HARVARD | SCHOOL OF PUBLIC HEALTH

Powerful ideas for a healthier world

Defeating Malaria
From the Genes to the Globe

The Inaugural Launch of the
Genes to the Globe Symposium Series

SYMPOSIUM AGENDA

&

POSTER SESSION ABSTRACTS

FRIDAY, MARCH 29, 2013

Kresge G1 & Kresge Cafeteria
Harvard School of Public Health

defeatingmalaria.harvard.edu

FROM THE GENES TO THE GLOBE
Symposium Series

Robust life sciences activity has always been a distinctive and pivotal component of the academic agenda at the Harvard School of Public Health (HSPH). By integrating biomedical, epidemiological, social, behavioral, and policy research, the School has consistently advanced a unique and multidimensional understanding of disease—one that spans from the genes to the globe.

While life sciences research enriches public health, public health also enriches the life sciences, by creating the kind of "mission-oriented" research that addresses some of the most profound problems facing humankind.

In March 2013, the School will launch the Genes to the Globe (G2G) Symposium Series. The symposia will:

- Bring together faculty, students, fellows and the School's broader research community to address major public health problems in new ways.

- Provide a transformational approach to organizing knowledge around big problems using multiple levels of analysis.

- Integrate the School's strengths across disciplines to advance a multidimensional understanding of public health challenges and the mechanisms of disease.

AGENDA

3:00 PM **WELCOME**
Dyann Wirth, PhD
Richard Pearson Strong Professor of Infectious Diseases, Chair, Department of Immunology and Infectious Diseases, HSPH

OPENING REMARKS
Karen Emmons, PhD
Associate Dean for Research, Professor of Social and Behavioral Sciences, HSPH

3:10 PM **SETTING THE STAGE: Challenges Ahead**
Marcia Castro, PhD
Associate Professor of Demography, HSPH

3:30 PM **PANEL DISCUSSION: Challenges for Malaria Control & Eradication within the G2G Framework**

Moderated by Marcia Castro, PhD
Associate Professor of Demography, HSPH

Jessica Cohen, PhD
Assistant Professor of Global Health, HSPH
Manoj Duraisingh, PhD
Associate Professor of Immunology and Infectious Diseases, HSPH
Günther Fink, PhD
Assistant Professor of International Health Economics, HSPH

PANEL DISCUSSION: Biological Challenges to Disrupting Malaria Transmission

Moderated by Marcia Castro, PhD
Associate Professor of Demography, HSPH

Caroline Buckee, PhD
Assistant Professor of Epidemiology, HSPH
Flaminia Catteruccia, PhD
Associate Professor of Immunology and Infectious Diseases, HSPH

Matthias Marti, PhD
Assistant Professor of Immunology and Infectious Diseases, HSPH
Daniel Neafsey, PhD
Group Leader - Malaria Genome Sequencing and Analysis, Broad Institute

4:55 PM **COFFEE BREAK**

5:10 PM **ROUNDTABLE DISCUSSION / Q&A**
Moderated by Barry Bloom, PhD
Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, HSPH

Marcia Castro, PhD
Associate Professor of Demography, HSPH
Michael Chu, MBA
Senior Lecturer of Business Administration, HBS
Manoj Duraisingh, PhD
Associate Professor of Immunology and Infectious Diseases, HSPH
Erin Hasselberg
Principal Advisor, Human Resources Capacity Development, John Snow, Inc.
Michael Reich, PhD
Taro Takemi Professor of International Health Policy, HSPH

5:55 PM **CLOSING REMARKS**
Dyann Wirth, PhD
Richard Pearson Strong Professor of Infectious Diseases, Chair, Department of Immunology and Infectious Diseases, HSPH

6:00 PM **NETWORKING RECEPTION / POSTER SESSION**
Kresge Cafeteria

SPEAKER BIOGRAPHIES

Barry Bloom, PhD, Harvard University Distinguished Service Professor and Joan L. and Julius H. Jacobson Professor of Public Health, HSPH.

A leading scientist in the areas of infectious diseases, vaccines, and global health and former consultant to the White House, Professor Bloom has dedicated his career as a scientist to researching the immune response to tuberculosis, a disease that claims more than two million lives each year.

He has been extensively involved with the World Health Organization (WHO) for more than 40 years. He is currently Chair of the Technical and Research Advisory Committee to the Global Programme on Malaria at WHO and serves on the editorial board of the Bulletin of the World Health Organization.

Dr. Bloom currently serves on the Ellison Medical Foundation Scientific Advisory Board and the Wellcome Trust Pathogens, Immunology and Population Health Strategy Committee. He is on the Scientific Advisory Board of the Earth Institute at Columbia University and the Advisory Council of the Paul G. Rogers Society for Global Health Research.

