

University of Washington  
School of Medicine



Fellowship Program in  
Infectious Diseases  
2009-2010

# UNIVERSITY OF WASHINGTON

## FELLOWSHIP PROGRAM IN INFECTIOUS DISEASES

The fellowship program of the Division of Allergy and Infectious Diseases at the University of Washington is a two to four year training experience intended for those interested in an academic career. Both M.D. and Ph.D. fellows are invited to apply. The fellowship is funded by training grants from the National Institutes of Health, private funding agencies, and institutional sources. Currently, 25 fellows participate in the fellowship program, with 7-10 new fellows accepted each year. More than 80% of past U.W. Infectious Diseases Fellowship trainees have obtained faculty positions in academic medicine.

### THE CITY

The city of Seattle is located on Puget Sound between the Cascade and Olympic mountain ranges, providing easy access to sailing, skiing, hiking, and other outdoor recreational activities. The city also offers diverse cultural opportunities including theater, ballet, symphony, and an internationally renowned film festival, in addition to high quality residential living close to University facilities.

### THE UNIVERSITY OF WASHINGTON

The University of Washington has a student population of 39,000 and grants approximately 6,500 bachelor's and 3,200 advanced degrees annually. The University of Washington is a major biomedical research institution, ranking first in the United States among public institutions (and second overall) in obtaining federal research funds. The School of Medicine has over 1,200 full-time faculty members, including clinical and basic science departments.

The well-established Division of Allergy and Infectious Diseases, within the Department of Medicine, consists of 72 full-time faculty members, 18 adjunct or affiliate faculty members, and 55 clinical faculty. The faculty include many nationally and internationally recognized investigators in diverse subspecialty areas, including phagocyte biology and function, sexually transmitted diseases, HIV/AIDS, viral diseases, immuno-compromised hosts, bacterial pathogenesis, geographic medicine, urinary tract infections, and the molecular biology of infectious diseases. The Infectious Diseases Fellowship Program is based at the University of Washington Medical Center and four affiliated institutions: Harborview Medical Center,

the Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance, Veterans Affairs Puget Sound Health Care System, and Children's Hospital and Medical Center.

### TRAINING PROGRAM

The goals of the Infectious Diseases Fellowship Program are to provide the highest quality clinical and research training in order to equip fellows with the skills they will need for a career in academic infectious diseases. Fellows are encouraged to focus early in their fellowship on a particular area of research and to devote much of their time to a productive investigative experience. Although formally accepted for a three-year commitment, many fellows will spend four years in fellowship training.

Research training can be selected with a major focus in laboratory investigation or in clinical epidemiology. Our program allows selected fellows, who choose clinical epidemiology, to pursue a M.P.H. degree in epidemiology during infectious diseases fellowship. Most inpatient clinical duties for fellows are completed by the end of the first year of the fellowship so that uninterrupted research time is available.

The selection of specific research projects is accomplished through discussions between individual investigators and fellows during and after the time of the initial interview and generally before the candidates actually start the program. Fellows will spend the majority of their fellowship working in their primary area of research.

Research training is offered in nine areas of special emphasis, representing the principal strengths of our faculty, though fellows can pursue interests that span different research areas. Each area offers the trainee a variety of well-developed and well-funded research programs from which to choose.

The Division of Allergy and Infectious Diseases also provides fellows with research opportunities in conjunction with the closely allied Department of Global Health and the basic science departments in the areas of microbial pathogenesis, immunology, microbiology, molecular virology, and parasitology.

# RESEARCH OPPORTUNITIES

## Pathogenesis of Viral Diseases

- Michael Boeckh, M.D.
- Corey Casper, M.D., M.P.H.
- Lawrence Corey, M.D.
- Michael Emerman, Ph.D.
- Denise Galloway, Ph.D.
- Adam Geballe, M.D.
- Geoffrey Gottlieb, M.D., Ph.D.
- Michael Katze, Ph.D.
- David Koelle, M.D.
- James Mullins, Ph.D.
- Julie Overbaugh, Ph.D.
- Anna Wald, M.D., M.P.H.
- Joe Zunt, M.D.

Offers an integrated interdisciplinary group of faculty for training in virology, with research activities ranging from basic molecular virology, to immunologic aspects of viral diseases, to the clinical epidemiology, prevention, and treatment of viral diseases. Expertise is especially concentrated in viral STDs, retroviruses, and viral infections of the immunocompromised host.

## Pathogenesis of Bacterial, Fungal, and Parasitic Diseases

- Fred Buckner, M.D.
- Patrick Duffy, M.D.
- David Fredricks, M.D.
- E. Peter Greenberg, Ph.D.
- Thomas Hawn, M.D., Ph.D.
- Tobias Hohl, M.D., Ph.D.
- Wim Hol, Ph.D.
- Sheila Lukehart, Ph.D.
- Christina Marra, M.D.
- Barbara Menzies, M.D.
- Samuel Miller, M.D.
- Steve Moseley, Ph.D.
- Dorothy Patton, Ph.D.
- Lalita Ramakrishnan, M.B.B.S., Ph.D.
- Craig Rubens, M.D., Ph.D.
- Walter Stamm, M.D.
- Ann Stapleton, M.D.
- Patricia Totten, Ph.D.
- Wesley Van Voorhis, M.D., Ph.D.
- Ted White, Ph.D.

Emphasizes molecular studies of the virulence determinants integral to bacterial, fungal, and parasite pathogenesis. Of special interest are mechanisms of attachment and cellular invasion in *Escherichia coli*, *Pseudomonas aeruginosa*, Group

B streptococci, Salmonella, *Chlamydia trachomatis*, *Haemophilus ducreyi*, *Treponema pallidum*, *Aspergillus fumigatus*, and *Candida albicans* infections. Potential drug targets and drug-development are being pursued for *Trypanosoma cruzi*, *Trypanosoma brucei*, *Leishmania* spp., and *Plasmodium falciparum*.

## Infectious Disease Immunology

- Alan Aderem, Ph.D.
- Philip Greenberg, M.D.
- Thomas Hawn, M.D., Ph.D.
- David Koelle, M.D.
- Sheila Lukehart, Ph.D.
- Uma Malhotra, M.D.
- Juliana McElrath, M.D., Ph.D.
- Wesley Van Voorhis, M.D., Ph.D.

Provides training opportunities in laboratories studying the immunobiology and immunogenetics of host cell responses to infectious agents, especially *Treponema pallidum*, CMV, HIV, other retroviruses, HSV, Chlamydia, and Listeria. Particular emphasis is placed on elucidating the roles of innate immunity, specific cytokines, and T cell subsets in these infections.

## Sexually Transmitted Diseases

- Corey Casper, M.D., M.P.H.
- Connie Celum, M.D., M.P.H.
- Lawrence Corey, M.D.
- Denise Galloway, Ph.D.
- Matthew Golden, M.D.
- Geoffrey Gottlieb, M.D., Ph.D.
- King Holmes, M.D., Ph.D.
- Mari Kitahata, M.D., M.P.H.
- Nancy Kiviat, M.D.
- David Koelle, M.D.
- Laura Koutsky, Ph.D., M.S.P.H.
- Christina Marra, M.D.
- Jeanne Marrazzo, M.D., M.P.H.
- Scott McClelland, M.D., M.P.H.
- Dorothy Patton, Ph.D.
- Walter Stamm, M.D.
- Patricia Totten, Ph.D.
- Wesley Van Voorhis, M.D., Ph.D.
- Anna Wald, M.D., M.P.H.

Offers a multi-disciplinary approach to the study of sexually transmitted infections, ranging from clinical and epidemiological studies in the United States and developing countries, to molecular pathogenesis and immune responses to STD

pathogens. Organisms of particular interest include *Chlamydia trachomatis*, *Treponema pallidum*, herpes simplex virus, human papilloma virus, and *Haemophilus ducreyi*.

### Human Immunodeficiency Virus Infection

- Corey Casper, M.D., M.P.H.
- Connie Celum, M.D., M.P.H.
- Ann Collier, M.D.
- Robert Coombs, M.D., Ph.D.
- Lawrence Corey, M.D.
- Michael Emerman, Ph.D.
- Carey Farquhar, M.D., M.P.H.
- Geoffrey Gottlieb, M.D., Ph.D.
- Philip Greenberg, M.D.
- King Holmes, M.D., Ph.D.
- Grace John-Stewart, M.D., Ph.D., M.P.H.
- Seymour Klebanoff, M.D., Ph.D.
- Christina Marra, M.D.
- Scott McClelland, M.D., M.P.H.
- Juliana McElrath, M.D., Ph.D.
- James Mullins, Ph.D.
- Julie Overbaugh, Ph.D.
- Judith Wasserheit, M.D., M.P.H.

Provides a wide range of opportunities to investigate the epidemiology, natural history, immunology, molecular virology, and clinical care of patients with HIV infection. NIH-sponsored AIDS Clinical Trials and AIDS Vaccine Evaluation Units are located at the University of Washington, as well as a Fogarty program for international AIDS investigation and training.

### Leukocyte Biology and Function

- Alan Aderem, Ph.D.
- Thomas Hawn, M.D., Ph.D.
- William Henderson Jr., M.D.
- Seymour Klebanoff, M.D., Ph.D.
- Henry Rosen, M.D.

Investigators focus on the mechanisms by which phagocytes recognize and kill microorganisms. The roles of mast cells and eosinophils in allergic responses and infectious diseases are also being studied, as is the role of apoptosis. Another area of emphasis is the role and function of phagocytes in acute inflammation and tissue injury.

### Immunocompromised Host

- Michael Boeckh, M.D.
- Robert Coombs, M.D., Ph.D.
- Lawrence Corey, M.D.
- David Fredricks, M.D.

- Adam Geballe, M.D.
- Philip Greenberg, M.D.
- Ted White, Ph.D.

Provides a wide variety of research opportunities through the Fred Hutchinson Cancer Research Center and the Seattle Cancer Care Alliance, the world's largest marrow transplant center. Studies range from the molecular biology of viral pathogens in transplant patients, especially CMV, HSV, and HCV, to clinical studies of the epidemiology, treatment, and prevention of CMV and fungal infections. Multiple collaborations between faculty in this track and those in the virology and immunology tracks foster interdisciplinary investigative opportunities.

### Clinical Epidemiology of Infectious Diseases

- Connie Celum, M.D., M.P.H.
- Lawrence Corey, M.D.
- Carey Farquhar, M.D., M.P.H.
- Thomas Fleming, Ph.D.
- Matthew Golden, M.D.
- King Holmes, M.D., Ph.D.
- Grace John-Stewart, M.D., Ph.D., M.P.H.
- Mari Kitahata, M.D., M.P.H.
- Laura Koutsky, Ph.D., M.S.P.H.
- Jeanne Marrazzo, M.D., M.P.H.
- Delia Scholes, M.P.H., Ph.D.
- Steven Self, Ph.D.
- Walter Stamm, M.D.
- Anna Wald, M.D., M.P.H.

Investigators are utilizing epidemiologic techniques to study the incidence, prevalence, and risk factors associated with various infections, especially STDs, HIV, sepsis, and urinary tract infections. A hallmark of these studies is close interaction with laboratory collaborators in order to utilize molecular epidemiologic techniques or study patient materials at the molecular and cellular level.

### Clinical Trials

- Connie Celum, M.D., M.P.H.
- Ann Collier, M.D.
- King Holmes, M.D., Ph.D.
- Walter Stamm, M.D.
- Anna Wald, M.D., M.P.H.

Interactions between clinical and laboratory investigators are utilized in the context of controlled clinical trials. Studies focus principally on STDs, urinary tract infections, and infections of the immunocompromised host. The expertise of highly experienced biostatistical faculty is available to trainees in this track.

## **RELATED FELLOWSHIP PROGRAMS**

The Division of Pediatric Infectious Diseases at the Children's Hospital and Medical Center and the University of Washington Medical Center provides training in **Pediatric Infectious Diseases** with research emphasis on the mechanisms of antibiotic resistance and immunology and molecular approaches to infections in newborns and children. Faculty members include C. Rubens, J. Burns, A. Melvin, L. Frenkel, G. Tamura, S. Smith, D. Zerr. Persons interested in the Pediatric Infectious Diseases program should contact Dr. Sherilyn Smith, Infectious Diseases Training Program, Division of Infectious Diseases, Children's Hospital and Regional Medical Center, 4800 Sand Point Way NE, CH-32, Seattle WA 98105; phone: (206) 987-2073; fax: (206) 987-3890; Email: [gtamura@u.washington.edu](mailto:gtamura@u.washington.edu).

The **Allergy** section of the Division of Allergy and Infectious Diseases, is located at the Center for Allergy and Inflammation, UW Medicine, 815 Mercer Street, Seattle, WA 98019. The Allergy and Immunology Fellowship Training Program (Program Director: William R. Henderson Jr., MD.; website: <http://depts.washington.edu/daid/Allergy%20Fellowship/overviewallergy.htm>) provides clinical and research training in allergy, asthma, and immunology at the University of Washington and affiliated institutions. Persons interested in the allergy program should contact Dr. William R. Henderson Jr., Department of Medicine, 815 Mercer Street, University of Washington, Seattle, WA 98109; phone: (206) 543-3780; fax (206) 685-9318; Email: [joangb@u.washington.edu](mailto:joangb@u.washington.edu).

