Symposium on Innovative Therapeutics for Cryptosporidium

January 22, 2016
University of California, San Francisco
Welcome to the Symposium on Innovative Therapeutics for Cryptosporidium.

Cryptosporidium is one of the leading causes of diarrheal disease among young children living in low-resource settings. Infection can lead to death and leave survivors suffering from chronic malnutrition and long-term consequences, including growth stunting and deficits in cognitive development.

Currently, there is only one drug approved for treatment. New therapies are urgently needed to alleviate the long-term effects of infection and reduce the global burden of Cryptosporidium.

This symposium was convened to speed progress by highlighting opportunities to develop new therapies.

We look forward to a robust discussion.
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8:30–8:45  Welcome and opening remarks

David Shoultz, PhD, MS, MBA, Program Leader, Drug Development and Devices and Tools; PATH
Eugenio de Hostos, PhD, MBA, Director of Research and Preclinical Development, Drug Development; PATH

8:45–9:10  Morbidity burden of cryptosporidia for infants in low-income countries

William A. Petri, Jr., MD, PhD, Chief, Division of Infectious Diseases & International Health; University of Virginia

We are studying the impact of cryptosporidia on health by conducting longitudinal studies of infants in urban and rural Bangladesh. Cryptosporidiosis was identified as the second-leading etiology of moderate to severe diarrhea in a case-control study of seven developing-country sites in infants by Global Enterics Multi-Country Study (GEMS), supported by the Bill & Melinda Gates Foundation (Kotloff KL, et al., Lancet 2013; 382:209–222). Independently, we have also demonstrated in a longitudinal cohort the importance of cryptosporidiosis in urban Bangladesh slum children (Mondal D, et al., Clin Infect Dis. 2012; 54:185–192). We are now building on these preliminary studies to accurately measure the health burden from cryptosporidiosis. Mothers identified in the second trimester are being recruited into the study. Gestational age is measured by ultrasound, and the child is observed from the first week after birth to two years of age. State-of-the-art quantitative polymerase chain reaction and antigen-detection tests are being used, with in-home, biweekly visits and monthly surveillance stool samples, to capture even mild or asymptomatic infections. The impact of cryptosporidia infection on health will be measured acutely by diarrhea severity, subacutely by 90-day impact on nutritional and health status, and chronically by nutritional and child development measures. We will add to this a comprehensive analysis of host and parasite factors associated with acute to chronic outcomes. The net result will be an accurate estimation of cryptosporidia burden on health in rural and urban Bangladesh.

9:10–9:30  Establishing a target product profile and screening cascade for Cryptosporidium therapeutics

Robert Choy, PhD, Associate Director of Research and Preclinical Development, Drug Development; PATH

New therapeutics are sorely needed to treat Cryptosporidium. However, with only one drug of moderate efficacy currently approved by the US Food and Drug Administration, the desired characteristics of such therapeutics are poorly defined. There are critical gaps, such as our understanding of the use cases, optimal pharmacokinetic profile, and spectrum of activity. Furthermore, as a neglected tropical pathogen, Cryptosporidium lacks well-characterized, uniform in vitro and in vivo screening methods for evaluating therapeutic candidates. Numerous cell-based assays and animal models have been reported, but their clinical
predictive value remains unclear. This presentation will highlight outstanding questions for Cryptosporidium drug developers and lay a groundwork for further exploration and definition of a target product profile and screening cascade over the course of the symposium.

Enabling Tools

9:30–9:55  Molecular genetics to drive Cryptosporidium drug discovery
Boris Striepen, PhD, Distinguished Research Professor and GRA Distinguished Investigator, Center for Tropical and Emerging Global Diseases and Department of Cellular Biology; University of Georgia  
Cryptosporidium is the second most important pathogen after rotavirus to cause severe diarrhea in children below two years of age. Cryptosporidium is also an opportunistic pathogen for immune-compromised individuals such as HIV/AIDS patients and organ transplant recipients. Currently, there are no fully effective drugs or vaccines to treat or prevent cryptosporidiosis. A main roadblock in the development of drugs and vaccines is the overall poor tractability of Cryptosporidium due to lack of a continuous culture system, poor animal models, and lack of genetic tools. We have now developed a powerful approach to genetically modify this pathogen. This system allows the stable introduction of a variety of reporter genes to derive robust measurements of infection in vitro and in vivo to assess the effectiveness of novel treatments. We have taken advantage of the opportunity to construct gene knockouts to understand the mechanistic underpinnings of drug sensitivity and resistance in Cryptosporidium.

