



3rd Annual Global Health &
Infectious Disease Conference

The Risk of Emerging Infectious Diseases: From Bench to Implementation in Research

Friday, April 10, 2015

Eric P. Newman Education Center

Washington University Medical Campus

Center for Global Health and Infectious Disease

 Washington University in St. Louis
SCHOOL OF MEDICINE

 Washington University in St. Louis
INSTITUTE FOR PUBLIC HEALTH

AGENDA

- 8:30 am **Check-in & Continental Breakfast**
- 8:30 am **Welcome**
Larry Shapiro, MD
Washington University
- 8:35 am *Translational Medicine & Global Infectious Diseases -
Need for Interdisciplinarity*
William Powderly, MD
Washington University
- 9:10 am *The Neglected Tropical Diseases Caused by Infections
with Helminth Parasites*
Edward Pearce, PhD
Washington University
- 9:45 am **Break**
- 10:05 am *Tuberculosis Vaccines: Barriers and Prospects on the Quest for a
Transformative Tool*
Chris Karp, MD
Bill & Melinda Gates Foundation
- 10:40am *Sneak, Hide, Attack: How Ebola Virus Evades Host
Immunity*
Gaya Amarasinghe, PhD
Washington University
- 11:15 am **Panel Discussion**
Responding to Emerging Threats
Moderators: **Steven Lawrence, MD, and Shanti Parikh, PhD**
Panelists: **Hillary Babcock, MD, MPH; David Curiel, MD, PhD;
Peter Ruminski, MS; and Indi Trehan, MD, MPH, DTM&H**
- noon **Lunch with Speakers**

- 1 pm **Poster Session**
- 2:00 pm *Using Genomics to Understand Schistosomes and Other Parasitic Worms*
Matt Berriman, PhD
Wellcome Trust Sanger Institute, UK
- 2:35 pm *Operational Research to Control and Eliminate Schistosomiasis in Africa: The SCORE Project*
Daniel Colley, PhD
University of Georgia
- 3:10 pm **Break**
- 3:25 pm *Developing New Anti-Virulence Strategies Against Mycobacterium tuberculosis*
Christina Stallings, PhD
Washington University
- 4:00 pm *Risk of Developing TB Disease in Infants Vaccinated with BCG*
Helen Fletcher, PhD
London School of Hygiene and Tropical Medicine, UK
- 4:35 pm *Leveraging Impact at Scale in Global Health- Conundrum and Opportunity in Infectious Disease Prevention and Control*
Wolfgang Munar, MD
Washington University
- 5:10 pm **Trainee Talk & Poster Awards and Closing Remarks**
William Powderly, MD
Washington University
- 5:30 pm **Forum for International Health & Tropical Medicine (FIHTM)**
Poster Session & Reception

INTRODUCERS & MODERATORS



Stephen Beverley, PhD

*Marvin A. Brennecke Professor and
Chairman, Department of Molecular Microbiology,
School of Medicine, Washington University*



Michael Diamond, MD, PhD

*Professor
Departments of Medicine, Molecular Microbiology,
and Pathology and Immunology,
School of Medicine, Washington University*



Victoria Fraser, MD

*Adolphus Busch Professor of Medicine and
Chairman, Department of Medicine,
School of Medicine, Washington University*



Steven Lawrence, MD

*Assistant Professor of Medicine,
Division of Infectious Disease,
School of Medicine, Washington University*



Audrey Odom, MD, PhD

*Assistant Professor
Department of Pediatrics and Molecular Microbiology,
School of Medicine, Washington University*



Shanti Parikh, PhD

*Associate Professor, Sociocultural Anthropology and
African and African-American Studies,
Arts & Sciences, Washington University*



Larry Shapiro, MD

*Vice Chancellor for Medical Affairs and
Dean of the School of Medicine, Washington University*

PRESENTERS & ABSTRACTS



Gaya Amarasinghe, PhD, is an assistant professor in the Departments of Pathology and Immunology, Division of Laboratory and Genomic Medicine and Biochemistry, and Molecular Biophysics at Washington University School of Medicine. Dr. Amarasinghe's research focuses on using combined methods from biochemistry, biophysics, cell biology, and virology to characterize host and viral components in order to determine how host signaling is altered during viral infections.