## **CLINICAL EXPERIENCE**

The Division of Allergy and Infectious Diseases provides the opportunity for training in virtually every aspect of clinical infectious diseases. Clinical training takes place both in the inpatient and the outpatient setting. All fellows participate in approximately 12 months of inpatient consultative service at affiliated hospitals. These clinical rotations include consultative experience with general medical and surgical patients (University of Washington Medical Center, Harborview Medical Center, and Veterans Affairs Puget Sound Health Care System), with specific opportunities in pediatric infectious diseases (Children's Hospital), with infectious diseases in immunocompromised hosts (Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance and the University of Washington Medical Center), and with AIDS patients and patients with other sexually transmitted diseases (Harborview Medical Center and the University of Washington Medical Center).

The clinical training provided by this program confers ID board eligibility after two years.

While nearly all of the Divisional faculty participate in clinical care, the following faculty participate more extensively in clinical and teaching activities of the Division:

### **Clinician Educators**

- Timothy Dellit, M.D.
- Shireesha Dhanireddy, M.D.
- Robert Harrington, M.D.
- Jan Hirschmann, M.D.
- Nina Kim, M.D.
- Ajit Limaye, M.D.
- Richard Miller, M.D.
- Paul Pottinger, M.D.
- David Spach, M.D.
- Marvin Turck, M.D.

## **OUTPATIENT TRAINING OPPORTUNITIES**

Several clinics are available for outpatient training in Infectious Diseases. Most fellows will work in one of the three HIV/AIDS clinics operated by the Division. This provides a long-term, continuity clinic and experience in managing HIV infected patients. Fellows will also participate in at least one other clinic rotation according to their interests and areas of research. Two years of weekly half-day outpatient clinics are completed during fellowship.

**Sexually Transmitted Diseases Clinic:** An academically oriented comprehensive genitourinary medicine clinic operated jointly by the Seattle-King County Department of Public Health and the University of Washington is located at Harborview Medical Center. The STD Clinic provides a focus for a number of research and training activities.

**Virology Research Clinic:** Located near Harborview Medical Center, this clinic serves as a research base (5,000 patient visits annually) for investigation of the natural history, pathogenesis, immunology, and therapy of genital herpes, human papillomavirus infection, hepatitis C virus, HHV-8, and other viral STD's.

<http://depts.washington.edu/herpes>

**HMC Viral Hepatitis Clinic:** This clinic focuses on hepatitis B and C, often managing HIV co-infection. Staffed by ID and GI attendings, Fellows learn comprehensive diagnosis and management of patients with hepatitis.

**HIV Clinics:** Outpatient facilities directed by the Infectious Diseases Division at Harborview Medical

Center, the University of Washington Medical Center, and the Veterans Affairs Puget Sound Health Care System currently serve approximately 3,500 patient visits annually. In addition to medical care, these clinics also provide substance abuse, nutritional, psychological, and social counseling services.

Tropical Medicine and Infectious Diseases Clinic: Located at University of Washington Medical Center to serve as a referral and primary clinic for general infectious diseases, tropical medicine, and travelers; the clinic currently handles approximately 1,000 patient visits per year.

Harborview Medical Center Infectious Diseases Clinic: A referral clinic for the evaluation and management of infectious disease problems other than HIV infection that can be managed in the outpatient setting.

### **COURSES, CONFERENCES, AND SEMINAR SERIES**

Fellows in the Infectious Diseases Program are strongly encouraged to participate in the many courses and seminar series which are offered both as a part of the program and by the University of Washington.

### **REQUIRED COURSES**

Upon arrival in July, all incoming first year fellows participate in a Core Curriculum consisting of formal courses, didactic exercises, and conferences. These are important for all fellows regardless of their specific research interest. The elements of the Core Curriculum include the following:

Orientation Course in Advanced Clinical Infectious Diseases: In July of their incoming year, all first year fellows attend a one-week orientation course in which Division faculty address the pathogenesis, diagnosis, and management of common infectious diseases. The course also introduces the fellows to the faculty and to one another.

Principles of STD and HIV Research: This course is also given each July by members of the Infectious Diseases Division and by faculty in other departments and from other institutions. All second year fellows attend, regardless of their eventual research activities, because the lectures provide basic information relevant to multiple research disciplines. The two-week course provides detailed information on a wide variety of molecular,

immunological, epidemiological, and biostatistical aspects of research.

Introduction to Clinical Microbiology: Each July, in conjunction with the Department of Laboratory Medicine, a one-week course is provided for each of our first year fellows on key elements of clinical microbiology, including practical experience in performing commonly utilized tests and evaluating microscopic specimens, including PCR and other methods utilized in molecular epidemiological investigations. In addition to this required course, a two to four-week intensive course is offered to interested fellows who wish to gain more experience in the Clinical Microbiology laboratory.

Department of Medicine Introductory Course for Postdoctoral Fellows: The Department of Medicine provides a one-week course focusing on issues of importance to physicians entering academic research careers. The agenda includes topics such as selecting a research problem, interaction with your mentor, ethics in biomedical research, grant writing, presentation at scientific meetings, and seeking an academic position.

Biomedical Research Integrity Lecture Series: Offered by the School of Medicine throughout each summer, this series consists of formal presentations and small discussion groups in Biomedical Ethics. It is required for all fellows in the program.

### **ELECTIVE COURSES**

Parasitology, Virology, and Mycology Courses: Three courses (Parasitology, Virology, and Mycology) are available each summer for interested fellows. The nine-day Parasitology course consists of morning lectures and afternoon laboratory sessions. The Virology and Mycology courses are five days each, with a format similar to that described for the Parasitology course. These courses are offered by the Department of Laboratory Medicine, with teaching contributions by members of our Division.

A Sexually Transmitted Diseases Clinical Update Course is provided four times a year consisting of an intensive weeklong exposure to clinical, diagnostic, laboratory, and therapeutic aspects of STDs.

### **CONFERENCES AND SEMINARS**

Weekly Infectious Disease Conference: The faculty and fellows of the Infectious Disease Division, as well as frequent attendees from Laboratory

Medicine, Microbiology, and other departments, participate in a weekly conference centering around recent clinical cases of particular interest.

Responsibility for the conference rotates between each of the hospitals within the system (including Children's Hospital Medical Center), and the fellow and faculty member on service that month share responsibility for presenting the conference. The presenting fellow and faculty review relevant microbiological and clinical aspects of the case, discuss pathogenesis and epidemiology, and provide a summary of the presentation and appropriate references in a handout posted on our internet site. Hospital epidemiology, including infection control is covered in this series. The inclusion of the pediatric faculty in the conference rotation assures the exposure to pediatric infectious disease problems every 4-5 weeks.

ID Curriculum: Every other week a general topic of interest for Infectious Diseases specialists is presented by a University of Washington Infectious Diseases faculty member.

HIV Journal Club: Held every other week, reviewing recent literature on all aspects of HIV, from pathogenesis to management.

STD Research and Clinical Conference: Held monthly, covering research and clinical topics in sexually transmitted diseases.

AIDS Clinical Conference: Held monthly, in which seminars on clinical, epidemiological, psychosocial, and research aspects of HIV infection are presented.

HIV/AIDS Research Conference: Held monthly, presenting new research findings on HIV/AIDS by faculty, fellows, or visiting scientists.

FHCRC Infectious Diseases and Virology Journal Club: Held monthly, this conference reviews journal articles dealing with virology, viral pathogenesis,

immunology, and infections in the immunocompromised host.

## **DIVISIONAL MEETINGS**

Infectious Disease Division Research Retreat:

The Division holds a yearly research retreat at the University of Washington. All of the faculty and fellows attend, and fellows are expected to present their ongoing research for discussion. The program allows for numerous presentations of ongoing research, with the opportunity for feedback in a relaxed atmosphere. This forum provides trainees the opportunity to develop skills in data analysis and presentation, and facilitates interaction and feedback from senior faculty concerning the research itself.

Infectious Disease Division Dinner Meeting:

Annually, the Division invites a speaker from another medical center to speak on his or her ongoing research in infectious diseases at a dinner meeting. All faculty and fellows within the Division attend, as do faculty from related disciplines. The meetings address topics of current national interest in infectious diseases and provide fellows with exposure to top-flight investigators from other institutions.

## **OTHER COURSES AND SEMINARS**

In addition to these offerings provided specifically for fellows, many related opportunities are available at the University. Of special note are courses in immunology, molecular biology, a student elective in clinical infectious diseases, and weekly seminars in the Departments of Epidemiology, Microbiology, Immunology, Pathology, and Global Health. A weekly journal club on microbial pathogenesis is held in the Department of Microbiology.

## FACULTY RESEARCH DESCRIPTIONS

### **Alan Aderem, Ph.D.**

#### ***Affiliate Professor of Medicine and Immunology Professor and Director, Institutes for Systems Biology***

Dr. Aderem, cofounder of the Institute for Systems Biology, is an internationally recognized immunologist and cell biologist who plays a central role in defining the scientific direction of the Institute and is responsible for overseeing the integration of the wide variety of disciplines within the organization. Dr. Aderem's focus is on the innate immune system - how it recognizes and formulates responses to infectious agents, and how it instructs the adaptive immune system to provide long-lived immunity to the pathogen. His initial studies defined how pattern recognition receptors, in particular the Toll-like receptors, identify bacteria - in essence, how the immune cell reads the molecular bar-code of the microbe and, thereby, precisely defines the nature of the threat. This precise recognition triggers a specific, highly regulated, response to the pathogen by the host. His laboratory is currently using high-throughput technologies to define these mechanisms and develop predictive, molecular models of immune and inflammatory responses. Dr. Aderem is also applying the tools of systems biology to the study of diseases that significantly impact global health with an emphasis on the role of the innate immune system in vaccine responses. His group is focused on deciphering the role played by the innate immune response to HIV vaccination on the subsequent development of protective immunity. Dr. Aderem's lab is also studying the host response to the influenza virus. Specifically, his research is focused on identifying mechanisms by which the highly-pathogenic viruses can evade and often dysregulate the innate immune system. Current trainees are involved in all aspects of the lab's research. Dr. Aderem collaborates with Drs. Stamm and Hawn.

Hawn TR, Verbon A, Janer M, Zhao LP, Beutler B, Aderem A. Toll-like receptor 4 polymorphisms are associated with resistance to Legionnaires' disease. *Proc Natl Acad Sci USA*. 2005; 102:2487-9.

Gilchrist M, Thorsson V, Li B, Rust AG, Korb M, Kennedy K, Hai T, Bolouri H, Aderem A. Systems Biology Approaches Identify ATF3 as a Negative Regulator of Innate Immunity. *Nature*. 2006; 441:173-8.

Miao, EA, CM Alpuche-Aranda, M Dors, AE Clark, MW Bader, SI Miller, and A Aderem. Cytoplasmic flagellin activates Caspase 1 and IL-1 $\alpha$  secretion through Ipaf. *Nature Immunology*. 2006; 7:569-75.

Andersen-Nissen E, Smith KD, Bonneau R, Strong

RK, Aderem A. A conserved surface on Toll-like receptor 5 recognized bacterial flagellin. *J Exp Med*. 2006; 204:393-403.

### **Michael Boeckh, M.D.**

#### ***Associate Professor of Medicine Member, Fred Hutchinson Cancer Research Center***

Dr. Boeckh heads clinical research program in transplant infectious diseases. He conducts laboratory research, observational studies as well as clinical trials of all phases. His major areas of interest are CMV, respiratory viruses, and most recently, the genetic basis of infectious diseases. Most of these projects are bench-to-clinic translational research. Dr. Boeckh's lab is focused on pathogen-specific immune reconstitution. One major area of research is CMV, including the immune reconstitution after transplantation, transmission of CMV, and disease management in the immunocompromised patient population. Recently, he also initiated studies to determine the role of CMV reactivation in the outcome of immunocompetent patients with sepsis and acute lung injury. Another active area of research is in respiratory viruses in immunocompromised patients. Studies are focused on the association of respiratory viruses and airflow obstruction, the adaptive immune response to respiratory viruses, viral dissemination and gene expression signatures as biomarkers for disease severity, and management strategies.

Nakamae, H., Kirby, K.A., Sandmaier, B.M., Norasetthada, L., Maloney, D.G., Maris, M.B., Davis, C., Corey, L., Storb, R., Boeckh, M. Effect of Conditioning Regimen Intensity on CMV Infection in Allogeneic Hematopoietic Cell Transplantation. *Biol. Blood Marrow Transplant*, in press, 2009.

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Limaye, A.P., Kirby, K.A., Rubenfeld, G.D., Leisenring, W.M., Bulger, E.M., Neff, M.J., Gibran, N.S., Huang, M.L., Santo, T.K., Corey, L., Boeckh, M. Cytomegalovirus Reactivation in Critically-Ill Immunocompetent Patients. *JAMA*. 300: 413-422, 2008.

Peck, A.J., Englund, J.A., Kuypers, J., Guthrie, K.A., Corey, L., Morrow, R., Hackman, R.C., Cent, A., Boeckh, M. Respiratory Virus Infection among Hematopoietic Cell Transplantation Recipients: Evidence for Asymptomatic Parainfluenza Virus Infection. *Blood* 111:1681-8, 2007.