Dr. Bloom came to HSPH to serve as Dean of the Faculty in 1998. He stepped down December 31, 2008 and is currently a Harvard University Distinguished Service Professor at HSPH. In his capacity as Dean, he served as Secretary Treasurer for the Association of Schools of Public Health (ASPH). Prior to that he served as chairman of the Department of Microbiology and Immunology at the Albert Einstein College of Medicine from 1978 to 1990, the year in which he became an Investigator of the Howard Hughes Medical Institute, where he also served on the National Advisory Board.

Caroline Buckee, PhD, Assistant Professor of Epidemiology, HSPH.

Dr. Caroline Buckee joined the Harvard School of Public Health in 2010. Dr. Buckee was a Sir Henry Wellcome Postdoctoral Fellow at the University of Oxford and an Omidyar Fellow at the Santa Fe Institute. Dr. Buckee's work focuses on the population dynamics of genetically diverse pathogen

species, including the malaria parasite and the meningococcus. She uses a range of modeling techniques to understand the relationship between the evolution of these species and the epidemiological patterns of infection and disease among human populations.

Together with Professors Manoj Duraisingh and David Cutler, she co-leads the *Defeating Malaria: From the Genes to the Globe* Undergraduate Colloquium, which targets Harvard College undergraduates.

Marcia Castro, PhD, Associate Professor of Demography, HSPH.

Dr. Castro's research is focused on geographical information systems, remote sensing, and spatial statistics, as well as proposed novel methods in spatial analysis. Dr. Castro has done extensive work in the Brazilian Amazon, and has experience working in Africa. Since 2004, she has been working on the Dar es Salaam Urban Malaria Control Program, promoting the use of environmental management approaches to improve urban health. Currently, her work includes a project that is measuring health, poverty and place by modeling inequalities in Accra, Ghana using RS and GIS. She is also investigating the use of remotely sensed imagery to predict urban malaria in Dar es Salaam, Tanzania. Dr. Castro is leading a project to assess the malaria poverty vicious cycle, and she started a project to propose a new methodology to assess spatio- temporal trends in a scenario of multiple control interventions. She is also working on the issues of human mobility and asymptomatic malaria infections in the Brazilian Amazon, as well as on the potential impacts of extreme climatic events on malaria transmission in the Amazon. Dr. Castro is also affilated with SEDAC, DRCLAS, CGA, Wittgenstein Centre for Demography and Global Human Capital's Scientific Advisory Board, and the Harvard Brazil Studies Program.

Flaminia Catteruccia, PhD, Associate Professor of Immunology and Infectious Diseases, HSPH.

Flaminia Catteruccia leads a group of scientists that focus on the analysis of the molecular and genetic basis underlying mating and reproduction in *An. gambiae s.s.* The main research focus of the group is the study of the genetic basis of fertilization and mating behavior in *Anopheles gambiae* mosquitoes, the major malaria vector, with the view to answer basic biological questions and develop new molecular and genetic tools for vector control programs.

The group is concerned with answering basic biological questions as well as developing new tools for vector control programs. Dr. Catteruccia achieved the first genetic manipulation of *Anopheles* mosquitoes and has contributed to the development of a number of molecular tools to perform functional studies in *Anopheles*. Her work includes field studies to confirm and expand the laboratory findings of her research group.

Michael Chu, MBA, Senior Lecturer of Business Administration, HBS.

Michael Chu was appointed a Senior Lecturer in the Initiative on Social Enterprise of the General Management Group of the Harvard Business School in July 2003. He is also Managing Director of the IGNIA Fund, an investment firm based in Monterrey, Mexico, dedicated to investing in commercial enterprises serving low-income populations in Latin America, which he co-founded in 2007. He continues to serve as Senior Advisor and a founding partner of Pegasus Capital, a private equity firm in Buenos Aires, with a portfolio which includes major companies and real estate developments in Argentina, and a real estate joint venture in Colombia.

Professor Chu teaches the second year elective *Business and the Base of the Pyramid*, a course developed with Professor V. Kasturi Rangan. He is Faculty Co-Chair of the Executive Education Program "Strategic Leadership for Microfinance". In the past, he has taught the course *Investing and Managing in Emerging Markets*, and *Effective Leadership of Social Enterprises*. Professor Chu is co-head of Project Antares, a collaboration between HBS and HSPH focusing on commercial approaches to deliver high-impact primary health care to low-income populations in developing nations.