9:55–10:20  A method for the continuous culture of Cryptosporidium parvum  
Nigel Yarlett, PhD, Distinguished Professor, Department of Chemistry and Physical Sciences, Director of Haskins Laboratories; Pace University  
Cryptosporidium sp. is a global cause of diarrheal disease and the only enteric disease member for which no treatment exists. One of the handicaps to developing chemotherapy is the lack of a reproducible long-term culture method permitting in vitro drug screening beyond 48 hours. Utilizing advances in hollow-fiber technology, we have developed a method that mimics the gut by delivering nutrients and oxygen to intestinal host cells from the basal layer up while permitting separate redox and nutrient control of the lumen for parasite development. Using this technique, parasites have been continuously cultured for more than 12 months with a yield of 106 to 108 per mL. Oocysts obtained from the culture were infective to dexamethasone immunosuppressed and T-cell deficient mice. Biochemical and molecular experiments of parasites after 12 months in culture indicate no differences are apparent to the Iowa isolate used to generate the culture.

10:20–10:45  A high-throughput phenotypic screen to identify anticyrptosporidial compounds  
Case McNamara, PhD, Principal Investigator, Infectious Diseases; California Institute for Biomedical Research  
Anticyrptosporidial drug discovery has primarily been restricted to target-based screens and repurposing focused collections of US Food and Drug Administration-approved drugs or antimarial compounds against phenotypic assays. To enable a high-throughput campaign against large, diverse libraries of small molecule compounds, we miniaturized and fully automated an established high-content imaging screen to a 1,536-well format. This assay detects inhibitors of Cryptosporidium parvum proliferation within the human intestinal epithelial cell line (HCT-8) and has achieved a weekly throughput of 50,000 compounds. To date, more than 500,000 compounds have been screened at 1.87 µM and application of a 70% inhibition cut-off and removal of cytotoxic compounds yielded a final hit rate of 0.29%. Interestingly, comparison of these anticyrptosporidial screen hits to those libraries also assayed against the asexual blood stages of the related apicomplexan, Plasmodium falciparum, reveal minimal chemical overlap and reinforce divergent pharmacological sensitivities.

10:45–11:15  Coffee break

Drug Discovery I

11:15–11:40  Bumped-kinase inhibitors to treat cryptosporidiosis: From X-ray structure to successful calf therapy  
Wesley C. Van Voorhis, MD, PhD, Head of the Division of Allergy and Infectious Diseases, Professor of Medicine and Adjunct Professor of Global Health and Microbiology, Director, Center for Emerging and Re-emerging Infectious Diseases; University of Washington  
New therapies to treat apicomplexan protozoan pathogens are urgently needed for both human and animal health. Bumped-kinase inhibitors (BKIs) specifically target calcium-dependent protein kinase 1 (CDPK1) of Cryptosporidium parvum, and other apicomplexan species have a very small gatekeeper residue, glycine, in the adenosine triphosphate (ATP) binding site of the protein kinase catalytic domain. This small gatekeeper residue allows BKIs to access a hydrophobic pocket that is blocked by the larger gatekeeper residues of mammalian protein kinases. In this way, we are able to design potent and highly-selective protein kinase inhibitors for CDPK1. We now show that BKI exposure leads to a reduction of parasite host cell invasion and replication in vitro, and the bulk of evidence supports that this action is mediated by inhibition of CDPK1. Treatment of mice infected with Cryptosporidium leads to a significant reduction in oocyte production, whether in the newborn mouse model or immunocompromised mouse model. We are trying to dissect how much systemic exposure and how much enteral (stool) exposure is necessary for BKIs to have favorable action in the mouse model. We have also shown efficacy in the C. parvum–newborn calf diarrhea model. Administration of BKIs twice a day significantly reduces oocyst shedding within 24 hours of initiation of therapy. Clinical evaluation scores are improved and diarrhea largely resolved within 48 hours of initiation of therapy. We now have advanced lead BKIs that have excellent pharmacokinetics, absorption, distribution, metabolism, and excretion; and toxicology parameters. Thus, BKIs are promising therapies for Cryptosporidium infections but the exact pharmacodynamics for successful therapy are not yet fully established.

11:40–12:05  Lessons learned on Cryptosporidium drug development using the Medicines for Malaria Ventures Malaria Box  
Christopher Huston, MD, Associate Professor, Departments of Medicine (Infectious Diseases) and Microbiology and Molecular Genetics, University of Vermont College of Medicine; University of Vermont  
Results from microscopy-based screening of the Medicines for Malaria Ventures Malaria Box library for compounds that inhibit Cryptosporidium parvum development in tissue culture, and results from follow-up testing using a NOD SCID gamma mouse model of chronic C. parvum infection. This screen yielded multiple active chemical scaffolds and one validated
lead compound that is being tested in dairy calves. This cell-based screening method has been/is being used by a number of groups, resulting in identification of numerous hits and a growing number of compounds with in vivo efficacy. Thus, we believe that ample "chemistry" is entering the Cryptosporidium drug development pipeline. Given this, critical next steps include understanding how to prioritize compounds for further testing, and validating a developmental cascade, to enable comparison of compounds and the appropriate distribution of resources. To help begin this discussion, this presentation will address additional assays that may be useful for compound prioritization.