**Frederick S. Buckner, M.D.**

***Associate Professor of Medicine***

Dr. Buckner's research concentrates on drug discovery for diseases caused by pathogenic protozoa. These include *Trypanosoma cruzi* (the cause of Chagas disease), *Trypanosoma brucei* (the cause of African sleeping sickness), *Leishmania* species (the cause of leishmaniasis), and *Plasmodium falciparum* (the cause of malignant malaria). The lab focuses mainly on several biochemical targets for developing antiparasitic drugs including sterol biosynthesis, protein prenylation, protein synthesis, and protein kinases. The general approach is to use molecular biology techniques to study enzymes involved in these pathways. This requires the molecular cloning and heterologous expression of these proteins. The enzymes are then characterized functionally and, in some cases, subjected to structural analysis by X-ray crystallography. The 3-dimensional structures are used to model molecules that can serve as enzyme inhibitors. The molecular and parasitology work are conducted in my laboratory. The X-ray crystallography and computer modeling work is done in collaboration with Dr. Wim Hol (Dept. of Biochemistry). The enzymology and organic synthesis of inhibitors is done by Dr. Michael Gelb's group in the Dept. of Chemistry. Inhibitors are tested for in vitro activity against enzyme targets and against the parasites grown in culture. Leads are refined by molecular modeling approaches (rational drug design). The compounds with the best antiparasitic activity and least toxicity to mammalian cells undergo testing in mouse models of these infectious diseases. The assembled team at UW working on anti-parasitic drug development represents one of the few collaborative efforts in the world dedicated to rational drug discovery for tropical pathogenic protozoa, and includes Dr. Hol, Dr. Van Voorhis, and Dr. Duffy from the training faculty.

Buckner F, Yokoyama K, Lockman J, Aikenhead K, Ohkanda J, Sadilek M, Sebti S, Van Voorhis W, Hamilton A and Gelb MH (2003). A class of sterol 14-demethylase inhibitors as anti-*Trypanosoma cruzi* agents. *Proc Natl Acad Sci U S A* 100:15149-53

Buckner FS and Wilson AJ. (2005) Colorimetric assay for screening compounds against

*Leishmania* amastigotes grown in macrophages. *Am J Trop Med Hyg* 72:600-5

Ojo KK, Gillespie JR, Riechers AJ, Napuli AJ, Verlinde CL, Buckner FS, Gelb MH, Domostoj MM, Wells SJ, Scheer A, Wells TN, Van Voorhis WC. (2008). Glycogen synthase kinase 3 is a potential drug target for African trypanosomiasis therapy. *Antimicrob Agents Chemother.* 52:3710-7.

Kraus JM, Verlinde CLMJ, Karimi M, Lepesheva GI, Gelb MH, Buckner FS. (2009). Rational modification of a candidate cancer drug for use against Chagas disease. *J Med Chem.* 52:1639-47. PMID: 19239254

**Corey Casper, M.D., M.P.H.**

***Associate Professor of Medicine***

***Assistant Member, Fred Hutchinson Cancer Research Center***

***Medical Director, Infection Control at Seattle Cancer Care Alliance***

Dr. Casper's research focuses on the transmission, natural history, pathophysiology and treatment of human herpesvirus-8 (HHV-8) infection. This work is aimed at developing novel strategies for the prevention and therapy of infection-associated malignancies. Dr. Casper oversees two main cohorts to address these research interests. The first cohort is based in Seattle, where a group of HHV-8-infected men are followed prospectively to characterize the frequency and correlates of viral replication, to observe transmission of HHV-8 between discordant couples, and to comprehensively characterize the immune response to HHV-8 infection. The second cohort is located in Kampala, Uganda, at the Uganda Cancer Institute. This cohort is comprised of HHV-8-infected children and adults, with and without HIV and Kaposi sarcoma, and examines factors governing the progression from chronic viral infection to malignancy. In addition to these projects, Dr. Casper leads studies of antiviral therapy for the treatment of HHV-8-associated disease, the epidemiology of HIV-associated cancers in Uganda, and healthcare-associated infections in the immunocompromised host.

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**Connie Celum, M.D., M.P.H.**

**Professor of Global Health**

**Director of the International Clinical Research Center, Global Health**

Dr. Celum's research currently focuses on clinical trials of biomedical HIV prevention and combination HIV prevention strategies with the objective to find effective strategies to reduce HIV acquisition and transmission.

Dr. Celum's recently completed international, multi-center HIV prevention trials include genital herpes suppression for prevention of HIV acquisition among heterosexual women in Africa and men who have sex with men in the Americas (HPTN 039) and among HIV infected persons in African serodiscordant couples to reduce HIV transmission and disease progression (Partners in Prevention).

Dr. Celum is the Principal Investigator of a phase 3 randomized, placebo-controlled trial of pre-exposure antiretroviral prophylaxis, of oral tenofovir and Truvada for prevention of HIV acquisition in serodiscordant couples in Kenya and Uganda. She is a co-investigator in the NIH-funded Microbicides Trials Network. Dr. Celum is PI of a NIH grant on combination HIV prevention strategies for the heterosexual HIV epidemic in Africa.

Most of her research is conducted through international collaborations, including with colleagues and sites in Peru, Kenya, and Uganda. She has many collaborators; among them, Drs. McElrath, Marrazzo, Corey, Wald, Lingappa, Baeten and Holmes.

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**Arturo Centurion, M.D.**

**Research Associate Professor**

Our research focuses on *Treponema pallidum*, the etiologic agent of syphilis. We are studying the tpr gene family of *T. pallidum*, which comprises 2% of the *T. pallidum* genome and is hypothesized to encode surface-exposed antigens that are important in syphilis pathogenesis. The Tpr antigens are major targets of the protective immune response and promising vaccine candidates.

Our main research projects are: 1. Transcription Factors. Tight regulation of expression of virulence factors is key for bacterial pathogens. We have experimentally characterized the first transcription factor in the syphilis spirochete (Tp0262, a CRP homolog). In *E. coli*, CRP regulates expression of more than 100 genes including several virulence factors. We have determined that Tp0262 activates or represses promoter activity in several tpr genes. Currently, in collaboration with Dr. Oleg Denisenko, we are identifying the members of the CRP regulon in the syphilis spirochete using chromatin immunoprecipitation (CHIP) analysis and 2. Antigenic Variation. Our group has identified the first mechanism of antigenic variation in syphilis responsible for the generation of tprK diversity. It involves donor cassettes, one expression site and non-reciprocal gene conversion mechanisms. Experimental data demonstrate sequential

acquisition of sequence diversity consistent with this mechanism. We are comparatively studying the patterns of sequence changes among syphilis isolates during infection, the role of immune pressure in selection of organisms with TprK variants and the implications of TprK diversity in immune evasion.

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**Michael Chung, M.D., M.P.H.**  
**Assistant Professor of Medicine and Global Health**

Dr. Michael Chung conducts HIV research and implements training and care programs in Nairobi, Kenya where has been based for the last 7 years. His research interests include breast milk transmission of HIV, HIV operations research, cervical cancer and HIV, and adherence to antiretroviral medications. He leads clinical activities at the Coptic Hope Center for Infectious Diseases, a set of free HIV clinics serving over 12,000 Kenyans and trains fellows at the University of Nairobi in HIV program management, health informatics, and health economics. More information on research opportunities can be found at: <http://depts.washington.edu/uwtree/>

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**Ann Collier, M.D.**

**Professor of Medicine**

**Director, UW Adult AIDS Clinical Trials Unit**

Ongoing clinical research projects include studies of antiviral treatments for HIV and the associated complications, natural and treated history of primary HIV, the effects of antiretrovirals on neurological aspects of HIV infection, and complex drug-drug interactions. Multiple therapies for treatment of HIV are under investigation. Ongoing treatment trials include Phase I, II, and III studies, and are both single and multicenter in nature. Ongoing collaborations include projects with Dr. James Mullins, Dr. Christina Marra, Dr. Sarah Holte, Dr. Jashvant Unadkat, Dr. Robert Coombs, and Dr. Mari Kitahara.

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**Robert W. Coombs , M.D., Ph.D.**

***Professor of Laboratory Medicine and Medicine***

The focus of Dr. Coombs' research activity is on the pathogenesis of HIV-1 and the quantification of viral load in the setting of therapeutic clinical trials involving both adult (Dr. Ann Collier, ACTG Network) and pediatric (Dr. Lisa Frenkel, IMPAACT Network) HIV-1 infected subjects. Of particular interest is validation of HIV-1 DNA and unintegrated episomal 2-LTR viral DNA as markers of infectivity when viral RNA levels are suppressed in the plasma with effective antiretroviral therapy. Through collaborations with Dr. John Krieger (Department of Urology) and other investigators at the UW, a research program has been established to elucidate the shedding of HIV-1 in the male and female genital tracts and the regulation of HIV-1 shedding by genital tract inflammation (Drs. Jane Hitti, Michael Boeckh and Connie Celum).

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**Lawrence Corey, M.D.**

***Professor of Laboratory Medicine  
Medicine Head, Virology Division, Laboratory  
Medicine Member & Co-director, Vaccine and  
Infectious Diseases Institute, Head Clinical  
Sciences Program, Fred Hutchinson Cancer  
Research Center***

The research areas associated with Dr. Corey include Herpes group infections, infections in the immunocompromised host, especially those undergoing bone marrow transplant, and HIV vaccine development. The Herpes Group program involves studies in HSV, CMV, HHV-6, and HHV-8. The genital HSV program has been the most

longstanding, having had NIH funding since 1978. Recently, emphasis has been on developing a greater understanding of host T cell immunity in HSV reactivation with the goal of developing an effective HSV vaccine. Dr. Corey's laboratory program is directed at understanding the immune control of HSV at the mucosal level. Several novel technologies, including in situ detection of antigen specific T cells and then interrogation by transcriptional arrays, are currently in place. Dr. Corey has directed the Diagnostic Virology Division of the University of Washington for more than 25 years. A comprehensive laboratory program in molecular diagnostics of viral infections supports the clinical research program. Dr. Corey is the overall PI of the NIAID supported HIV Vaccine Trials Network (HVTN), a multicenter, multi-international program that is given the charge of developing candidate HIV vaccines. Opportunities in clinical epidemiology of viral infections are available, including interactions between herpesviruses and HIV-1.

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**Patrick E. Duffy, M.D.**

***Affiliate Associate Professor of Pathobiology,  
Department of Global Health  
Full Member, Seattle Biomedical Research  
Institute***

***Chief, Laboratory of Malaria Immunology and  
Vaccinology, NIAID/NIH (starts Nov 2009)***

Dr. Duffy's laboratory studies the immunoepidemiology and molecular pathogenesis of malaria, and uses the knowledge gained from these studies to develop vaccines against malaria parasites. Our research primarily focuses on *Plasmodium falciparum* infections of pregnant women and young children. We discovered that a distinct parasite phenotype sequesters in the placenta and causes pregnancy malaria, and are now leading an international consortium to develop a vaccine that targets placental parasites in order to protect pregnant women. We are also studying cohorts of mother-infant pairs in Tanzania to determine whether distinct parasite phenotypes may cause the severe malaria syndromes that kill African children. We apply advanced technologies including microarrays and proteomic tools to study host-parasite interactions in the context of these large cohort studies. Our laboratory also leads an international research training program on malaria for young African scientists. Collaborators include Dr. Van Voorhis.

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**Michael Emerman, Ph.D.**

***Affiliate Professor of Microbiology  
Member, Fred Hutchinson Cancer Research  
Center***

This laboratory studies the regulatory and structural genes of the human immunodeficiency virus (HIV) in order to understand the molecular basis for its pathogenicity. Our focus is on identifying and characterizing host cell functions that are used to serve specific functions for viral replication and host functions that oppose viral replication. HIV is unusual in its ability to infect non-dividing cells such as terminally differentiated macrophages. Unlike most retroviruses, HIV can enter the nucleus at any stage of the cell cycle. We are trying to understand events that occur immediately after the virus has entered the cell that allow HIV to infect non-dividing cells. We also study intrinsic host defenses to retroviruses such as HIV. Primates have evolved a number of gene families that limit or restrict retroviral infections. In collaboration with the lab of Harmit Malik at the FHCRC we study the evolution and function of these anti-viral genes. We have found that some of these genes have been rapidly evolving throughout the history of primates and some have been under selective pressure in recent human history. Collaborators include Harmit Malik and Julie Overbaugh. Further information on the lab and recent publications at <http://www.fhcrc.org/science/labs/emerman/>.

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Voronin, Y, Holte, S, Overbaugh, J., and Emerman, M. (2009) Genetic Drift of HIV Populations in Culture. *PLoS Genetics* 5, 1-8. E1000431. PMID: 19300501

**Carey Farquhar, M.D., M.P.H.**

***Associate Professor of Medicine and  
Epidemiology***

Carey Farquhar, MD, MPH, is an Associate Professor in the Departments of Medicine and Epidemiology, and the Director of the International AIDS Research and Training Program (IARTP) at

the University of Washington (UW). Dr. Farquhar received her MD at Harvard Medical School, and completed a residency and chief residency in internal medicine and a fellowship in infectious disease at the University of Washington, where she also earned a Masters in Public Health. She currently spends approximately 2-3 months each year in Nairobi mentoring US and Kenyan trainees and conducting research on correlates of immunity against HIV-1, HIV-discordant couples, and mother-to-child HIV-1 transmission. Ongoing studies explore immune responses in HIV-exposed, uninfected infants and adults, with a focus on examining basic science questions from an epidemiologic perspective. She has published more than 40 peer-reviewed papers and is the Editor-in-Chief of the new online journal, *Retrovirology: Research and Treatment*. Dr. Farquhar teaches two courses in the School of Public Health, "AIDS: A Multidisciplinary Approach" and "Responsible Conduct of International Research." In addition, she sees HIV-infected patients one half-day per week and attends on the wards at Harborview Medical Center 6-8 weeks each year.