Before Pegasus, as President & CEO of ACCION International, a nonprofit microfinance pioneer, Professor Chu worked to develop financial services for low income sectors as a new segment of banking capable of outstanding returns. He participated in the founding of several regulated microfinance institutions and banks throughout Latin America, including Banco Solidario in Bolivia, Mibanco in Peru and Compartamos Banco in Mexico.

Jessica Cohen, PhD, Assistant Professor of Global Health, HSPH.

In addition to her position at the Harvard School of Public Health, Professor Jessica Cohen is Non-Resident Fellow at the Brookings Institution, Faculty

Affiliate at the Harvard Center for International Development, and Malaria Technical Adviser to the Clinton Health Access Initiative. Her current research applies the methods of program design, randomized trials, and impact evaluation to maternal and child health programs and policies in sub-Saharan Africa. She also has conducted research on sustainable financing for public health programs and financing vehicles to reduce aid volatility. Dr. Cohen is co-editor (with William Easterly) of the book "What Works in Development?: Thinking Big and Thinking Small." She is currently working on a number of field trials in Africa related to appropriate treatment for malaria, technology adoption, messaging and behavior change, and pharmaceutical supply chains.

Dr. Cohen's work has been referenced in major national and international publications, including The Economist, Boston Globe, New York Times and Nature. She has advised the government of Zanzibar on its malaria control program and the Canadian International Development Agency on its child survival programs. Dr. Cohen received her Bachelors degree in economics from Wesleyan University and was a National Science Foundation Graduate Research Fellow at MIT, where she received her doctorate in economics.

Manoj Duraisingh, PhD, Associate Professor of Immunology and Infectious Diseases, HSPH.

Manoj Duraisingh joined the Harvard School of Public Health in 2002, and is an Associate Professor in the Department of Immunology and Infectious Diseases. He is also an Associate Member at the Broad Institute, and a Burroughs Wellcome Fund New Investigator in the Pathogenesis of Infectious Diseases. He obtained his BA in Biochemistry from the University of Oxford, and an MSc and PhD in Molecular Parasitology from the London School of Hygiene and Tropical Medicine, conducting research on the molecular mechanisms of drug-resistance in the malaria parasite. Before joining the Harvard School of Public Health, Professor Duraisingh pursued postdoctoral research in molecular parasitology at the Walter and Eliza Hall Institute, applying molecular genetic approaches to study host cell invasion and the epigenetic regulation of malaria parasites.

Professor Duraisingh's research program focuses on the biology of host-parasite interactions in malaria. He is a world leader in the latest technologies associated with P. falciparum molecular genetics and has trained many researchers in these techniques. His laboratory uses transfection-based molecular and cell biological approaches to study the molecular mechanisms underlying the recognition and

invasion of the human erythrocyte by the malaria parasite, and epigenetic regulation of multigene families that govern virulence processes in *Plasmodium*-infected erythrocytes. More recently, reverse genetic methods have been developed to functionally analyze host red blood cell determinants of malaria infection. Efforts are being made towards establishing in vitro culture and genetic systems for other human *Plasmodium* parasites, including *P. vivax* and *P. knowlesi*. Professor Duraisingh is also engaged in field projects with collaborators and training programs in malaria-endemic areas, in particular Senegal, focused on studying parasite and host genetic determinants of malaria infection in natural populations.

Together with Professors Caroline Buckee and David Cutler, he co-leads the *Defeating Malaria: From the Genes to the Globe* Undergraduate Colloquium, which targets Harvard College undergraduates.

Karen Emmons, PhD, Associate Dean for Research, Professor of Social and Behavioral Sciences, HSPH.

Professor Emmons was appointed Associate Dean for Research at HSPH in 2009 and subsequently created the HSPH Office of Research Strategy and Development (ORSD). Under Karen's leadership, the ORSD provides critical services, supports and strategic direction to: increase HSPH faculty competitiveness for extramural research funding; build and diversify the School's research portfolio; and advance the School's capacity to adhere to the highest research standards.

She is a faculty member in the Center for Community-Based Research at the Dana-Farber Cancer Institute and maintains an extensive NIH-funded research portfolio in community-based approaches to cancer prevention and control. Her expertise is in behavior change and policy interventions for behavioral cancer risk factors, particularly for low income communities. She also has expertise in cancer disparities, and in efforts to increase dissemination/knowledge translation in low-resource settings.

Dr. Emmons is a Fellow in the Society of Behavioral Medicine, and served as its President in 2010-2011. She received the Society's Distinguished Research Mentor Award in 2004, and the Morse Distinguished Researcher Award from the Dana-Farber Cancer Institute in 2005.

Günther Fink, PhD, Assistant Professor of International Health Economics, HSPH.