12:05–12:30  Oxaborole compounds for treatment of cryptosporidiosis
Yvonne Freund, PhD, Director of Pharmacology; Anacor Pharmaceuticals, Inc.

Potent in vitro hits against Cryptosporidium parvum have been identified from three advanced Anacor programs: (1) Global Alliance for Livestock and Veterinary Medicine (GALVmed), (2) Medicines for Malaria Ventures, and (3) an internal leucyl-tRNA synthetase inhibitor program. Anacor is exploring repositioning compounds from these programs for use against Cryptosporidium, leveraging investments in these programs into an area of acute need with potential for rapid advancement into human clinical trials. The Anacor oxaborole library was screened in vitro against C. parvum. Hits from the three programs, as well as from the Gates Foundation oxaborole expansion library were confirmed. A compound from the animal trypanosomiasis (GALVmed) program was tested in a murine C. parvum model and demonstrated better reduction in fecal parasite load than paromomycin. This compound will progress to newborn calf studies. Our goal is to quickly assess the potential of repositioning existing Anacor compounds as candidates for treatment of cryptosporidiosis.

12:30–13:30  Lunch

In Vivo Models

13:30–13:55  The piglet diarrhea model of cryptosporidiosis: Investigating species that infect humans
Saual Tzipori, DVM, PhD, DSc, FRCVS, Distinguished Professor and Chair, Department of Infectious Disease and Global Health, Agnes Varis University Chair in Science and Society, Cummings School of Veterinary Medicine; Tufts University

This presentation will describe the piglet model as a tool for the investigation of significant enteric pathogens of human origin, with a focus on cryptosporidiosis attributed to key species which include Cryptosporidium parvum, (bovine and anthropotonic), C. hominis, and C. meleagridis. Examples of the utility of the model will include evaluation of immune cross-protection among the species, the role of passive vs. active immunity, humoral vs. T-cell responses, and evaluation of drug efficacy. The nature and the characteristics of the human and the anthropotonic Cryptosporidium strains used in this laboratory will be described in some detail.

13:55–14:20  The neonatal calf model for evaluation of candidate anticyptosporidials
Michael W. Riggs, DVM, PhD, Diplomate, American College of Veterinary Pathologists, Professor, School of Animal and Comparative Biomedical Sciences; University of Arizona

In the neonatal calf model, calves develop profuse watery diarrhea commencing two to three days post infection (PI), which diminishes or sometimes resolves by day ten PI (Vet. Parasitol. 2012; 188:41–47). Manually delivered, pathogen-free calves are confined individually in elevated stanchions (BSL2) and infected with Cryptosporidium parvum oocysts at 36 to 48 hours of age. Treatment with candidate anticyptosporidials or control vehicle commences at 48 hours PI. Calves are examined and assigned comprehensive clinical scores twice daily. The total fecal volume excreted daily is determined to provide a quantitative measure of diarrhea severity and to determine total daily oocyst counts. Using this model in an ongoing collaboration with the University of Washington group (led by W. Van Voorhis), we have demonstrated that calves treated with bumped kinase inhibitors have improved clinical scores, fewer days of diarrhea, reduced diarrhea volume, and reduced oocyst shedding compared to control calves (P < 0.05). The results will be reviewed.

14:20–14:45  Using a Cryptosporidium human challenge model as a platform to guide development of vaccines and therapeutics
Caroline Lyon, MD, MPH, Associate Professor of Medicine; University of Vermont

Cryptosporidium infection has long been recognized as an important enteric disease and part of the cycle of enteric infection, diarrhea, and malnutrition in the developing world. The current therapeutic and preventive options for cryptosporidiosis are limited, especially for the populations at highest risk of severe disease and long-term sequelae. Re-establishment of a human challenge model is a safe and efficient approach to accelerating development of vaccines and improved therapeutics. For studies to test potential new therapeutics, the controlled environment afforded by infection of healthy adult volunteers can mitigate many of the difficulties of testing drugs in endemic or field settings, reducing the expense and time required and eliminating the complications of interpreting the results that arise from the presence of multiple pathogens. Furthermore, the human challenge model offers a controlled setting in which to evaluate the human immune response to Cryptosporidium and determine vaccine feasibility. This presentation will discuss the design, development, and regulatory considerations of a human Cryptosporidium challenge model.