Farquhar C, VanCott TC, Mbori-Ngacha DA, Horani L, Bosire RK, Kreiss JK, Richardson BA, John-Stewart GC. Salivary secretory leukocyte protease inhibitor is associated with reduced transmission of human immunodeficiency virus type 1 through breast milk. *J Infect Dis* 2002; 186:1173-6.

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**Thomas Fleming, Ph.D.**  
***Professor and Chair, Biostatistics***

Dr. Fleming has had considerable involvement with the local Seattle AIDS research community as a biostatistical collaborator, consultant, and co-investigator. He has assisted Dr. King Holmes, Director of the UW Center for AIDS Research (CFAR). He is Director of the Biostatistics/ Epidemiology Core of CFAR, working in close collaboration with the Associate Director, Dr. James Hughes. He has worked locally and nationally with Dr. Larry Corey. He has developed a collaborative relationship with Dr. William Lafferty, head of the clinical research program jointly coordinated by Washington State and the CDC. He has collaborated with Dr. Grace John-Stewart on clinical research from the International AIDS Research Program, and has served as chair of the DSMB of her major Phase III randomized trials evaluating the role of breast-feeding in perinatal HIV transmission and the microbicide nonoxynol-9 in sexual transmission.

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**David N. Fredricks, M.D.**

**Associate Professor of Medicine**

**Adjunct Associate Professor of Microbiology**

**Associate Member, Fred Hutchinson Cancer Research Center**

The human body hosts a collection of complex microbial ecosystems where microbes frequently outnumber human cells, and hundreds to thousands of bacterial species may be represented. The Fredricks laboratory based at the Fred Hutchinson Cancer Research Center studies the human indigenous microbiota to determine how changes in microbial communities impact human health. We use tools in molecular biology such as broad range 16S rRNA gene PCR to describe microbial diversity in human body sites with a focus on the vaginal microbiota and the common condition bacterial vaginosis (BV). BV is a poorly understood condition associated with preterm birth, pelvic inflammatory disease, HIV acquisition, and other STDs. The Fredricks lab has identified several fastidious bacterial species that are useful markers of BV and are associated with adverse health outcomes. There are many research projects available for fellows that will develop laboratory research skills in molecular biology, microbiology, immunology, and cell biology. Alternatively, there are opportunities to focus on clinical epidemiology by applying the laboratory data to populations of women. We have ongoing research collaborations with Jeanne Marrazzo and Scott McClelland in this area.

The Fredricks laboratory also develops molecular diagnostic tests for the detection and identification

of bacterial and fungal pathogens in immunocompromised hosts. Patients with cancer are prone to a variety of infections as a result of cytotoxic therapies, defective mucosal barriers, and use of immunosuppressive drugs. The diagnosis of many such infections remains challenging due to the poor sensitivity and specificity of conventional diagnostic tests. We use quantitative PCR assays targeting ribosomal RNA genes to detect bacterial and fungal pathogens in blood, bronchoalveolar lavage fluid, and other tissues obtained from patients with cancer. Syndromes of interest include fever with neutropenia, fungal pneumonia, and unexplained pneumonia. Both laboratory and clinical research opportunities are available for fellows interested in this patient population.

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Khot PD, Ko DL, Hackman RC, Fredricks DN. Development and Optimization of quantitative PCR for the diagnosis of invasive aspergillosis using bronchoalveolar lavage fluid. *BioMed Central Infectious Diseases*, 2008;8:73.

**Denise Galloway, Ph.D.**

**Research Professor of Microbiology**

**Member & Program Head, Fred Hutchinson Cancer Research Center**

Our lab is interested in the mechanisms by which human papillomaviruses (HPVs) contribute to epithelial cancers. Most of our research has focused on the E6 and E7 oncogenes of the HPVs that have a high risk of progression to cervical cancers, such as HPV 16. In addition to mechanistic studies, we have had long-standing collaborations with epidemiologists and clinicians to understand the natural history of genital HPV infections, and the risk factors that cause only a small subset of women infected with high risk HPVs to progress to cancer. More recently we have begun to study a different group of HPVs, known as the genus beta HPVs. These beta HPVs commonly

infect skin, and may play a role in squamous cell skin cancers (SCSC). We have developed new serologic assays to detect antibodies to many HPVs and to human polyomaviruses.

Egelkroun, E. M., Galloway, D. A., Biology of genital human papillomaviruses. in <sup>3</sup>Sexually Transmitted Diseases, 4th edition<sup>2</sup>, editors K.K. Holmes, P.F. Sparling, W.E. Stamm, P.Piot, J.N. Wasserheit L.

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**Adam P. Geballe, M.D.**  
**Professor of Medicine**  
**Member, Fred Hutchinson Cancer Research Center**

Human cytomegalovirus (HCMV) infections are very common and result in life-threatening diseases in newborns and immunocompromised patients. As well, HCMV provides a valuable model system for studies of regulation of eukaryotic gene expression at the translational level. After infection by many viruses, including HCMV, cells continue to synthesize proteins despite activation of host cell responses designed to shut off translation and thereby prevent viral replication. Studies in the Geballe lab have identified genes in HCMV and related viruses that are capable of blocking antiviral responses, especially those activated by double-stranded RNA. The proteins encoded by the HCMV genes act in part through an unconventional double-stranded RNA binding domain. As well, they self-associate and bind to the critical cellular kinase PKR. Efforts are now underway to determine the origin of the activators of PKR produced during HCMV infection and to elucidate the mechanisms by which the viral genes actually block the antiviral responses. As well, new efforts are underway to clarify how cytomegalovirus antagonists have contributed to the rapid adaptation of PKR during primate evolution. Another new line of research aims to identify the genes and

mechanisms by which poxviruses evade PKR and related host dsRNA-activated anti-viral pathways. These studies should reveal new insights into the host-virus interactions that are likely to be key determinants of the pathogenesis of viral infections and may have implications for the design of viral vaccines and vectors.

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**Matthew Golden, M.D.**  
**Associate Professor of Medicine**  
**Director, PHSKC STD Control Program**

Our group's primary focus is on operational research evaluating new public health interventions to control sexually transmitted infections (STIs), including HIV. This work is conducted as a collaboration between UW and Public Health – Seattle & King County (PHSKC), and provides fellows training opportunities that integrate research and public health practice. (Dr. Golden is the Director of the Public Health - Seattle & King County HIV/STD Control Program.) Ongoing projects include a community-level randomized trial of expedited partner therapy for gonorrhea and chlamydial infection, a program to increase antiretroviral use to prevent HIV transmission, a cohort study of young men who have sex with men, studies related to HIV testing, and a wide spectrum of surveillance projects. The group's research is interdisciplinary and seeks to capitalize on the diverse expertise available through the university and PHSKC. Opportunities for fellows with an interest in public health include both long-term research projects, and public health practicums completed as part of the requirements for an MPH degree.

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**Geoffrey S. Gottlieb, M.D., Ph.D.**  
**Assistant Professor of Medicine**

Dr. Gottlieb is the PI of a study in Senegal, West Africa on the effect of antiretroviral therapy (ART) on HIV-2 disease outcomes, emergence of drug resistance, and genital shedding. HIV-2 is intrinsically resistant to the non-nucleoside reverse transcriptase inhibitors (NNRTI), Fusion inhibitors (enfuvirtide), partially resistant to some protease inhibitors (PI) (and has a low genetic barrier to nucleoside reverse transcriptase inhibitors (NRTI) resistance), making treatment algorithms in resource-limited settings challenging. He is also involved in understanding the differences between the natural history, clinical, immunologic and virologic aspects of HIV-1 and HIV-2 infection. HIV-2 is generally less pathogenic than HIV-1. Compared to HIV-1, HIV-2 infection is characterized by a much longer asymptomatic stage, lower plasma viral loads, slower decline in CD4 count, lower mortality rate due to AIDS, lower rates of mother to child transmission and lower rates of sexual transmission. In addition, he has been studying the effects of dual infection with HIV-1 and HIV-2 on disease outcomes and ART in Senegal. This work is an ongoing collaborative effort between the UW and the University of Dakar, Senegal, since the early 1990's. Projects opportunities include both Senegal field work and Seattle based lab studies. Dr. Gottlieb is also a Co-investigator in a study to understand the occurrence and outcome of

infection with more than one strain of HIV-1. Dual HIV-1 infection (both Co- and Super-infection) as been associated with higher viral loads, faster rate of CD4 decline, and more rapid progression to AIDS. The "Superinfection Project" is a collaborative effort, between Jim Mullins' group at the UW and the MACS cohort, to elucidate the virologic and host factors associated with infection with more than one strain of HIV-1.

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**Everett Peter Greenberg, Ph.D.**  
**Professor of Microbiology**

As a microbiologist, Dr. Greenberg is interested in the social behavior of bacteria. A primary focus has been on the coordination of activities in groups of bacteria with an emphasis on cell-to-cell communication and a phenomenon that is known as quorum sensing. Many bacteria use chemical signals as cues to coordinate activities of individuals in groups. This allows population density dependent differential gene expression, and it can function in the development of specialized sessile communities known as biofilms. Signaling plays a critical role in the development of chronic and persistent bacterial infections. Investigators in my laboratory have determined the structures of several signal molecules, elucidated the mechanism of signal synthesis, and studied how the signals activate gene expression. Our current

research examines the role of cell-to-cell signaling in bacterial virulence, and the basic mechanisms of the signaling process. Our work is currently focused on opportunistic pathogens like *Pseudomonas aeruginosa* and how bacteria adapt phenotypically and genetically for persistence in the host. We are also interested in self vs. non-self discrimination in bacteria. Dr. Greenberg collaborates with Dr. Miller.

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**Philip D. Greenberg, M.D.**

***Professor of Medicine and Immunology  
Member & Program Head, Fred Hutchinson  
Cancer Research Center***

Our laboratory is focused on developing cellular and molecular strategies to modulate T cell function for the purpose of treating viral and malignant diseases. Studies in our lab in murine models developed the principles and technologies for performing adoptive T cell therapy, in which rare antigen-specific T cells present in the host are isolated, cloned, and expanded to large numbers in vitro, and re-infused into the host to establish a potent immune response. The laboratory has also been pursuing strategies to genetically engineer T cells using retroviral-mediated gene transfer to acquire additional functions that may enhance therapeutic efficacy and antiviral activity. In particular, we have developed methods to disrupt regulatory pathways operative intracellularly in CD8+ CTL that limit the efficacy of these T cells in the context of targeting high antigen burdens or a persistent replicating antigen, such as occurs in HIV infection. Finally, our lab is pursuing a basic/preclinical vaccine development project in which we are developing transgenic and knockout

mice with immune systems that better mimic the human immune response, and using these mice to analyze the nature, magnitude, and tissue localization of responses elicited by candidate HIV vaccines, as well as to elucidate the mechanisms that particular vaccines may engage or fail to engage to provide a basis for designing strategies to facilitate development of potentially more effective vaccines. We are also creating B cell transgenic mice that have the capacity to produce HIV neutralizing antibodies, and are using these mice in collaborative studies to design and test novel immunogens that might provide better protection from HIV infection. Other training grant faculty with whom members of this laboratory interact and/or collaborate include Larry Corey, Julie McElrath, Jim Mullins, Denise Galloway, and Michael Emerman.

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**Robert Harrington, M.D.**

***Professor of Medicine***

Dr. Harrington is a Professor of Medicine in the clinician teacher pathway. He is also the medical director of the Harborview Madison (HIV) Clinic and director of the UW CFAR Clinical Research Core and HIV Specimen Repository. He attends on the general medicine and infectious diseases services at Harborview Medical Center and lectures frequently on a variety of HIV and infectious diseases topics. He is a recipient of the Beeson

award for housestaff teaching. His interests are in general infectious diseases, clinical HIV and translational HIV research. He's published over 50 manuscripts and book chapters on HIV and infectious diseases.

**Thomas Hawn, M.D., Ph.D.**

***Associate Professor of Medicine***

We are investigating immunologic mechanisms of disease pathogenesis with an emphasis on genetic, cellular, and molecular studies of the innate immune response. These studies are directed towards understanding why individuals have different susceptibility to infections and whether these insights can lead to novel treatment and vaccine strategies. We are using several approaches to understand this question. First, we are pursuing case-control human genetic studies to find associations of polymorphisms in innate immune response genes with disease susceptibility. Second, we are using ex vivo and in vitro immunologic, cellular and molecular assays to understand how these genes and their variants mediate a protective immune response. Finally, we are complementing these studies with in vivo infection models in mice with targeted gene deletions to elucidate mechanisms of disease pathogenesis. We are using these methods to study the pulmonary innate immune response to *Mycobacterium tuberculosis* and *Legionella pneumophila*. In addition, we are examining susceptibility to *E. coli* and urinary tract infections. We are comparing and contrasting the host immune response to these different pathogens to gain a better understanding of immunogenetics and human susceptibility to infections.