Sneak, Hide, Attack: How Ebola Virus Evades Host Immunity

The Ebola outbreak in West Africa has claimed more than 10,000 lives and with more than 20,000 reported infected individuals, including imported infections in non-West African countries. A hallmark of Ebola viral infection, which is shared among all Ebola viruses, is the ability to achieve a very high level of host immune suppression by virally encoded multifunctional proteins. These proteins, namely glycoprotein (GP), viral protein 35 (VP35) and viral protein 24 (VP24) are largely responsible for the ability of the Ebola virus to “sneak” into the host, “hide” from sentinel pattern recognition receptors, and to “attack” interferon-mediated immune responses, respectively. Events leading to viral entry and host immune evasion are complex and highly choreographed events. Recent studies, including our own, are beginning to uncover regulatory mechanisms at key host-viral interfaces, which facilitate viral immune evasion. I will discuss these findings and their impact on our understanding of Ebola virus biology and implications for antiviral development.



Hillary Babcock, MD, MPH, is an associate professor in the Division of Infectious Diseases at Washington University School of Medicine. She is Medical Director of the BJC Infection Prevention and Epidemiology Consortium, and Medical Director of Occupational Health (Infectious Disease) for Barnes-Jewish and St. Louis Children's Hospitals. In all of these roles, she provides medical direction for policies and procedures in place at BJC hospitals to prevent transmission of infections among patients and between patients and healthcare providers. Her two main areas of interest are infection prevention and occupational health, specifically related to healthcare workers.



Matthew Berriman, PhD, is the Head of Parasite Genomics at the Wellcome Trust Sanger Institute in the United Kingdom. Dr. Berriman's research covers the breadth of parasites, particularly the medically important Apicomplexan and Kinetoplastid protozoa, and parasitic helminths. He is interested in the genomic basis of key biological features of parasites and major phenotypic differences within and

between species, such as their complex life cycles, virulence, the ability to establish chronic infections and the ability to evolve resistance to therapeutic drugs. Helminths are a major interest of the group. Since publishing the draft genome of *S. mansoni*, large-scale genome-improvement work has been continued. Deep RNA-seq data from several life cycle stages has also been used to improve the accuracy of gene calling and to identify genes active at discrete points in the life cycle. Dr. Berriman has also recently led an international consortium to analyse the genomes of four tapeworm species, and is a principle investigator for the new WormBase-ParaSite database.

Using Genomics to Understand Schistosomes and Other Parasitic Worms

A combination of small research communities, a paucity of molecular tools, and inadequate genomic resources have significantly impeded progress for many helminthic diseases, despite their impact. However, eight years ago a draft genome for a filarial worm was published and two years later, drafts were also published for two schistosome species. Since then, more than a dozen genomes have been published for human-infective helminths species. The genomes provided basic parts-lists including hundreds of potential new drug targets and as well as exploitable insights into parasite biology. Access to whole genome data has transformed the study of gene expression, opened new windows on evolution, and increased the power of genetics. However, with each genome, >10,000 new genes—of variable accuracy—become available.

To address the challenge of vast amounts of poorly characterized data, we are taking a number of approaches. First, we are using comparative genomics over a range of evolutionary distances to identify genes that distinguish different lineages and may therefore underlie unusual aspects of their biology. Second, for highly significant species, such as *Schistosoma mansoni*, we are systematically improving their underlying sequences and annotation. Third, we are incrementally increasing the amount of functional information for all genes by using large-scale transcript sequencing during the establishment of mammalian infections. In this presentation I will describe progress in each of these areas, efforts to integrate the data, and outline some of our major next steps.



Daniel Colley, PhD, is a professor of microbiology, and director of the Center for Tropical and Emerging Global Diseases, at the University of Georgia. For over four decades, his research has been immunoregulation in chronic parasitic infections and the mechanisms of human resistance to reinfection by schistosomes. He has worked extensively in endemic areas (including Brazil, St. Lucia, Egypt, and Kenya), establishing long-term immunology research collaborations. He also directs the SCORE program with operational research in nine African countries on control and elimination of schistosomiasis.