14:45–15:15  Coffee break

Drug Discovery II

15:15–15:40  Targeting IMP dehydrogenase for Cryptosporidium
Lizbeth Hedstrom, PhD, Professor of Biology and Chemistry; Brandeis University

The Cryptosporidium gene for IMP dehydrogenase (IMPDH) appears to have been obtained from bacteria via horizontal gene transfer, and thus is very different from the host. We identified specific inhibitors of Cryptosporidium IMPDH in a high-throughput screen and have been engaged in a medicinal chemistry optimization program to develop these compounds into anticyptosporidial drugs. We now have potent and selective inhibitors in six different scaffolds. Two of these compounds display activity in a mouse model of Cryptosporidium infection with better efficacy than paromomycin. These compounds suggest that intestinal exposure, rather than plasma exposure, is critical for antiparasitic activity.
15:40–16:05 Exploring the unique metabolic features in Cryptosporidium for developing therapeutics

Guan Zhu, PhD, Professor, Department of Veterinary Pathobiology, College of Veterinary Medicine & Biomedical Sciences; Texas A&M University

*Cryptosporidium* has many unique metabolic features, such as its inability to synthesize any nutrients de novo (e.g., fatty acids, amino acids, and nucleosides) and the lack of cytochrome-based respiration (anaerobic). Our laboratory has been studying and exploring several key enzymes involved in the fatty acid and energy metabolism as novel drug targets, including fatty acyl-CoA synthetase (ACS), acyl-CoA binding protein (ACBP), hexokinase (HK) and lactate dehydrogenase (LDH). We have demonstrated that the ACS inhibitor, triacsin C, could inhibit the growth of *Cryptosporidium parvum* in vitro and in vivo at low nanomolar and mg/kg levels. We have also shown that the growth of *C. parvum* can be inhibited by targeting the parasite ACBP, HK, and LDH. Moreover, we have developed a high-throughput real-time reverse transcription polymerase chain reaction assay for screening anti-cryptosporidial drugs in vitro, and identified at least one US Food and Drug Administration-approved drug that displays satisfactory efficacy in vitro and in vivo for potential repurposing.

16:05–16:30 Oleylphosphocholine inhibits *Cryptosporidium parvum* infection

Momar Ndao, DVM, PhD, MSc, Assistant Professor to the Faculty of Medicine; Associate Member, McGill Institute of Parasitology, Department of Microbiology & Immunology, Department of Physiology, and Department of Experimental Medicine; Laboratory Director, National Reference Centre for Parasitology at the Research Institute McGill University Health Center; McGill University, Canada

There is no drug on the market at the moment that can efficiently prevent the infection, kill the parasite, or cure cryptosporidiosis. Our goal was to determine the efficiency of oleylphosphocholine (OIPC) to prevent first, *Cryptosporidium parvum* infection in HCT-8 cells in vitro, and second, clinical signs of cryptosporidiosis in interferon gamma receptor knock-out mice. Our in vitro studies in *C. parvum* infected HCT-8 cells showed that there is no cell toxicity at OIPC concentrations of at least 50 mM and that the EC50 is 18.84 nM. We reported a dose-dependent reduction of *C. parvum* burden with increasing concentrations of OIPC; miltefosine showed a similar efficiency, but OIPC was less toxic for the cells. In a lethal model of cryptosporidiosis, mice were infected with 4,000 oocysts and PBS-control mice all died during the first 10 days post-infection. All surviving treated mice were sacrificed at day 30 post-infection and, at that time, all 40 mg/kg/day OIPC-treated mice were alive and free of cryptosporidiosis clinical signs. In fact, these mice had a 100% elimination of *C. parvum* oocyst shedding in stool samples, 99.97% *C. parvum* parasite burden reduction in intestinal samples, and complete absence of *C. parvum* oocysts or inflammation in histological sections of ileum (distal part of the intestine). So, OIPC is a non-toxic compound that inhibits *C. parvum* infection in vitro and can be used efficiently at a dose as low as 1mM. This compound is therefore safe, reliable, and efficient to prevent/treat *C. parvum* infection.