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**William Reed Henderson Jr., M.D.**

***Professor of Medicine***

Research in Dr. Henderson's laboratory focuses on (1) 5-Lipoxygenase products in airway inflammation and remodeling in asthma and (2) chemogenomics to identify new molecular targets in pulmonary fibrosis. From the 5-lipoxygenase products of arachidonic acid metabolism studies, we are trying to determine the role of specific sPLA2s vs. cPLA2 and cysteinyl leukotrienes in the mediation of airway inflammation and remodeling in a mouse asthma model. Functional genomic studies (i.e., microarray and proteomic analyses) are being performed to determine the molecular mechanisms that mediate allergen-induced airway inflammation and remodeling. Research to identify new molecular targets in pulmonary fibrosis involve studies to determine the effect of novel antifibrotic agents on profibrotic gene expression in the airways in a mouse model of PF. These studies represent a focused effort using chemogenomics to identify, develop, and validate small molecule inhibitors of AP-1/TGF $\beta$ -driven profibrotic gene expression (microarray and proteomic studies) as novel therapies in PF patients.

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#### **Tobias Hohl, M.D., Ph.D.**

**Assistant Professor of Medicine,  
Assistant Member, Clinical Research Division,  
Fred Hutchinson Cancer Research Center**

Our laboratory research focuses on the host-pathogen relationship between medically relevant fungi and the vertebrate immune systems. Invasive aspergillosis is the most common invasive mold infection worldwide and represents a major cause of infectious morbidity and mortality in patients that receive treatment for leukemia or that undergo bone marrow transplantation. Our goal is to develop a detailed mechanistic understanding of molecular and cellular host defenses against *Aspergillus fumigatus*, the most common etiologic agent of invasive aspergillosis to develop novel therapeutic strategies to augment or supplement current antifungal drugs. To this end, we use a murine model of infection and rely on a combination of cell biological, immunological, and imaging techniques to probe the host-pathogen interface.

Specific projects in the laboratory include;(1)In vivo analysis of Toll-like receptor and lectin signaling pathways in murine host defense against *A. fumigatus*,(2)Dissection of molecular mechanism required for the initiation of *A. fumigatus*-specific CD4 T cell responses in the lung, and (3) Development of antibody-based molecular probes to target fungal cell growth.

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#### **Wilhelmus G. J. Hol, Ph.D. Professor of Biochemistry**

Wim Hol is interested in protein crystallography for structure-based design of drugs for tropical diseases. The major goals of our laboratory are to unravel the three-dimensional structures of key protein molecules, to explore the relationships among protein structure, function, and dynamics, and to exploit this insight for the design of new medically relevant molecules, in particular for the treatment of infectious tropical diseases. This includes:

(1) We have recently solved the high-resolution structures of three editosome proteins from the sleeping sickness parasite *Trypanosoma brucei*: the RNA-editing ligase (REL1), the RNA-editing terminal uridylyl transferase (RET2), and the key structural protein "A6" which keeps the multi-million Dalton complex together.

(2) In our research on cholera toxin and heat-labile enterotoxin, we recently have solved over 20 crystal structures of 10 different protein components from the large Type 2 Secretion System (T2SS), which translocates the toxins from the periplasm into the lumen of the human host.

(3) For understanding the host cell invasion machinery of the malaria parasite, the structures of the *Plasmodium falciparum* MyoA-tail with the MyoA tail interaction protein (MTIP) has been very informative, and forms the basis of structure-based

design of new anti-malaria compounds with collaborators in the Departments of Biochemistry and Medicine.

(4) Within the framework of the Medical Structural Genomics of pathogenic Protozoa (MSGPP) program project we have solved numerous structures of potential drug target proteins from Plasmodium, Trypanosoma, Leishmania, Toxoplasma and Cryptosporidium species. On the basis of these studies low nanomolar inhibitors of these parasites in cell assays have already been obtained.

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**King K. Holmes, M.D., Ph.D.**  
**Professor of Medicine**  
**Head, Division of Infectious Diseases,**  
**Harborview Medical Center**  
**Chair, Department of Global Health**

Dr. Holmes chairs the Department of Global Health, is the Director of the University of Washington Center for AIDS and STDs, a WHO Collaborating Center, which involves 265 UW-affiliated faculty and research scientists and 85 pre- and post-doctoral trainees. He is the principle investigator for the NIH-funded UW Center for AIDS Research

and the UW STI Cooperative Research Center, and PI for the International Training and Education Center on HIV (I-TECH), and co-PI on NIH-funded AIDS/STD pre-doctoral and post-doctoral research training program, and a Fogarty International Center International AIDS Research Training Program. UW-based post-doctoral trainees in STI/HIV-related research have often extended their training to international sites with support from our Fogarty International Center or to the Centers for Disease Control and Prevention with CDC STI research fellowship funding.

He has participated in research on STIs for 40 years and in research, training, and technical assistance on HIV/AIDS and other STIs in Africa, Latin America, SE Asia, and the Western Pacific for over 20 years. He has participated in the design and conduct of six randomized controlled trials of STI prevention. He currently leads an NIH-funded randomized trial of topical microbicide use by Kenyan men in fishing communities on Lake Victoria for prevention of STI/HIV acquisition and a Wellcome Trust/NIH-funded 20-city randomized trial of STD/HIV prevention in Peru. He has trained and/or mentored over 100 scientists involved in HIV/STI research and care in the U.S. and other countries throughout the world.

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**Grace John-Stewart, M.D., M.P.H., Ph.D.**  
**Associate Professor of Medicine**

Dr. John-Stewart's major research interest is the epidemiology and transmission of HIV-1 infection in Africa. She directs several large cohort studies aimed at defining mechanisms of HIV transmission between sexual partners and from mother to infants in Nairobi, Kenya. In addition, her group is conducting studies to evaluate HIV-1 progression, with studies targeted to evaluate the role of lactation, contraception, and co-infections on HIV-1 pathogenesis. Particular research interests include determinants of mother-to-child transmission of HIV-1, breast milk transmission of HIV-1, correlates of immune protection from HIV-1, HIV-1 treatment and resistance following HAART in resource-poor settings, and pediatric HIV-1 pathogenesis. Molecular epidemiology studies and clinical trials are the focus of her research group. She collaborates with Drs. Farquhar, Richardson, Overbaugh, Chung, and Walson.

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**Michael G. Katze, Ph.D.**  
**Professor of Microbiology**  
**Associate Director, Washington National Primate Research Center**

Research in the Katze lab is focused on understanding the complex interplay between

viruses and the cells they infect and the diverse mechanisms used by viruses to avoid cellular defense mechanisms. The lab is at the forefront in using systems biology—including high-throughput genomic and proteomic technologies and computational methods—to study and model the wide constellation of changes in cellular gene expression, protein abundance, and molecular signaling that occur in response to virus infection. This approach is used to study a broad range of viruses, including influenza virus, hepatitis C virus (HCV), Ebola virus, SARS-coronavirus, herpes simplex virus, and human and simian immunodeficiency virus. Dr. Katze heads several large research programs, including a National Institute on Drug Abuse P30 Center focused on using genomic and proteomic technologies to better understand the molecular mechanisms underlying the progression of HCV-associated liver disease, AIDS, and HCV/HIV-1 dual infection; the Division of Functional Genomics and Infectious Disease at the Washington National Primate Research Center, which is focused on developing genomic and immunologic resources to enhance the use of nonhuman primates as models for human virus infection; and a Systems Biology contract focused on modeling the host response to highly pathogenic influenza virus and SARS-coronavirus. Dr. Katze is also Co-Director of the Pacific Northwest Regional Center of Excellence where research activities are aimed at providing a deeper understanding of innate and adaptive immune responses to infection and the age-related defects in immunity that lead to immunosenescence and increased vulnerability to disease.

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**H. Nina Kim, MD, MSc**

***Assistant Professor of Medicine***

***Harborview Medical Center***

***Academic Director, UW HIV/STI Graduate Certificate Program***

Dr. Kim works as a clinician-educator at the Harborview (HMC) Hepatitis & Liver Clinic and at the HMC Madison Clinic. She serves as a Co-Editor for Hepatitis Webstudy, a UW web-based tutorial for viral hepatitis and directs Conjoint 553, a UW graduate-level course entitled "Clinical Management of HIV," which is offered to both local and international students. Her research includes work on chronic hepatitis B natural history, particularly in HIV-coinfected patients, and hepatitis B vaccination.

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**Mari M. Kitahata, M.D., M.P.H.**

***Associate Professor of Medicine***

Dr. Kitahata is Director of the Clinical Epidemiology and Health Services Research Core of the UW Center for AIDS Research (CFAR) and the PI of the UW HIV Cohort, a longitudinal observational study of HIV-infected patients who receive primary care in the UW Harborview Medical Center Madison HIV Clinic and the UW Medical Center Virology Clinic from 1995 to the present. She developed the UW HIV Information System (UWHIS) to integrate comprehensive clinical data on the HIV Cohort

including demographic, medication, CD4+ T cell count, HIV-1 RNA level, hematologic, viral resistance, diagnoses, and causes of death data, linked to biological specimens to support HIV clinical, epidemiological, and translational research. Dr. Kitahata's research focuses on clinical outcomes in HIV disease including studies of effectiveness of antiretroviral treatment, optimal strategies for when to initiate and switch ART, and the effect of physicians' experience with HIV disease on survival. Dr. Kitahata has established national and international multi-cohort HIV research collaborations to address critical questions in HIV treatment and management that can't be addressed through single cohorts or clinical trials. She is the UW PI of the CFAR Network of Integrated Clinical Systems (CNICS) project and directs the CNICS Data Core, which designed and built the CNICS Data Repository housed at UW, that currently integrates comprehensive data on 21,000 patients from nine CFAR sites (UW, UAB, CWRU, UCSD, UCSF-GIVI, Harvard/Fenway, Johns Hopkins, Vanderbilt, UNC), and developed a web-based suite of standardized, validated questionnaires and implemented tablet PC-based prospective data collection of Patient-based Measures of Health, including adherence, mental health, sexual behavior, quality of life, body composition (lipodystrophy), and symptoms collected routinely at each CNICS site. Dr. Kitahata is the UW PI and directs the Data Core for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) integrating data on over 100,000 patients from more than 60 sites across the US and Canada, as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) project.

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Kitahata MM, Koepsell TD, Deyo RA, et al. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med* 1996;334:701-6.

**Nancy Kiviat, M.D.****Professor of Pathology**

Dr. Kiviat's research focuses on studies of HIV-1, HIV-2, and HPV related cancers, as well as breast cancer, especially in Africa. In addition, she directs projects examining issues related to cervical cancer control both in developing countries and in the U.S., as well as studies exploring management of women with abnormal pap smears in this country. She directs several studies examining risk factors for HIV-1 and HIV-2 genital tract shedding in women and men. In addition, over the last seven years Dr. Kiviat has been involved in several projects examining the development of biomarkers for detection of cervical, heart, and ovarian cancer. Currently there are ongoing NIH-funded projects in Seattle and Senegal, West Africa. In both African and Seattle we are examining the relationship between HIV, specific types of HPV, immunosuppression, and risk of cervical and anal cancer. In West Africa, in collaboration with Dr. Julie McElrath's lab at Fred Hutchinson Cancer Research Center, we are using ELISPOT assays to describe and contrast the immune response to HIV-1 and HIV-2 in order to understand why humans are able to control HIV-2 but not HIV-1. We have also been following prostitutes and non-prostitutes to examine the relationship between HIV-1, HIV-2, specific HPV types, and specific HPV 16 variants, immuno-suppression, and development of neoplasia. We recently received funding for a study that will be done in conjunction with Dr. McDougall at the Fred Hutchinson Cancer Research Center that will examine the molecular characteristics of cancers arising in women with and without HIV infection. Other ongoing projects in Senegal include a study examining and contrasting factors associated with genital tract virus shedding among those with HIV 1 and HIV 2. We have several studies examining new approaches to screening for cervical cancer and management of women with ASCUS and LGSIL. Various screening approaches are being examined, including the use of new assays for HPV DNA and recently developed technologies for improving cytology-based cervical cancer control. We have recently started several studies in which we are using microarrays to identify markers for detection and treatment of cervical and breast cancer. Dr. Kiviat collaborates with Drs. Koutsky, McElrath, and Mullins.

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**Seymour J. Klebanoff, M.D., Ph.D.****Professor Emeritus of Medicine**

Research is directed at elucidating the mechanisms of the host defense against microbial invasion, with emphasis on the mechanisms by which phagocytes destroy pathogenic organisms. Emphasis is on the role of phagocyte-derived oxidants, particularly those formed by the myeloperoxidase-H<sub>2</sub>O<sub>2</sub>-halide system. Although emphasis is on the phagocyte rather than the microbe, some studies deal with the destruction of special pathogens (e.g., HIV). H<sub>2</sub>O<sub>2</sub> can be generated by certain microorganisms, including strains of lactobacilli, and the H<sub>2</sub>O<sub>2</sub> so formed contributes to the control of infections in the vagina where H<sub>2</sub>O<sub>2</sub>-generating lactobacilli are a normal component of the microbial flora. Studies deal with the role of the lactobacillus-peroxidase system in the control of vaginal infections, particularly bacterial vaginosis. Studies are underway dealing with the characterization of factors released by strains of staphylococci which activate NFκB, induce cytokine release, and activate the HIV-1 LTR in cells of macrophage lineage and, thus, may play a role in the pathogenesis of infections induced by these organisms. Dr. Klebanoff collaborates with Drs. Rosen, Hawn, and Van Voorhis.