Operational Research to Control and Eliminate Schistosomiasis in Africa: The SCORE Project

The main goals of World Health Assembly 65.21 (2012) for global schistosomiasis efforts are “to intensify control programs in most disease-endemic countries and initiate elimination campaigns, where appropriate.” But how best can national NTD program managers do that? Do current WHO guidelines make optimal use of existing tools, or sufficiently encourage use of intervention combinations? Operational research is needed both to support tool development and provide answers that can be used for policy and program decisions. Operational research should also contribute to the discussion needed for the fundamental conceptual shift that will be essential to help ministries move from morbidity control to elimination.

The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) was founded and developed to help provide evidence for these purposes. SCORE efforts have contributed to evaluating and optimizing separate assays for mapping and approaching elimination, and many of the large SCORE intervention studies in Africa are now approaching the home stretch. They will soon yield data that will hopefully contribute to needed discussions on how best to gain control of, sustain control of, and eliminate schistosomiasis.



David Curiel, MD, PhD, is a professor of radiation oncology and cancer biology in the Molecular Microbiology and Microbial Pathogenesis Program in the Division of Biology and Biomedical Sciences at the Washington University School of Medicine. The focus of his research program is to exploit adenoviral agents for applications to the applied contexts of cancer therapeutics.



Helen Fletcher, PhD, works at the London School of Hygiene and Tropical Medicine as an Assistant Professor/Senior Lecturer in Immunology. Her group, which is based in the Immunology and Infection Department, Faculty of Infectious and Tropical Diseases, focuses on the host responses to TB vaccination. She is currently developing a biological/functional assay to determine if blood samples from vaccinated subjects can better control the growth of live mycobacteria *in vitro*. Through her work she has collaborated with colleagues across Sub-Saharan Africa, and travelled in East, West, and Southern Africa.

Risk of Developing TB Disease in Infants Vaccinated with BCG

Despite the global use of the bacillus Calmette-Guérin (BCG) vaccine, there are 9 million new cases of tuberculosis (TB) each year and an urgent need for improved vaccines. Better understanding of the risk of development of TB is important for the design of improved vaccines. Samples collected during clinical TB vaccine trials for the investigation of antigen-specific immune responses may be used for the identification of immune mechanisms of TB susceptibility.

In a series of studies we have found that an increased frequency of myeloid cells is associated with reduced capacity to control mycobacterial growth *in vitro* and that in clinical cohorts a high frequency of monocytes is associated with risk of developing TB disease. Using stored PBMC from infants enrolled into a Phase IIb efficacy trial of the viral vector vaccine MVA85A (a candidate TB vaccine), we have further explored immune responses in case and control infants to identify immune correlates of TB disease risk. Understanding why TB vaccination fails to protect in endemic populations will help guide the development of more effective vaccination strategies in the future.



Chris Karp, MD joined the Bill & Melinda Gates Foundation in 2012 as Deputy Director (Vaccines & Host-Pathogen Biology) of Global Health Discovery & Translational Sciences. He received a BA in Philosophy from Brandeis University and an MD from the University of North Carolina, where he was a Morehead Fellow. After training in Internal Medicine at Brown and Georgetown Universities, he did a post-doctoral fellowship (leishmania, immunology) at the Laboratory of Parasitic Diseases at NIAID, and a clinical infectious diseases fellowship at Johns Hopkins. On the faculty of the Departments of Medicine and Molecular Microbiology & Immunology at the Johns Hopkins Schools of Medicine and Public Health until 2000, he then founded the Division of Molecular Immunology at Cincinnati Children's Hospital Medical Center, where he was Gunnar Esiason/Cincinnati Bell Professor and Director of the Cystic Fibrosis Research Center. His research

has focused on defining the molecular mechanisms underlying the regulation and dysregulation of inflammatory responses in infectious, allergic, genetic and metabolic diseases, with a focus on diseases of children and diseases with increased prevalence in the tropics.