16:30–16:55 An exploratory drug discovery effort against cryptosporidiosis

Ujjini H. Manjunatha, PhD, Senior Investigator, Drug Discovery Unit; Novartis Institute for Tropical Diseases, Singapore

Apicomplexan parasite *Cryptosporidium* is the second most important diarrheal pathogen causing life-threatening diarrhea in children leading to 100,000 deaths each year and is also associated with long-term growth faltering and cognitive deficiency. Cryptosporidiosis is still an underappreciated global health concern with no satisfactory treatment options. To identify compounds active against *Cryptosporidium parvum* (*Cp*), we have established a high-content imaging and also a novel cytopathic effect (CPE) based assay in HCT8 cells. Further, to explore functional conservation of molecular targets across protozoan parasites and to identify lead compounds, we have assembled and screened a “parasite library” in *Cp*:HCT8 infection assay. This talk will present exploratory drug discovery efforts by the Novartis Institute for Tropical Diseases.

17:00–17:25 Wrap-up and summary

David Brown, PhD, FRSC, FRSM, Chair, Scientific Advisory Committee, Drug Development; PATH

17:25–17:30 Concluding remarks

David Shoultz, PhD, MS, MBA, Program Leader, Drug Development and Devices and Tools; PATH

Eugenio de Hostos, PhD, MBA, Director of Research and Preclinical Development, Drug Development; PATH

17:30–19:30 Cocktail reception and networking
SPEAKERS

David Brown PhD, FRSC, FRSM
Dr. Brown has 40 years of experience in the pharmaceutical and biotechnology industry. He has served with four of the top ten pharmaceutical companies: Zeneca, Pfizer, GlaxoWellcome, and Hoffman La-Roche; and also as President and Chief Executive of Cellzome AG. During his time at Pfizer, he was named co-inventor on the patent for Viagra, and for eight years he led the team that invented and developed Viagra through to proof of clinical efficacy in male impotence. The drug is also marketed for treatment of pulmonary hypertension under the trade name Revatio. Dr. Brown also had a pivotal role in the discovery of Relpax, a treatment for migraine. Together these drugs have achieved sales of more than $30 billion. While at Roche in Switzerland, he was a director of the company and Global Head of Drug Discovery. He was responsible for the productivity of more than 2,000 scientists at five research sites in the United States, Europe, and Asia.

Dr. Brown has a strong interest in entrepreneurialism. He coaches CEOs and entrepreneurs at Cambridge University Business School and is an angel investor in high-technology start-up companies. He co-founded Crescendo Biologics and also serves on the boards of Healx Ltd. (Chair), ProFactor Pharma Ltd. (Chair), and Babraham Institute Enterprise Ltd. (Chair). He is a trustee (Director) of two charities, Antibiotic Research UK, dedicated to solving the looming problem of antibiotic resistance; and Friends of Manjushree Vidyapith School and Orphanage, a charity he co-founded in 2005 to help destitute orphans in South Tibet.

Robert Choy, PhD
Dr. Choy is Associate Director of Research and Preclinical Development in PATH’s Drug Development program, which seeks to discover, develop, and deliver safe, effective, and affordable treatments for neglected diseases. Dr. Choy contributes his expertise in enteric diseases to the design, execution, and analysis of studies evaluating candidates in PATH’s enteric diseases portfolio. This includes therapeutics against Cryptosporidium, soil-transmitted helminths, and acute secretory diarrhea. Before joining PATH in 2010, Dr. Choy was a senior scientist at Exelixis, where he worked on target discovery and validation, antibody therapeutics, and small molecule modulators of stem cell growth and differentiation. He received his PhD in molecular and cellular biology from the University of Washington.

Eugenio de Hostos, PhD, MBA
Dr. de Hostos serves as Director of Research and Preclinical Development for PATH’s Drug Development program, where he leads its enteric disease portfolio and serves as a project leader on the helminth program. He has more than 15 years of experience in pharmaceutical research and drug development. Prior to joining PATH, he was a research scientist at Cytokinetics and Exelixis and an assistant professor at Rice University. He has been involved with the Master of Biotechnology Program at San Jose State University since 2007 and serves as adjunct associate professor. He completed his MBA with a focus on socially and environmentally responsible business at the Presidio School of Management in San Francisco in 2010. After he received his PhD in 1989 from Stanford University, he was a postdoctoral fellow at the Max Planck Institute for Biochemistry in Munich and at the University of California, San Francisco.
Yvonne Freund, PhD
Dr. Freund is project leader on the Gates Foundation-funded Cryptosporidium Drug Discovery project and Director of Pharmacology at Anacor Pharmaceuticals, Inc. Dr. Freund has worked in neglected tropical diseases drug discovery for Anacor since 2005, when she initiated screening of the oxaborole library in collaboration with Drs. Phillip Rosenthal and James McKerrow at the University of California, San Francisco. Anacor is currently involved in approximately ten neglected tropical disease drug discovery programs including malaria, tuberculosis, and trypanosomal and helminthic diseases. Prior to Anacor, Dr. Freund led the Immunology and Immunotoxicology group at SRI International, and did National Institutes of Health-funded research on Toxoplasma gondii at both SRI and Palo Alto Medical Foundation. Dr. Freund has consulted for Bay Area biotech companies in the areas of immunology and infection diseases and has been a speaker at US and international meetings on topics in neglected tropical disease drug discovery and immunology.

