS AND INDUSTRY AGREEMENTS

Grant and Contract	Awards Annual Direct/Project Period Direct
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**Bernstein, D**

The Natural History of CMV-Related Hearing Loss		
National Institutes of Health (University of Alabama at Birmingham)		
N01 DK 000008	06/01/05 – 05/31/12	\$88,940/\$1,079,552
Evaluation of Control Measures Against Diseases Other Than AIDS		
National Institutes of Health		
N01 AI 025459	06/01/02 – 05/31/07	\$2,729,925/\$15,465,676
Bernstein	\$2,291,029	Part A
Cohen	\$438,896	Part C
Phase III Vaccine Trial in Sero-Negative Women		
National Institutes of Health (St. Louis University subcontract)		
N01 AI 045250	11/01/02 – 08/31/06	\$345,150/\$1,380,600
Animal Models of Human Viral Infections for Evaluation of Experimental Therapies		
National Institutes of Health		
N01 AI 015438	05/01/01 – 04/30/08	\$399,309/\$2,179,143

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**Brady, R**

CASG Subcontract		
National Institutes of Health (University of Alabama-Birmingham subcontract)		
N01 AI 030025	08/01/03 – 07/31/10	\$1,889/\$13,224

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**Jiang, X**

Characterization of Human Caliciviruses		
National Institutes of Health		
R01 AI 037093	7/15/02 – 6/30/07	\$225,000/\$750,000
Norway-Like Viruses and Their Receptors		
National Institutes of Health		
R01 AI 055649	08/01/05 – 01/31/10	\$219,713/\$1,012,500
Development of Strategies to Treat and Prevent Norovirus Infections		
Department of Defense		
	02/01/04 – 01/31/08	\$375,724/\$1,782,443
Role of Human Milk in Infant Nutrition and Health – Molecular Biology Core		
National Institutes of Health		
P01 HD 013021	06/30/03 – 03/31/08	\$102,962/\$668,579
Role of Human Milk in Infant Nutrition and Health – Gastroenteritis Project		
National Institutes of Health		
P01 HD 013021	06/30/03 – 03/31/08	\$137,607/\$500,253

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**Sawtell, N**

Molecular Analysis of HSV-1 Reactivation from Latency		
Yamanouchi USA Foundation		
	11/30/03 – 11/29/06	\$30,000/\$90,000
Molecular Analysis of HSV-1 Reactivation from Latency		
National Institutes of Health		
R01 AI 032121	02/01/03 – 01/31/08	\$225,000/\$1,125,000
Ocular HSV Infection Latency and Pathogenesis		
National Institutes of Health (University of Cincinnati subcontract)		
R01 EY 013168	09/01/03 – 08/31/07	\$87,393/\$343,454

Staat, M		
Enhanced Surveillance for Newly Vaccine Preventable Diseases		
Centers for Disease Control		
U38 CCCU522352	09/30/02 – 09/29/07	\$612,876/\$1,939,227
Current Year Direct		\$5,581,488
Industry Contracts		
Bernstein, D		
Aventis		\$1,155
GlaxoSmithKline		\$125,048
PPD Development		\$13,808
AHPC Corporation		\$4,803
Brady, R		
GlaxoSmithKline		\$41,687
Gerber, M		
Novartis		\$207
Wyeth Ayerst Laboratories		\$22,384
Schiff, G		
Protein Science Corporation		\$34,519
Staat, M		
Merck Research Laboratories		\$211,322
Strasser, J		
Corixa Corporation		\$24,336
Wyeth Ayerst Laboratories		\$109,973
Ward, R		
Wyeth Ayerst Laboratories		\$26,256
Merck & Co., Inc.		\$953,266
Procter & Gamble		\$31,879
Numico Research		\$456
Protein Science		\$34,499
Sanofi		\$181,656
Virus Research Institute		\$333,355
Current Year Direct Receipts		\$2,150,609
<b>TOTAL</b>		<b>\$7,732,097</b>

## PUBLICATIONS

- Bernstein D. Glycoprotein D adjuvant herpes simplex virus vaccine. *Expert Rev Vaccines* 2005;4(5):615-27.
- Bernstein DI. Rotavirus infections. In: Burg FD, Ingelfinger JR, Polin RA, editors. *Current pediatric therapy*; 18th ed. Philadelphia: Saunders Elsevier; 2006. p. 797-799.
- Bernstein DI, Spruance SL, Arora SS, Schroeder JL, Meng TC. Evaluation of imiquimod 5% cream to modify the natural history of herpes labialis: a pilot study. *Clin Infect Dis* 2005;41(6):808-14.
- Bravo FJ, Cardin RD, Bernstein DI. Effect of maternal treatment with cyclic HPMPC in the guinea pig model of congenital cytomegalovirus infection. *J Infect Dis* 2006;193(4):591-7.
- Glass RI, Bhan MK, Ray P, Bahl R, Parashar UD, Greenberg H, Rao CD, Bhandari N, Maldonado Y, Ward RL, Bernstein DI, Gentsch JR. Development of candidate rotavirus vaccines derived from neonatal strains in India. *J Infect Dis* 2005;192 Suppl 1:S30-5.