Tuberculosis Vaccines: Barriers and Prospects on the Quest for a Transformative Tool

The road to a more efficacious vaccine that could be a truly transformative tool for decreasing tuberculosis morbidity and mortality, along with *Mycobacterium tuberculosis* transmission, is quite daunting. Despite this, there are reasons for optimism. Abetted by better conceptual clarity, clear acknowledgment of the degree of our current immunobiological ignorance, the availability of powerful new tools for dissecting the immunopathogenesis of human tuberculosis, the generation of more creative diversity in tuberculosis vaccine concepts, the development of better fit-for-purpose animal models, and the potential of more pragmatic approaches to the clinical testing of vaccine candidates, the field has promise for delivering novel tools for dealing with this worldwide scourge of poverty.



Wolfgang Munar, MD, is a senior scholar at Washington University's Brown School and the associate director of the Global Health Center. He is a senior global development and global health leader with a proven ability to convene, steer, and manage multicultural and multidisciplinary teams and communities of practice in global development agencies.

In addition, he is a multilateral finance expert with two

decades of senior technical and managerial experience in large-scale programs in Latin America & the Caribbean, Eastern Europe, South Asia and East Africa. In his current role, he is developing an exploration program to address global development challenges at the interface of agriculture, food and nutrition. His career has culminated in continued research and consulting in the application of systems science to key global development challenges such as: scaling-up maternal and neonatal survival innovations, addressing policy challenges to universal health coverage, and developing the use and limitations of financial incentives to improve primary care performance.

Leveraging Impact at Scale in Global Health- Conundrum and Opportunity in Infectious Disease Prevention and Control

During the last decade we have witnessed a marked increase in funding for global health. New actors entered the global health scene and provided large amounts of financial resources that revived the global research and development space and, to a lesser extent, has re-energized the long-standing debate on health delivery platforms in low- and middle-income countries.

In the field of infectious disease prevention and control, examples include the Bill & Melinda Gates Foundation, the Global Fund to Fight HIV/AIDS, Malaria and Tuberculosis and the Global Alliance for Vaccines and Immunization, among others. Existing funders of Official Development Assistance have also been influenced by the new discourse that these organizations have brought into global development in general. Discursive highlights that have now become mainstream include constructs like outcomes-based funding, accountability, data sharing, and many others. The global health ecosystem has adopted many of these principles and values and has translated them into new rules, governance structures, and organizational routines.

In this presentation I describe the evolution of the concept of “scaling-up,” a construct that was in the realm of the impossible until the beginning of this century but that, given the inflow of funds, is nowadays not only feasible but a highly desirable attribute for global infectious disease prevention and control programs.

As a theoretical construct scaling-up has been articulated in many different fashions. But as a practical element, central to ongoing discussions about the effectiveness of global health interventions, it remains fuzzy and ambiguous. In this presentation I will discuss a framework for scaling-up impact. The latter is of potential value for program designers, policy-makers, and implementers alike.



Edward Pearce, PhD, is a professor in the Department of Pathology and Immunology at Washington University School of Medicine. He has been the recipient of a New Investigator Award and a Scholar Award in Molecular Parasitology from Burroughs Wellcome and his research, which is funded by the NIH, focuses on Type 2 immunity and on the role of cellular metabolism in immune cell function and fate during infection and cancer.

The Neglected Tropical Diseases Caused by Infections with Helminth Parasites

Infections with helminth parasites disproportionately affect people and domestic animals in developing countries. Diseases caused by these metazoan pathogens are usually chronic in nature and can be associated with considerable morbidity. In the absence of vaccines, current control programs are focused around repeated mass drug administrations. The scope and nature of disease caused by parasitic helminths will be discussed, with a focus on schistosomiasis.



William Powderly, MD, is the J. William Campbell Professor of Medicine and Co-Director of the Division of Infectious Diseases in Washington University's School of Medicine, and director of the Institute for Public Health and its Global Health Center. For more than 25 years, Dr. Powderly has been actively engaged in research to improve treatments for patients with HIV. His initial studies focused on evaluating

drug cocktails to identify effective first-line treatment for HIV. More recently, he has also been involved in research to understand the long-term side effects of HIV medications, particularly metabolic problems like diabetes, lipid abnormalities, and osteoporosis. Dr. Powderly's global health interests include findings solutions to develop human capital in resource-limited settings through shared educational and research endeavors.