Lizbeth Hedstrom, PhD
Dr. Hedstrom is a Professor of Biology and Chemistry at Brandeis University, where she leads the Hedstrom laboratory, which studies enzyme structure/function relationships and inhibitor design. Her work elucidating the structural basis of substrate specificity in trypsin and chymotrypsin is found in many textbooks. Current projects address the development of IMPDH-targeted antiparasitic and antibiotic drugs and the structural basis of reaction specificity in the IMPDH/GMPR family. Her laboratory is also developing small molecules strategies to induce selective protein degradation. She is a Searle Scholar (1993), Beckman Young Investigator (1995), and American Association for the Advancement of Science Fellow (2010). Dr. Hedstrom received her PhD in Biochemistry from Brandeis University and completed her postdoctoral training at UCSF.

Christopher Huston, MD
Dr. Huston is Associate Professor in the Departments of Medicine (infectious diseases), and Microbiology and Molecular Genetics at the University of Vermont College of Medicine. His laboratory focuses on the cell biology of Entamoeba histolytica, and on using phenotypic assays and animal models for Cryptosporidium drug development. Dr. Huston received his MD in 1994 from Cornell University Medical College. He then served as an intern, resident, and chief resident in internal medicine at the University of Vermont. From 1998 to 2000, he was a fellow in infectious diseases at the University of Virginia, after which he received a Howard Hughes Postdoctoral Fellowship to continue his training.

Caroline Lyon, MD, MPH
Dr. Lyon completed her undergraduate education at Washington University in St. Louis and obtained a Master in Public Health from Boston University. She completed her medical education and internal medicine training, including a year as chief resident, at the University of Vermont. She is currently an Associate Professor of Medicine at the University of Vermont College of Medicine, an attending physician in Hospital Medicine at the University of Vermont Medical Center, and an investigator with the University of Vermont Vaccine Testing Center (UVM VTC). In her role as a hospitalist, she cares for patients in the hospital, teaches medical students and residents, and participates in several institution-wide committees aimed at physician recruitment, patient safety, and medical education. She also directs an annual continuing medical education conference in hospital medicine. As an investigator with the UVM VTC, Dr. Lyon has participated in clinical trials evaluating vaccine safety and efficacy, and human immunology centered on enteric diseases of global importance, including cholera, typhoid, and Campylobacter.

Case McNamara, PhD
Dr. McNamara is a Principal Investigator, Infectious Disease at California Institute for Biomedical Research (Calibr), where he helps lead a Gates Foundation-funded initiative to identify and develop small molecule inhibitors against parasitic nematodes and prominent protozoan parasites, including those responsible for malaria and cryptosporidiosis. Prior to joining Calibr in 2014, he spent seven years at the Genomics Institute of the Novartis Research Foundation, where he participated in the development of multiple preclinical antimalarial compounds (two of which are now in Phase II clinical trials) and the identification of key antimalarial drug targets. Dr. McNamara received his PhD in biochemistry from the University of California, San Diego.

Momar Ndao, DVM, PhD, MSc
Dr. Ndao is a member of the Infection and Immunity Axis of the Research Institute of the McGill University Health Centre (MUHC), Montreal, Canada. He is funded by various Canadian national funding agencies, including Fonds de recherche du Québec—Santé (FRQS), the Canadian Institute for Health Research, and the Canada Foundation for Innovation. Dr. Ndao has supervised many trainees and students and serves on the review committees of a wide variety of agencies, scientific journals, and governments. He is an Assistant Professor in the Faculty of Medicine at McGill and an Associate Member of the McGill Institute of Parasitology, Department of Microbiology and Immunology; Department of Physiology; and Department of Experimental Medicine. Since 2000, he has also served as Laboratory Director of the National Reference Centre for Parasitology at the MUHC Research Institute.