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**David M. Koelle, M.D.**  
**Professor of Medicine**

The laboratory studies host innate and acquired cellular immune responses to infections, pathogen genetic variation, and the relationship between host genomics and infection severity. Pathogens of interest include herpes simplex viruses types 1 and 2, vaccinia (the vaccine agent for smallpox), Merkel cell polyoma virus, and *P. falciparum*. These agents mostly have large genomes, so determination of the antigens that drive T-cell responses is a non-trivial problem. Our specific technical expertise is in the use of genomic libraries and genome-spanning ORF sets, which we combine with artificial or defined antigen presenting cells to interrogate CD8 and CD4 T-cell responses to a high level of definition. In addition to monitoring immune responses in blood, a specific focus of the lab has been measuring cellular immunity at sites of infection, such as skin, the female genital tract, the cornea, and the trigeminal ganglia. We have recently determined which HSV-1 antigens and epitopes are recognized in human trigeminal ganglia using autopsy material. Homing markers identified with this approach are being studied at the mechanistic level to understand how virus-specific T-cells, after priming by local infections, are programmed to turn into memory cells that can rapidly return to these sites. Innate immune responses to HSV-2 mediated by plasmacytoid dendritic cells contribute to homing molecule expression and are being correlated with HSV disease severity in a cross-sectional study. The lab also does translational research in HSV and HIV vaccines and therapeutics. We do mouse immunogenicity and efficacy studies in the HSV-2 system with antigens discovered in the lab using modern vaccine formats/adjuvants. We have tested candidate HSV-2 vaccines in phase I human clinical trials, performing T-cell immunogenicity studies on serially collected blood samples. Immunity to poxviruses is being investigated to optimize their use as vaccine vectors for HIV, and for basic studies into T-cell memory. International collections of HSV-2 isolates are being sequenced for variation in key T-cell recognition and drug target genes.

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protein 70-herpes simplex virus type 2 peptide-based vaccine designed to prime or boost CD8 T-cell responses in HSV-naïve or HSV-2-infected subjects. *Clinical and Vaccine Immunology* 15:773-782.

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**Laura A. Koutsky, Ph.D., M.S.P.H.**  
**Professor of Epidemiology**

Dr. Koutsky's research concerns the epidemiology of human papillomavirus (HPV) infections and the prevention of HPV-related neoplasms. Studies to date have demonstrated that genital HPV infections are commonly acquired within a year of first intercourse, a high percentage of infected women develop a cervical, vaginal or vulvar HPV-related squamous intraepithelial lesion, and that prophylactic HPV vaccines are highly effective in preventing vaccine-type infections and lesions. Ongoing projects are designed to (1) define the natural history of HPV infections in men, (2) identify risk factors for oro-pharyngeal HPV infection, (3) assess the frequency and outcome of disclosing positive HPV test results to partners, (4) determine immunologic responses to initial and persisting genital HPV infections, and (5) evaluate the effectiveness and cost-effectiveness of new technologies for cervical cancer prevention. Dr. Koutsky collaborates with Drs. Holmes, Kiviat, Hughes, and Galloway.

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#### **Ajit Limaye, M.D.**

##### **Associate Professor of Laboratory Medicine and Medicine**

Dr. Limaye serves as Associate Director of Clinical Microbiology at UWMC and as the Director of the Solid Organ Transplant Infectious Disease Program. He interacts with trainees at "plate rounds" and as an attending physician on the general and SOT ID services. His clinical and research activities are focused on viral and fungal infections in immunocompromised hosts.

#### **Sheila A. Lukehart, Ph.D.**

##### **Professor of Medicine & Global Health Adjunct Professor, Microbiology, Oral Biology Asst. Dean for Research & Graduate Education, Harborview Medical Center**

The Lukehart laboratory focuses on the pathogenesis of syphilis and the immune response to *Treponema pallidum* in humans and in animal models. The current major interest is the newly-identified polymorphic *tpr* gene family of *T. pallidum*, which comprises 2% of the *T. pallidum* genome and is hypothesized to encode surface-exposed antigens that are major targets of the protective immune response, may be involved in

immune evasion, and are promising vaccine candidates. One member of the *Tpr* family, *TprK*, has been demonstrated by us to undergo antigenic variation; studies related to the immunological relevance and molecular mechanism of this variation are ongoing. Our work to date has indicated that the protective immune response to *Treponema pallidum* is mediated by Th1-type CD4+ lymphocytes and infiltrating macrophages. Ongoing projects in the laboratory include the cloning and characterization of major T cell antigens of *T. pallidum* and investigation of cytokine induction by these antigens. The laboratory is also working to identify the surface molecules that are targets of opsonization and to define the kinetics of and requirements for bactericidal activity by macrophages. Many of the projects described above involve collaborations with Drs. Arturo Centurion-Lara and Lorenzo Giacani. Additionally, our laboratory is involved in studies of clinical aspects of syphilis. We know that invasion of the central nervous system by *T. pallidum* occurs in the early weeks of infection. With Dr. Christina Marra (Neurology), the laboratory is exploring the molecular basis for neuroinvasion, the immunologic response to *T. pallidum* within the CNS, and the efficacy of recommended therapy for CNS syphilis in immunocompetent and HIV-infected patients. Other studies involve the investigation of emerging macrolide resistance and development of a molecular typing method for *T. pallidum*.

Centurion-Lara A, LaFond RE, Hevner K, Godornes C, Molini BJ, Van Voorhis WC, Lukehart SA. Gene conversion: a mechanism for generation of heterogeneity in the *tprK* gene of *Treponema pallidum* during infection. *Molec Micro* 52:1579-96, 2004.

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Subfamily II genes of *Treponema pallidum* subsp. *pallidum*. Mol Microbiol. 72(5):1087-99, 2009

**Christina M. Marra, M.D.**  
**Professor of Neurology and Adjunct Professor of Medicine**

I am Board Certified in Neurology. After my Neurology training, I completed a fellowship in Infectious Diseases. The focus of my research is on clinically relevant problems that relate to infections of the nervous system. My laboratory-based work centers on syphilis and neurosyphilis. We began a study of neurosyphilis in 1996. Broadly stated, the goal of the project is to identify which patients with syphilis are at increased risk for neurosyphilis, to identify means to better diagnose neurosyphilis in HIV-infected patients, and to determine the best ways to assess the success of neurosyphilis treatment.

Part of our work has focused on identifying molecular differences in strains of *Treponema pallidum* (the bacterium that causes syphilis). As we are able to identify individual syphilis strains, we can examine changes in circulating organisms over time in Seattle. We are also studying whether there is an association between the clinical manifestations of syphilis, including central nervous system (CNS) disease, and strain type.

I participate in clinical research studies on neurological complications of HIV conducted by the UW AIDS Clinical Trials Unit, which is part of the national AIDS Clinical Trials Group. These studies address the pathophysiology of HIV-associated neurological diseases, as well as treatment and prognosis. I have been particularly interested in the role of CNS penetration of antiretrovirals in treatment of HIV-associated cognitive impairment. Clinically, I have cared for HIV-infected people with neurological problems since 1988. I also attend on the Neurology in-patient service and in Neurology clinic at Harborview.

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**Jeanne M. Marrazzo, M.D., M.P.H.**  
**Associate Professor of Medicine**

Current research is centered in several areas: the molecular epidemiology of vaginal flora, including bacterial vaginosis (BV), and role of newly defined bacteria in the pathogenesis and diagnosis of BV; application of molecular approaches to clarifying the etiology and epidemiology of sexually transmitted diseases (STD)-related syndromes; evaluation of vaginal and oral pre-exposure prophylaxis (PrEP) for prevention of HIV acquisition in African women; STD, cervical neoplasia and BV, in women who report sex with women (WSW); and clinical aspects and epidemiology of genital chlamydial infections. Our work has expanded the microbiologic spectrum of BV-associated organisms, and we are now planning to study predictors of infection with these bacteria, their role in diagnosis of vaginal infections, the host immune response in BV, and potential reservoirs (including male partners) that may help explain BV's association with specific sexual practices. The major objectives of work related to HIV PrEP is to evaluate the effectiveness of oral vs. vaginally delivered antiretroviral medications in preventing HIV acquisition in young HIV-uninfected women in sub-Saharan Africa. Research related to *C. trachomatis* seeks to assess the relationship of this pathogen to clinically evident cervicitis, and define epidemiology in and prevention approaches to understudied, vulnerable populations. Collaborators in these efforts include Dr. David Fredricks, Dr. Jared Baeten, and Dr. Connie Celum.

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**R. Scott McClelland, M.D., M.P.H.**  
**Associate Professor of Medicine, Epidemiology, and Global Health**

Dr. McClelland leads the Mombasa HIV/STD Research Site and the associated Mombasa Female Sex Workers Cohort, established in 1993. His research focuses on HIV epidemiology and prevention in high-risk women. This includes both primary prevention strategies for reducing the risk of HIV acquisition in seronegative women and secondary prevention aimed at reducing infectiousness and risk behavior in women living with HIV.

Dr. McClelland is the PI for the NIAID grant, "Antiretroviral Medications and HIV-1 Infectivity in Women." This grant supports series of studies evaluating the time course, magnitude, and durability of genital HIV-1 suppression among women initiating and continuing antiretroviral therapy (ART). The study also seeks to identify risk factors for genital HIV-1 shedding among women receiving ART, including adherence, resistance, CD4 count, viral load, STIs, and hormonal contraception. In addition, the study will evaluate changes in sexual risk behavior among women on ART.

Dr. McClelland is also the Protocol Chair for a Sexually Transmitted Infections Clinical Trials Group funded study entitled, "Preventing Vaginal Infections (PVI Study)." This double-blind, randomized trial will evaluate the efficacy of monthly treatment with topical metronidazole and fluconazole co-formulated suppositories versus placebo for preventing vaginal infections in HIV-1-seronegative women. Vaginal infections have been associated with increased risk for HIV-1 acquisition, and may account for a high population attributable risk of HIV-1 infection. This trial will utilize data collection at 2-3 sites in Africa, and is expected to initiate enrollment in early 2010.

Additional work ongoing at the Mombasa field site includes: (1) Studies of the virological and immunological changes that occur during acute and chronic HIV-1 infection in collaboration with Dr. Julie Overbaugh. (2) Studies using nucleic acid amplification techniques for characterization of vaginal flora populations in collaboration with Dr. David Fredricks. A new study utilizing molecular techniques to evaluate the association between vaginal flora and HIV-1 acquisition is expected to initiate field work in late 2009.

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randomized trial. *J Infect Dis.* 2008; 197:1361-1368.

**M. Juliana McElrath, M.D., Ph.D.**

**Professor of Medicine**

**Member, Fred Hutchinson Cancer Research Center**

Dr. McElrath's laboratory research is focused on the identification and characterization of cellular immune responses that may provide protection against HIV infection or disease. Her studies entail understanding immune responses in persons who demonstrate unique control of infection through cohort studies in Seattle and internationally. A major aspect of her studies is to apply these mechanisms of HIV control to HIV vaccine development. Specific questions under current investigation include: (1) What components of T cell immunity elicited early in HIV-1 infection contribute to the control of HIV-1 disease? (2) Do T cell immune responses play a role in resistance to HIV-1 infection in persons repeatedly exposed by sexual contact? (3) What is the contribution of antigen-specific mucosal T cells in protecting against HIV-1 exposure? (4) What elements of immunity correlate with protection against HIV-1 infection by vaccination? And 5) How can innate immunity contribute to improved vaccine design. These studies are performed in collaboration with Drs. Connie Celum, Larry Corey, Steve Self, Tuofu Zhu, James Mullins, Florian Hladik and Steve De Rosa.

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**Samuel I. Miller, M.D.**

**Professor of Medicine**

The Miller laboratory is focused on defining the molecular basis of bacterial pathogenesis and interactions with eukaryotic cells. The laboratory has a particular interest in bacterial interactions with innate immunity. This work involves the use of animal and tissue culture (mice, macrophages, epithelial cells) models of infection. Research interests include Salmonellae-induced typhoid fever and gastroenteritis, bacterial dysentery caused by *Shigella spp* and *E. coli* O157, the chronic *Pseudomonas* airway disease of cystic fibrosis patients, and Gram-negative organisms important to biodefense, including *Francisella tularensis*, *Burkholderia spp.* and the plague bacillus *Yersinia pestis*.

The lab is organized into research groups focusing on the study of: (1) The effect of bacterial type III effector proteins on mammalian cells; (2) The assembly and regulation of the type III secretion system of *Salmonella typhimurium*, which translocates proteins into mammalian cells on contact; (3) The environmental remodeling of the gram-negative bacterial surface that occurs when bacteria infect host tissues; (4) The characterization of the phenotypic adaptation of *Pseudomonas aeruginosa* to the unique environmental niche of the CF airway; (5) Analysis of bacterial genes and proteins using bioinformatics; (6) Development of new antimicrobial compounds inhibiting pathogenic factors; (7) Understanding sensing and signaling by bacterial receptors, particularly the PhoQ protein of *Salmonella*; and (8) the development of methods to study the diversity of human susceptibility to bacterial infection. Current projects organized by group include the study of: (1) Salmonellae translocated effectors (which are delivered across the phagosome membrane and recruited to the actin cytoskeleton, nucleus, and phagosome) and function as glycerol cholesterol transferases, guanine nucleotide exchange factors, and ubiquitin ligases; (2) Assembly and structure-function of the type III secretion system needle complex of *S. typhimurium*; (3) Analysis of bacterial membrane remodeling that occurs in environmental conditions typical of infection (4) Analysis of *Pseudomonas aeruginosa* adaptation during CF with special attention to loss of regulatory genes that confer a metabolic advantage for growth; (5) Bioinformatic analysis, DNA sequencing and comparison of Gram-negative bacterial genomes of outbreak

strains responsible for diarrheal disease; (6) Screening and characterization of specific molecules that target the secretin component of bacterial type II and type III secretion systems; (7) Using NMR and crystallography to define molecular mechanisms by which PhoQ responds to antimicrobial peptides and low pH; and (8) Development of *in vitro* assays as surrogates to measure human susceptibility to infection.