Translational Medicine & Global Infectious Diseases - Need for Interdisciplinarity

Major global public health challenges are strongly correlated with economic development. The conditions in which people are born, grow, live, work and age are at the root of much inequality in health, and these social determinants are relevant to infectious and non-communicable diseases alike. For 1/6 of the world's population, the traditional challenges associated with extreme poverty—malnutrition, maternal mortality, premature childhood death from diarrhea and respiratory illness, and infectious diseases (especially HIV, malaria, tuberculosis and other neglected tropical diseases)—remain important problems. However, in many developing countries, economic advances have led to a rapid transition to a greater problem of diseases of lifestyle, with obesity, diabetes and cardiovascular disease, and cancer now the greatest threat to health these countries face.

Global infectious diseases straddle these two separate domains—most pandemics emerge from developing countries but provide a global threat to all. To address the challenge of global infectious diseases, there is a need to build up public health infrastructure in resource-poor countries, to allow for early detection of emerging problems. We also need to continue to apply scientific discovery to these problems to allow innovative solutions to be developed. In addition, as new technologies are developed (whether they are in diagnosis, treatment, or prevention,) there is a need to consider implementation early in the process so that deployment in resource-limited settings is planned early in development rather than, as is often the case currently, being considered 20 to 30 years late. However, we cannot expect to be able to translate scientific discovery without paying close attention to the economic, social, and political environment in which infectious diseases—endemic and epidemic—flourish.



Peter Ruminski, MS, is the executive director of the Center for World Health & Medicine at Saint Louis University, which is made up of a full team of former Pfizer pharmaceutical scientists with expertise in drug discovery and development. Its mission is developing new therapies for neglected and rare diseases.



Christina Stallings, PhD, is an assistant professor of molecular microbiology at Washington University. Her research program focuses on molecular pathogenesis of mycobacteria, with a particular interest in identifying, characterizing, and targeting pathways required by the bacteria to persist in the patient. She has identified a number of factors involved in mycobacterial stress responses and persistence and has been awarded multiple NIH grants to fund work in these areas. She has recently expanded her investigations to novel models of persistence to identify new players in pathogenesis by embarking into studies of mycobacterial biofilms. She continues to investigate how the virulence mechanisms in pathogenic bacteria can be inhibited in new chemotherapeutic strategies to treat mycobacterial infections. In addition, she is also exploring the host responses necessary to control mycobacterial infections.

Developing New Anti-Virulence Strategies Against Mycobacterium tuberculosis

The ability of *Mycobacterium tuberculosis* (Mtb) to withstand antibiotic treatment and host immune pressure has led to a worldwide epidemic of persistent Mtb infection. In order to define ways to target persistent Mtb, *in vitro* models of mycobacterial persistence must be developed. Toward this end, we have implemented mycobacterial biofilm formation as an *in vitro* model of persistence since the characteristics of Mtb within a biofilm recapitulate many of the features of bacteria during chronic infection, including stress resistance and antibiotic tolerance. Using this model, we have identified a family of structurally related small molecules with potent anti-biofilm activities in Mtb and have named these compounds MBIs for Mycobacterial Biofilm Inhibitors. Treatment with MBIs restrains the bacteria in a drug-sensitive state where they can be more effectively killed by reactive oxygen species and the drug isoniazid, a key component of anti-tuberculosis therapy that is otherwise ineffective against persistent bacteria. Investigations into the effects of MBIs on Mtb physiology revealed a newly described lipid maturation profile associated with biofilm formation that also occurs during infection and is inhibited by MBI treatment. This work reveals new aspects of Mtb physiology and identifies potential ways to target protective processes employed by persistent Mtb.

ACKNOWLEDGEMENTS

Center for Global Health & Infectious Disease Committee

William Powderly, MD
Daniel Goldberg, MD, PhD
Edward Pearce, PhD
Gary Weil, MD
Amanda Lewis, PhD
Shabaana Khader, PhD
Audrey Odom, MD, PhD
Jacaranda van Rheenen, PhD

Institute for Public Health

William Powderly, MD
Graham Colditz, MD, DrPH
Victoria Anwuri, MPH
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