William A. Petri, Jr., MD, PhD
Dr. Petri is Chief of the Division of Infectious Diseases & International Health at the University of Virginia, where he practices internal medicine and the subspecialty of infectious diseases. His studies focus on enteric infections and their consequences on the health of children. Dr. Petri leads the Performance of Rotavirus and Oral polo Vaccines in DEveloping countries (PROVIDE) study of the Gates Foundation, which is exploring new solutions for oral poliovirus and rotavirus vaccine failures in the developing world. He also studies amebiasis, one of the top ten causes of diarrhea among children in the developing world. He has molecularly defined its ability to kill cells, developed the first US Food and Drug Administration-cleared test for its diagnosis, and was the first person to discover that children were immune to reinfection. He has also discovered that the obesity hormone leptin plays a critical role in defense of the gut from ameba. In 2014, Dr. Petri received the Commonwealth of Virginia Outstanding Faculty Award, and the University of Virginia has recognized him with several awards, including All-University Teaching, Excellence in Faculty Research, and Inventor of the Year. He has also served as the President of the American Society of Tropical Medicine and Hygiene and Editor of Infection and Immunity. He has received the Squibb Award of the Infectious Diseases Society of America, Burroughs Wellcome New Investigator and Scholar Awards in Molecular Parasitology, and Lucile P. Markey Scholar in Biomedical Research. Dr. Petri has served on advisory committees for the National Institutes of Health.
Michael W. Riggs, DVM, PhD
Dr. Riggs is a professor at the Veterinary Diagnostic Laboratory, School of Animal and Comparative Biomedical Sciences at the University of Arizona. His research program centers on the immunobiology of cryptosporidiosis caused by Cryptosporidium parvum and C. hominis. The focus has been on characterizing protective immune responses; developing recombinant vaccines; immunotherapeutic and other new drug discovery; definition of the molecular pathogenesis of host cell recognition, attachment, and invasion; and animal models for C. parvum and C. hominis. Since 1989, his Cryptosporidium research program has been continuously supported by funding from the National Institutes of Health, the United States Department of Agriculture, and donors from the public and private sectors. His discoveries have so far led to 13 issued patents for Cryptosporidium inventions, two foreign patents pending, and more than 40 refereed publications and scholarly book chapters.

David Shoultz, PhD, MS, MBA
Dr. Shoultz directs two of PATH’s product development programs: the Drug Development program, which seeks to discover, develop, and deliver safe, effective, and affordable treatments for neglected diseases, and the Devices and Tools program, which focuses on advancing appropriate, affordable, and accessible technologies to improve the health of underserved populations. Prior to joining PATH in 2014, Dr. Shoultz served as the Director of Grants and Partner Engagement and as a member of the leadership team at the Gates Foundation, where he led an effort to strengthen the Gates Foundation’s relationships with its partner organizations to facilitate ongoing interactions and help achieve maximum impact. Previously, he served as Deputy Director in the Gates Foundation’s Global Health Program, Infectious Disease, where he was central to strategy, planning, and management for four program teams focused on malaria, enteric diseases, pneumonia, and neglected tropical diseases. Prior to these roles, Dr. Shoultz was part of the senior management team for a number of clinical research organizations participating in the development of new medicines. He has been a member of the affiliate faculty for the departments of Global Health and Epidemiology at the University of Washington since 2000 and sits on the board of the Geneva Foundation, where he is also inaugural chair of the Scientific Advisory Committee. Dr. Shoultz earned his PhD and MS from the School of Public Health and Community Medicine at the University of Washington. He holds an MBA from the Albers School of Business and Economics at Seattle University, where he is a faculty member in the Executive MBA Program.

Boris Striepen, PhD
Dr. Striepen is a Distinguished Research Professor and a Georgia Research Alliance Distinguished Investigator in the Center for Tropical and Emerging Global Diseases at the University of Georgia, where he studies infectious diseases caused by protozoan parasites, in particular Toxoplasma and Cryptosporidium. His laboratory is known for the genetic analysis of parasite cell biology and metabolism. In addition, Dr. Striepen is interested in education and training and has taught in a variety of settings, including the Biology of Parasitism course at the Marine Biology Laboratory in Woods Hole for which he served as faculty and director. Dr. Striepen was trained as a biologist at the Universities of Bonn and Marburg (Germany) and conducted postdoctoral research at the University of Pennsylvania.

Saul Tzipori, DVM, PhD, DSc, FRCVS
Dr. Tzipori is a Distinguished Professor and Chair of the Department of Infectious Disease and Global Health at the Cummings School of Veterinary Medicine at Tufts University. He has many years of research experience working with infectious diseases of humans and animals, with a particular emphasis on food and waterborne enteric pathogens and bacterial toxins.