6. Heineman TC, Schleiss M, Bernstein DI, Spaete RR, Yan L, Duke G, Prichard M, Wang Z, Yan Q, Sharp MA, Klein N, Arvin AM, Kemble G. A phase 1 study of 4 live, recombinant human cytomegalovirus Towne/Toledo chimeric vaccines. *J Infect Dis* 2006;193(10):1350-60.
7. Kahn JA, Bernstein DI. Human papillomavirus vaccines and adolescents. *Curr Opin Obstet Gynecol* 2005;17(5):476-82.
8. Kahn JA, Bernstein DI, Rosenthal SL, Huang B, Kollar LM, Colyer JL, Tissot AM, Hillard PA, Witte D, Groen P, Slap GB. Acceptability of human papillomavirus self testing in female adolescents. *Sex Transm Infect* 2005;81(5):408-14.
9. Kahn JA, Slap GB, Bernstein DI, Kollar LM, Tissot AM, Hillard PA, Rosenthal SL. Psychological, behavioral, and interpersonal impact of human papillomavirus and Pap test results. *J Womens Health (Larchmt)* 2005;14(7):650-9.
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11. Lee BP, Azimi PH, Staat MA, Louie L, Parada E, Berke T, Ward RL, Bernstein DI, Matson DO. Nonmedical costs associated with rotavirus disease requiring hospitalization. *Pediatr Infect Dis J* 2005;24(11):984-8.
12. Madhi SA, Cutland C, Zhu Y, Hackell JG, Newman F, Blackburn N, Murphy BR, Belshe RB, Karron RA, Deatly AM, Gruber WC, Bernstein DI, Wright PF. Transmissibility, infectivity and immunogenicity of a live human parainfluenza type 3 virus vaccine (HPIV3cp45) among susceptible infants and toddlers. *Vaccine* 2006;24(13):2432-9.
13. Phua KB, Emmanuel SC, Goh P, Quak SH, Lee BW, Han HH, Ward RL, Bernstein DI, Vos BD, Bock HL. A rotavirus vaccine for infants: the Asian experience. *Ann Acad Med Singapore* 2006;35(1):38-7.
14. Riedesel JM, Rosenthal SL, Zimet GD, Bernstein DI, Huang B, Lan D, Kahn JA. Attitudes about human papillomavirus vaccine among family physicians. *J Pediatr Adolesc Gynecol* 2005;18(6):391-8.
15. Rosenthal SL, Zimet GD, Leichter JS, Stanberry LR, Fife KH, Tu W, Bernstein DI. The psychosocial impact of serological diagnosis of asymptomatic herpes simplex virus type 2 infection. *Sex Transm Infect* 2006;82(2):154-7; discussion 157-8.
16. Ward JI, Cherry JD, Chang SJ, Partridge S, Lee H, Treanor J, Greenberg DP, Keitel W, Barenkamp S, Bernstein DI, Edelman R, Edwards K. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med* 2005;353(15):1555-63.
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18. Treanor JJ, Schiff GM, Couch RB, Cate TR, Brady RC, Hay CM, Wolff M, She D, Cox MM. Dose-related safety and immunogenicity of a trivalent baculovirus-expressed influenza-virus hemagglutinin vaccine in elderly adults. *J Infect Dis* 2006;193(9):1223-8.
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21. Gerber MA. Group A streptococcal infections. In: Burg F, Ingelfinger J, Polin R, Gershon A, editors. *Current pediatric therapy*; 18th ed. Philadelphia: Saunders Elsevier; 2006. p. 730-733.
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29. Sawtell NM, Thompson RL, Haas RL. Herpes simplex virus DNA synthesis is not a decisive regulatory event in the initiation of lytic viral protein expression in neurons in vivo during primary infection or reactivation from latency. *J Virol* 2006;80(1):38-50.
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31. Staat MA. Immunization in special clinical circumstances: refugees and immigrants. In: Pickering LK, editor. *Redbook: 2006 report of the Committee on Infectious Diseases*; 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006. p. 67-103.
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38. Ward RL, Greenberg HB, Estes MK. In: Mestecky J, editor. *Mucosal immunology*; 3rd ed. Amsterdam ; Boston: Elsevier Academic Press; 2005. p. 887-903.
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44. Ward RL. Rotavirus vaccines: is the second time the charm? *Curr Opin Investig Drugs* 2005;6(8):798-803.
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