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### **Stephen L. Moseley, Ph.D.** **Professor of Microbiology**

Our laboratory is studying a family of fimbrial adhesins of *Escherichia coli* associated with diarrheal diseases and urinary tract infections. The Dr family of adhesins recognizes decay accelerating factor (DAF), type IV collagen, and carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) as receptors. We are carrying out genetic, biochemical, structural, and evolutionary analyses of receptor binding by these adhesins. DAF and CEACAMs have important functions related to complement regulation, cell adhesion, and signal transduction. We are seeking to understand how bacterial adhesin binding to these molecules affects the normal cellular functions of the molecules, and how the simultaneous engagement of two signaling molecules by a single adhesin molecule might provoke unique responses contributing to pathogenesis. Another project in the laboratory is focused on a novel ADP-ribosylating toxin, SpyA, of *Streptococcus pyogenes*. We are carrying out structure-function and pathogenesis studies of this toxin. Our collaborators include Dr. Ann Stapleton and Dr. Evgeni Sokurenko.

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### **James Mullins, Ph.D.**

#### ***Professor of Microbiology***

The Mullins laboratory uses the techniques of molecular, computational, and virus biology to provide basic insights into the HIV-human host relationship. Our goals are to assist the fight against AIDS by gaining insight into the establishment of infection and the development of the disease in order to assist creation of effective vaccines and to refine therapies. Current effort utilizes a variety of techniques to define and understand the implications of HIV's extraordinary evolutionary rate and ensuing genetic diversity as well as testing new approaches to vaccine immunogen design. These techniques include virology, molecular biological and statistical analysis of nucleotide sequences. Collaborators include Drs. Corey, McElrath, Collier, Horton, Mittler, Zhu, Gottlieb, Lingappa and Celum.

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### **Julie Overbaugh, Ph.D.**

#### ***Member, Fred Hutchinson Cancer Research Center***

The emphasis of research in Dr. Overbaugh's laboratory is the study of retrovirus biology, particularly the biology of HIV-1. A long-term goal of the research is to define the characteristics of virus variants that are transmitted, and to understand the interplay of subsequent viral variation in persistent infection and pathogenesis in the host. Dr. Overbaugh's group has shown in the SIV model that changes in viral envelope protein that evolve during the course of disease alter the ability of host neutralizing antibodies to recognize the virus. Such escape mutants replicate to much higher levels in the host and drive disease progression. Studies of HIV-1 infection in humans also focus on how changes in envelope may affect the properties of

the virus and contribute to viral transmission, persistence, and pathogenesis. These population-based studies are performed in collaboration with Drs. John-Stewart and McClelland using samples from Kenyan cohorts. These studies include analysis of viruses transmitted vertically from a mother to her infant, as well as sexually, during heterosexual contact. Dr. Overbaugh collaborates with Drs. Farquhar, John-Stewart, McClelland and Richardson.

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#### **Dorothy Patton, Ph.D.**

##### ***Professor of Obstetrics and Gynecology***

The Patton Lab utilizes several macaque models to study the pathogenesis, treatment and prevention of chlamydial infections. First, the role of the topical microbicides in prevention of sexual transmission of Chlamydia is investigated in both vaginal or rectal flora, changes in the vaginal, cervical, and rectal epithelial tissues, and efficacy in preventing chlamydial infection, both cervical and rectal. Recently, efficacy in preventing *Trichomonas vaginalis* has been added to the vaginal model. The development of a microbicidal gel which women could use intravaginally or rectally would provide a much needed female-controlled means of STI prevention. We have also initiated studies examining the effects of post coital events and their effects on the cervicovaginal environment. Next, we will assess the effects of topical microbicide use with coital activity. Second, the macaque model of pelvic inflammatory disease (PID) models upper genital tract disease resulting from ascending cervical infection. This model has been used to

evaluate antibiotic and anti-inflammatory treatments for existing chlamydial disease, the immunologic responses to chlamydia, and genetic predisposition to PID. The model is also evaluating safety, immunogenicity and protective efficacy of a number of *C. trachomatis* vaccine candidates. A new focus of this model is to investigate immunologic factors including the role of Toll-like receptors, which may contribute to ascending versus local cervical chlamydial genital tract infection. Third, the salpingeal auto transplant ("pocket") model is being used to evaluate the role of various chlamydial antigens and of host immune factors (cytokines) in evoking the typical delayed-type hypersensitivity (DTH) response seen in PID. In collaborations with Dr. W. Van Voorhis and Dr. W. Stamm, we have shown that chlamydial heat shock protein 60 (cHSP60) is a major factor eliciting the DTH response in salpingeal tissues. This finding suggests that the immunologic response seen in PID, a TH1 cytokine pattern, may be one of the host factors that exacerbates the disease by encouraging production of cHSP60. In collaboration with Dr. Patricia Totten, the autotransplant model is also being used to investigate the pathogenesis of *Mycoplasma genitalium* infection. All studies in the research program are aimed at improving women's reproductive health care, and ultimately eradicating chlamydial infection.

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#### **Paul Pottinger, M.D.**

##### ***Assistant Professor of Medicine***

Dr. Pottinger is an Assistant Professor in the ID Division's Clinician-Educator Pathway. He is Associate Director of the ID Training Program, where his efforts focus on optimizing the training experience for the first-year ID fellows. He also directs the Antimicrobial Stewardship Program at UWMC, which aims to improve the use of anti-infective medications for the complex and heterogeneous patient population there. He also directs the UWMC Tropical Medicine & General ID clinic, which brings ID fellows into contact with a broad variety of infectious diseases, including illnesses among returning travelers, solid organ transplant recipients, and congenitally immunosuppressed patients. He attends on the UWMC inpatient General ID consult service, Solid Organ Transplantation ID consult service, Seattle Cancer Care Alliance ID Consult service, and General Medicine Ward service. He is the author of textbook chapters, monographs, and abstracts dedicated to topics in general ID. He is a reviewer for the IDSA Journal Club. He teaches a variety of courses at the School of Medicine, and delivers approximately 40 formal lectures per year to students, residents, fellows, and attending. He has earned a reputation as an outstanding teacher, and has won the Beeson Housestaff Teaching Award.

#### **Lalita Ramakrishnan, M.D., Ph.D.**

##### ***Professor of Microbiology, Medicine and Immunology***

Our laboratory studies the pathogenesis of tuberculosis and is interested in the host and pathogen contributions to mycobacterial persistence which is accompanied by the development and maintenance of granulomatous infection. We study *Mycobacterium marinum*, a human and fish pathogen (and a close genetic relative of *M. tuberculosis*) in its natural host the zebrafish. The developing zebrafish is an ideal model host as it is optically transparent and amenable to genetics and small molecule screens. We can view in real-time the cellular events leading to granuloma formation and assess the contribution of individual host and pathogen determinants to discrete steps in the process. We have identified new host determinants that impact susceptibility to tuberculosis by conducting forward genetic screens.

Similarly, we are trying to understand bacterial virulence determinants and determinants of long-term persistence by using bacterial mutants and inducible fluorescence reporters again taking advantage of our unique animal models. We have developed the zebrafish as a platform for tuberculous drug discovery. Finally, we find that the zebrafish can also be used as a model organism to study other bacterial pathogens.

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#### **Henry Rosen, M.D.**

##### ***Professor and Associate Chair for Research, Department of Medicine***

The Rosen laboratory focuses on understanding interactions between bacteria and human neutrophils. Recent emphasis has been on using the bacterial response to neutrophil phagocytosis (mRNA expression profiles) to reflect bacterial prioritization of the multifactorial threats to microbial survival within the neutrophil phagosome. Upregulated genes are used to identify systems that may be important for microbial survival under these conditions. Targeted gene deletions are used to evaluate the importance of the gene products for microbial survival in neutrophils and virulence in a murine infection model. Dr. Rosen collaborates with Dr. Klebanoff.

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**Craig E. Rubens, M.D., Ph.D.**  
**Professor of Pediatrics and Microbiology,**  
**Executive Director, Global Alliance to Prevent Prematurity and Stillbirth**

Dr. Rubens has a long-standing research program on the molecular pathogenesis of bacterial perinatal infections. Group B streptococci (GBS) are a major cause of perinatal infections, including intrauterine infections, and pneumonia, sepsis and meningitis in newborn infants. Using this organism, he has explored how this pathogen causes disease using molecular techniques, cell, and animal models that emulate human reproductive infections during pregnancy and infection of the neonate during parturition. Molecular approaches are used to identify the genetic and biochemical basis of specific bacterial virulence traits—such as

epithelial/endothelial cell entry and transcytosis, evasion of innate immune mechanisms by inhibiting complement activation and phagocytic uptake, and microbial survival in various host environments (bloodstream, reproductive system, and neonatal lung). His laboratory pioneered genetic techniques to identify the genes and biosynthetic mechanisms important for the production of capsular polysaccharide and other virulence traits by GBS. Projects also include characterizing the early stages of bacterial pneumonia by investigating the host/pathogen interactions using genomic and proteomic techniques. This project characterizes the bacterial response to the lung airway, specific traits critical for microbial persistence in the face of lung innate immunity, and has begun to characterize the host airway proteome for the proteins and other factors that contribute to innate immune mechanisms. Recently, his laboratory is developing a model to understand the mechanisms of infection-induced preterm labor and premature birth. This model explores how bacteria ascend in the female reproductive track to incite inflammation during pregnancy that leads to preterm labor and intra-amniotic infection. Insights from the above studies have begun to identify new means of preventing or treating pneumonia, preterm labor, perinatal bacterial infections, and improving reproductive outcomes.

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**Delia Scholes, M.P.H., Ph.D.**

***Affiliate Professor of Epidemiology, UW  
Senior Scientific Investigator, Group Health  
Cooperative***

Dr. Scholes received her training in epidemiology at the University of Washington. She is currently a Scientific Investigator at Group Health Cooperative's Center for Health Studies and an Affiliate Professor in the Department of Epidemiology at the University of Washington. Dr. Scholes' research interests focus on women's health, with emphasis in genitourinary infections, sexually transmitted diseases, contraceptive practices, and bonehealth. She has been principal or co-investigator on numerous projects employing a variety of epidemiological methodologies and has extensive experience utilizing the automated databases available at this HMO. Her most recent award as Principal Investigator is a 5-year NIH-funded prospective cohort study of hormonal contraception and bone density in women. Dr. Scholes collaborates with Drs. Stamm, Stapleton, Marrazzo, Golden, Hawn, and Holmes.

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**Steven Self, Ph.D.**

***Professor of Biostatistics  
Member, Fred Hutchinson Cancer Research  
Center***

Dr. Self is currently Full Member and Head of the Program in Biostatistics and Biomathematics and Co-Director (with Drs Corey and McElrath) of the Vaccine and Infectious Disease Institute (VIDI) at the Hutchinson Cancer Research Center. Dr. Self's research program over the past several years has been directed at the overarching goal of identification and evaluation of a broadly effective HIV vaccine. This work is organized in the broad areas of Phase I/II Vaccine trial designs, Vaccine trial endpoints and Immunologic correlates of protection

Dr. Self has a long-standing interest in the analysis of genomics data and has maintained this interest largely by advising graduate students in their dissertation research in this area.

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**David Spach, M.D.**

***Professor of Medicine***

Dr. Spach is a clinician-teacher based at Harborview Medical Center. His primary clinical focus is in the area of HIV/AIDS. Dr. Spach is the Principle Investigator for the Northwest AIDS Education and Training Center and is actively involved in web-based education. He is the co-editor for two federally-funded educational web sites: HIV Web Study ([www.HIVwebstudy.org](http://www.HIVwebstudy.org)) and Hepatitis Web Study ([www.hepwebstudy.org](http://www.hepwebstudy.org)).

**Walter E. Stamm, M.D.**

**Professor of Medicine**

Current research is being conducted in two main areas: urinary tract infection (UTI) and chlamydial infections. The general aim of the studies on urinary tract infection is to better understand their pathogenesis by studying host-parasite interactions. Current studies are aimed at: (1) defining the role that *E. coli* invasion of the bladder epithelium plays in persistence, treatment failure, and recurrent infections; (2) defining the association of susceptibility to pyelonephritis or recurrent cystitis with known or novel mutations in selected host genes; (3) utilizing high density microarrays and whole genome mutation scanning to characterize the molecular adaptation that *E. coli* strains undergo in the course of recurrent infections; and (4) determining the effectiveness and mechanisms of a *Lactobacillus crispatus* probiotic in preventing UTIs. Collaborators in these studies include Drs. Tom Hawn, Evgeni Sokurenko, Ann Stapleton, Delia Scholes, and Scott Hultgren. The major goals of studies with *Chlamydia trachomatis* include: (1) utilize comparative whole genome sequencing to elucidate the molecular basis of three chlamydial phenotypes, namely rectal tropism, formation of secondary inclusions, and formation of nonfusing inclusions; (2) employ a newly developed cloning and selection technique to identify naturally occurring mutant pairs of chlamydia that can be used to define the role of specific mutations in chlamydial physiology and pathobiology; and (3) utilize a novel chlamydial transformation system to identify and characterize chlamydial isogenic mutants. Collaborators in these studies include Drs. Daniel Rockey, King Holmes, and Dorothy Patton.