This includes investigating the relative contribution of virulence attributes to pathogenesis and disease, which can aid both the screening and evaluation of chemical or immune-based therapeutic agents and vaccine development and evaluation. He has contributed notably to available literature on diseases such as cryptosporidiosis, microsporidiosis, E. coli O157:H7, and shigellosis. PubMed currently lists more than 274 publications for Dr. Tzipori and his team, of which nearly 100 are on cryptosporidiosis. Dr. Tzipori has directed multiproject and multicenter scientific programs nationally and globally, supported by funders including the National Institutes of Health (NIH), the US Agency for International Development (USAID), and the Gates Foundation. He is currently the principal investigator of an NIH-funded project on vaccine development against cryptosporidiosis, and the Tufts principal investigator on the USAID-funded global health project on Emerging Pandemic Threats (EPT2). Prior to these efforts he served as the associate director and division head at the International Center for Diarrheal Diseases Research in Bangladesh.

Ujjini H. Manjunatha, PhD
Dr. Manjunatha is a senior investigator in the Drug Discovery Unit at Novartis Institute for Tropical Diseases (NITD), Singapore. He also has an honorary adjunct faculty position at the National University of Singapore. He received his PhD from the Indian Institute of Science, Bangalore in 2001. He was then awarded a five-year John E. Fogarty International visiting post-doctoral research fellowship to work at the National Institutes of Health where he worked on mechanism of action of a promising tuberculosis drug, Protomanid. Dr. Manjunatha joined NITD in 2007, and has been working on drug discovery and development against various neglected tropical diseases. He has led a multidisciplinary team of microbiologists, biochemists, pharmacologists, and medicinal chemists to identify a novel class of anti-tuberculosis candidates including indolcarboxamides and hydroxyl-pyridones. Currently, Dr. Manjunatha is leading exploratory drug discovery efforts against cryptosporidiosis at NITD. He recently received Wellcome Trust’s Pathfinder Award grant in collaboration with the University of Georgia. Dr. Manjunatha has published more than 40 research articles in highly reputed international journals and has a number of patents to his credit.

Wesley C. Van Voorhis, MD, PhD
Dr. Van Voorhis practices medicine, teaches, and leads the Division of Allergy and Infectious Diseases (80 faculty and 250 staff) at the University of Washington (UW). He is the director of Center for Emerging and Re-emerging Infectious Diseases (CERID) at UW, which takes a multidisciplinary approach to identifying and developing diagnostic, therapeutic, and vaccine solutions to emerging infectious diseases. In addition, CERID is developing a new Center for the Intestinal Microbiome. For the past 25 years, Dr. Van Voorhis has worked on preclinical drug development for malaria, trypanosomes, leishmaniasis, tuberculosis, and Cryptosporidium. He has recently received Wellcome Trust’s Pathfinder Award grant in collaboration with the University of Georgia. Dr. Manjunatha has published more than 40 research articles in highly reputed international journals and has a number of patents to his credit.
Nigel Yarlett, PhD
Dr. Yarlett is a distinguished professor in the Department of Chemistry and Physical Sciences and the Director of Haskins Laboratories. He has been awarded the Seymour Hutner Prize in protozoology (1995), Keenan Award for Teaching Excellence (2003), Drugs for Neglected Diseases initiative project of the year (2011), and Fellow of the Royal Society of Chemistry (2012). He was the co-principal investigator of the group that discovered difluoromethylornithine (Efornithine), currently in clinical use, and SCYX (oxoborale), currently in phase II clinical trial for the treatment of human African trypanosomiasis. Dr. Yarlett’s current laboratory research centers on developing a continuous culture system for *Cryptosporidium parvum* and *C. hominis* with a view to establishing drug targets for chemotherapy. He received his PhD in biochemistry jointly from Cardiff University and Hannah Research Institute, Scotland, and conducted doctoral research in the laboratory of Christian deDuve, Rockefeller University and Cambridge University.

Guan Zhu, PhD
Dr. Zhu is a professor in the Department of Veterinary Pathobiology, College of Veterinary Medicine & Biomedical Sciences, Texas A&M University. He has more than 23 years of experience in translational research on cryptosporidiosis, focusing on developing therapeutics through an understanding of parasite biology. His research has led to several important discoveries in *Cryptosporidium* biology, including the lack of an apicoplast, and the Type I fatty acid and polyketide synthetic pathways in the parasite. More recently, Dr. Zhu and his colleagues have demonstrated that key enzymes involved in fatty acid biosynthesis, glycolysis, and DNA metabolism in *Cryptosporidium* could serve as drug targets for developing novel anti-cryptosporidial therapeutics that are highly efficacious in vitro and in vivo. Dr. Zhu received his PhD degree in parasitology/coccidiosis from the University of Georgia.
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**STREET ADDRESS:** 2201 Westlake Avenue, Suite 200, Seattle, WA 98121 USA

**MAILING ADDRESS:** PO Box 900922, Seattle, WA 98109 USA