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**Ann Stapleton, M.D.**

**Professor of Medicine**

Research in the lab is focused on the pathogenesis of *Escherichia coli* urinary tract infections (UTIs), especially the role of caveolae and glycosphingolipids (GSLs) in these infections, as well as how resident vaginal lactobacilli help protect against these infections. We are studying how *E. coli* invade bladder epithelium via caveolae, using a model of cultured primary bladder epithelium developed in the lab and characterized with respect to GSLs. Since the vaginal epithelium is a key staging area for uropathogenic *E. coli*, which colonize this mucosa and the periurethra prior to causing UTI, our second major area of investigation is vaginal physiology at baseline and near the time of UTI. We are studying the roles of resident commensal and probiotic lactobacilli in this system using a model of cultured primary vaginal epithelial cells, also developed in the lab, as well as clinical and probiotic *Lactobacillus* isolates. Other projects include: (1) studies of cranberry products as a means of preventing UTI, including in vitro and clinical studies; and (2) studies of the molecular epidemiology of *E. coli* virulence determinants in various populations. We collaborate with several University of Washington colleagues including Drs. Walter Stamm, Steve Moseley, David Fredricks, Delia Scholes, and Tom Hawn. Outside the University, we work with Drs. Anthony Atala, Wake Forest University; Thomas ("Mac") Hooton, University of Miami; Harry Mobley, University of Michigan; and Soman Abraham, Duke University.

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**Joanne Stekler, M.D., M.P.H.**  
**Assistant Professor of Medicine**  
**Advisor, Public Health - Seattle & King County HIV/AIDS Control Program**

Dr. Stekler's research is focused in two primary areas: 1) HIV prevention through earlier diagnosis of HIV infection and 2) the clinical consequences of primary HIV infection. With the Public Health - Seattle & King County HIV/AIDS Program, Dr. Stekler is working to expand routine HIV antibody testing and access to pooled HIV nucleic acid amplification testing to diagnose acute HIV infection. She leads several studies investigating novel methods to diagnose acute and early HIV infection; comparisons of rapid HIV tests; and home, self-testing for HIV infection.

Dr. Stekler also works at the University of Washington Primary Infection Clinic within the clinical core of the Seattle Primary Infection Program (SeaPIP), a collaboration of local and national virologists, immunologists, and clinicians. Since 1992, the Primary Infection Clinic has enrolled and followed over 300 persons with acute

and early HIV infection. Dr. Stekler's interests include interdisciplinary research to understand factors associated with HIV transmission, consequences of transmitted drug resistance, viral dynamics following HIV acquisition, and clinical outcomes of antiretroviral therapy during primary HIV infection.

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**Patricia Totten, Ph.D.**  
**Research Associate Professor of Medicine**  
**Adjunct Research Associate Professor,**  
**Department of Pathobiology**

My research focuses on the discovery, detection, epidemiology, and molecular pathogenesis of organisms associated with reproductive tract diseases (RTD) in men and women. We have studied the molecular pathogenesis of *Haemophilus ducreyi*, the causative agent of chancroid, by identifying possible virulence factors, then analyzing their effect in vitro and in vivo. For example, we showed that a cytolytic toxin (cytolysin) from *H. ducreyi* damages macrophages, epithelial cells, and fibroblasts in vitro, which may in part explain the tissue damage and persistence of this organism in chancroidal ulcers. Using our newly developed primate model and isogenic mutants of *H. ducreyi*, we have demonstrated that this toxin, in conjunction with a cytolethal distending toxin, is essential for full virulence and survival of this organism in vivo.

Further, we have shown that rabbits immunized with the cytolysin are partially protected from chancroidal disease, supporting its use along with other proteins in a vaccine for to prevent chancroidal ulcers. We have also identified novel bacteria associated with several STD syndromes that frequently have no etiology. In collaborative studies with clinicians and epidemiologists, we have shown that *Mycoplasma genitalium* is associated with urethritis in men and cervicitis, endometritis, and pelvic inflammatory disease in women, using our newly developed PCR assay to detect this organism. Further, we have shown that this extremely fastidious organism can persist for months, if not years, in infected women. We defined a possible mechanism for this persistence by demonstrating that the genes encoding two immunodominant surface proteins are heterogeneous within isolated strains and vary by reciprocal recombination with archived partial gene sequences on its minimal chromosome. The identification and regulation of recombination genes required for this variation, the effect of gene variation on the antigenicity of the resulting proteins, and the role of antigenic variation on immune evasion are current studies ongoing the Totten laboratory. We anticipate that these studies will lead to further research on the molecular pathogenesis of *M. genitalium*, the bacterium with the smallest genome of any free-living cellular form of life. In addition to the study of the disease associations and molecular pathogenesis of *M. genitalium*, the Totten laboratory is exploring other possible etiologies of STD syndromes. Two newly defined *Ureaplasma* species, *U. urealyticum* and *U. parvum*, are being assessed for their differential role in the etiology of STD syndromes. Using broad range ribosomal DNA PCR, a technique that will amplify DNA from all bacterial, followed by DNA sequencing of the PCR products to establish phylogeny, we have identified novel organisms associated with salpingitis (fallopian tube infections) in women. Many of these organisms, detected only by their "signature" ribosomal DNA sequences, have not been previously cultured or reported from this site, presumably due to their fastidious culture requirements. The taxonomic classification and disease associations of these novel organisms are areas of future study in my laboratory.

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**Wesley C. Van Voorhis, M.D., Ph.D.**  
**Professor of Medicine, Adjunct Professor of**  
**Global Health and Microbiology**  
**Head, Allergy and Infectious Diseases Division**

There is a great need for new drugs for parasitic diseases, such as malaria, African Sleeping Sickness, Chagas' disease, and leishmaniasis. Each year, these diseases sicken or kill over 200 million people. Though some pharmaceutical companies devote some research effort to discover drugs to cure some of these diseases there is little done given the need; the people with these parasitic diseases have little money to pay for medicine. Wes' research group uses emerging knowledge about the genomes of these parasites to aid in rational drug discovery. His group, in collaboration with 4 other groups in Pennsylvania, Argentina, England and Australia, has developed a website called TDRtargets.org which allows pharmaceutical companies and scientists to select optimal drug targets from the genomes of parasite. His group is also involved in discovering the molecular targets of cell-active compounds that are potential drugs. They have discovered promising anti-parasitic compounds, based on enzymatic targets from the genomes of these parasites, that show great promise as drug leads. Some of the most promising compounds are inhibitors that block kinases necessary for parasite growth. The group uses structure based drug discovery, in collaboration with X-ray crystallographers and chemists, and pharmacokinetic and toxicology information from the laboratory, to optimize compounds to become drug candidates for clinical development.

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**Anna Wald, M.D., M.P.H.**  
**Professor of Medicine**

Current research centers on the epidemiology and natural history of genital herpes infection in immunocompetent and immunocompromised hosts. The goals of the studies are (1) to characterize the biology and epidemiology of HSV acquisition and transmission; (2) to develop strategies for prevention of HSV transmission from women to neonates at birth; (3) to determine the immunogenetic predictors of HSV shedding in the genital area; and (4) to evaluate the impact of HIV infection on genital HSV-2 infection, the ability of HAART to restore immune control of HSV infection, and the effect of anti-HSV chemotherapy on HIV shedding from genital herpes lesions. Additional studies investigate the epidemiology of HHV-8 infection, the risk of mucosal HHV-8 shedding of in HIV seronegative and HIV seropositive populations, and the effect of antiviral therapy on HHV-8 shedding and progression to Kaposi sarcoma. Collaborators in these studies include Dr. Larry

Corey, Dr. David Koelle, Dr. Corey Casper, and Dr. Connie Celum. In addition, the clinic conducts studies of investigational vaccines and novel adjuvants.

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**Judith Wasserheit, M.D., M.P.H.**  
**Professor of Global Health and Medicine**  
**Vice Chair, Department of Global Health**  
**Affiliate Investigator, Fred Hutchinson Cancer Research**

Judith N. Wasserheit MD, MPH is currently Professor of Medicine and Global Health and Vice Chair of the Department of Global Health at the University of Washington in the Schools of Medicine and Public Health & Community Medicine. She is also an Affiliate Investigator the Fred Hutchinson Cancer Research Center. She was formerly the Director of the HIV Vaccine Trials Network, a global clinical trials platform linking 28 sites on four continents in evaluating preventive HIV vaccines; led the CDC's national STD prevention program for almost a decade; and was the founding chief of the NIH's STD research branch. She has had extensive experience in sexually transmitted disease (STD) and HIV research, policy development and program implementation both in the United States and in developing countries. Her previous research has included one of the first laparoscopic studies of pelvic inflammatory disease

etiology conducted in the US, the first population-based study of the prevalence and etiologic spectrum of STDs among rural women in the Indian Subcontinent, and research on the interrelationships between STDs and contraceptive practices in other parts of the developing world, including Indonesia, and Egypt. She has also worked in Columbia, Thailand and Zambia. Her development of the concept of epidemiological synergy between HIV infection and other STDs has had a major influence on HIV prevention policy and programs around the world. Current research interests include: mathematical modeling of the combined effects of biological co-factors such as HSV-2 infection, malaria and TB on HIV epidemic trajectory; examining the impact of HSV-2 infection and other STDs on response to HIV vaccine candidates; designing and evaluating combination HIV prevention packages for sub-Saharan Africa; developing and evaluating multi-components interventions to reduce STDs, HIV and pregnancy among adolescents and developing and evaluating approaches to adaptation to climate change to reduce the impact on human health.

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#### **Theodore C. White, Ph.D.**

**Member, Seattle Biomedical Research Institute  
Affiliate Professor, Department of Global Health**

Dr. White studies fungi that are pathogenic to humans, including *Candida*, *Aspergillus*, *Cryptococcus* and dermatophytes (the causes of tinea and athlete's foot). His research is focused on antifungal drugs, with emphasis on *Candida albicans*, which is commensal in most healthy people and causes mucosal and systemic infections in patients with altered immune function, such as AIDS patients. Dr. White focuses on the interactions of antifungal drugs with the fungal cell, using drug resistant isolates to understand the responses of the fungal cell to the presence of drug. Dr. White and others have characterized the basic mechanisms of resistance to antifungal drugs, which include mutation and over-expression of the target enzyme and over-expression of at least two types of efflux pumps. Current efforts are focused on understanding gene regulation of the target enzyme and the pumps. Recently, a master sterol regulator and transcription factor, UPC2, has been identified that appears to regulate sterols in fungi in a similar manner to the regulation of cholesterol in mammalian cells. Other research avenues currently being studied include the analysis of drug/cell interactions in other pathogenic fungi and a genomic analysis of five dermatophytes, including *Trichophyton rubrum*, the major cause of athlete's foot. .

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#### **Joseph Zunt, M.D.**

##### **Associate Professor of Neurology**

Over the past twelve years, Dr. Zunt has built a collaborative research network involving the University of Washington and several medical centers, NGOs, and Universities in Peru. His NIH-funded research interests encompass clinical and virologic manifestations of HIV, HTLV-I, and HTLV-II infections upon the nervous system; retroviral co-infection and viral meningoencephalitis in Peru; and training programs for U.S. and Peruvian medical students and residents. His research focuses upon the clinical epidemiology and neurologic manifestations of these infections, with collaborations with scientists in Peru and the United States. Peruvian populations included in these studies are mainly marginalized populations, such as commercial sex workers, men who have sex with men, and people with neurologic disabilities.

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## APPLICATION PROCEDURE

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**Fellowship Program Website  
Application Process:**

<http://depts.washington.edu/daid/fellowship.htm>

Information on Letters of Recommendation and the Personal Statement are also found on this website.

We participate in the Electronic Residency Application Service (ERAS) through the Association of American Medical Colleges. Applications will be accepted exclusively through ERAS. The application process begins at ERAS as early as two years before a position is desired. In Mid-November, applicants can select the U. of WA ID program for positions opening 19 months later in July (e.g., Nov 2007 for July 2009). Applications are downloaded from ERAS December 1 through February 1 (contact the fellowship office if you missed the Feb 1 deadline). Application materials and information can be found at: <http://www.aamc.org/students/erasfellow/start.htm>.

After receipt and review of applications, those fellows with competitive applications will be invited to interview.

**Interviews are mandatory** for fellow applicants who are seriously interested in the program. Interviews are arranged with 6-8 faculty, usually over 1 day. Those applicants invited to interview should indicate potential areas of research interest and/or specific faculty with whom they wish to meet.

The University of Washington is an equal opportunity/ affirmative action employer. We are strongly committed to increasing the number of minorities entering careers in academic Infectious Diseases and we encourage application by minority candidates to our program.