Günther Fink's research interests cover a wide range of topics related to economic development, with a particular focus on the interactions between health and human capital on one side, and economic welfare on the other. Most of his more recent work focuses on identifying the consequences of exposure to infectious diseases in the sub-Saharan African context. As part of these efforts, Professor Fink is currently the PI of the Zambia Early Childhood Development Project, a longitudinal study which measures the returns to early childhood investment in health and education. Dr. Fink is currently also working on a series of related projects in Burkina Faso, Ghana, and Uganda, which aim at finding mechanisms to reduce the burden of disease generated by ill health in general, and malaria in particular.

Erin Hasselberg, Principal Advisor, Human Resource Capacity Development, John Snow, Inc.

Ms. Erin Hasselberg is the Principal Advisor for Human Resource Capacity Development on the SCMS Project through the John Snow Inc. Research & Training Institute. With nearly a decade of experience working with public health supply chains in resource-limited settings, Ms. Hasselberg has focused primarily on strengthening the capacity of people and organizations in supply chain management. She has worked with Ministries of Health, US Government, non-governmental organizations, private companies and academic institutions in more than a dozen countries in Africa, Asia, and Latin America via her technical roles on the USAID Deliver Project, PEPFAR's flagship Supply Chain Management System project, and the Board of the People that Deliver Global Initiative. Ms. Hasselberg has her MS from Harvard School of Public Health and BS from the University of Illinois at Urbana-Champaign.

Matthias Marti, PhD, Assistant Professor of Immunology and Infectious Diseases, HSPH.

Professor Marti's research efforts are focused on basic and translational aspects of malaria transmission stages. His lab has developed the first high throughput screen targeting malaria transmission stages. More recent work focuses on development of tools for the detection and quantification of malaria

transmission stages during human infection. He is also studying the formation and development of these stages in human red blood cells using an in vitro model. His group is investigating the development and tissue distribution of transmission stages during human infection. Dr. Marti is involved in several malaria specific field collaborations in Malawi and Nigeria.

Daniel Neafsey, PhD, Group Leader, Malaria genome Sequencing and Analysis, Broad Institute.

Dan Neafsey's work focuses on the population genomics of malaria parasites and their Anopheline mosquito vectors. In his primary role as Group Leader of Malaria Genome Sequencing and Analysis at the Broad Institute, he plans and executes genome sequencing and high-throughput genotyping projects related to malaria and coordinates analysis of the data.

He applies analyses and tools from the fields of population genetics and molecular evolution to investigate questions such as the role of natural selection in *Plasmodium* and *Anopheles* genomes, the structure of parasite and vector populations, and the mechanisms by which resistance to drugs and insecticides evolves in parasites and vectors. He also coordinates efforts to adapt parasite genome sequencing to the constraints imposed by the small quantity and often poor quality of samples from clinical field studies of malaria.

Michael Reich, PhD, Taro Tameki Professor of International Health Policy, HSPH.

Professor Reich has been a member of the Harvard faculty since 1983, and serves as Director of the Takemi Program in International Health. He received his PhD in political science from Yale University in 1981, and has an undergraduate degree in molecular biophysics and biochemistry. His current research addresses the political dimensions of public health policy, health system reform, and pharmaceutical policy. He has provided policy advice for national governments, international agencies, non-governmental organizations, private foundations, and private corporations. His software for political analysis, PolicyMaker 4.0, is available for free at www.polimap.com. His recent books include: Pharmaceutical Reform: A Guide to Improving Performance and Equity (with Marc J. Roberts; World Bank, 2011); Access: How Do Good Health Technologies Get to Poor People in Poor Countries? (with Laura J. Frost, 2008, downloadable for free at www.accessbook.org); and Public-Private Partnerships for Public Health (editor; Harvard University Press, 2002).

Dyann Wirth, PhD, Richard Pearson Strong Professor of Infectious Diseases, Chair, Department of Immunology and Infectious Diseases, HSPH.

Professor Dyann Wirth has been a major leader in the area of malaria research. Her work has provided completely new insight into how the malaria parasite has evolved, specifically in the areas of population biology, drug resistance and antigenicity. The Wirth laboratory blends the scientific environments of the Harvard School of Public Health, the Broad Institute, and collaborators from around the globe to create a unique malaria research and training network that brings together scientists with expertise in molecular biology, genetics, genomics, population genetics, chemistry, cell biology, epidemiology, computational biology, biostatistics, and leading clinicians in infectious diseases and pathology. Using this approach, the Wirth group is working to understand the mechanismsof drug resistance in *Plasmodium falciparum*, the major human malaria parasite. Leveraging the genomic tools of the human genomic project, the group has applied state of the art technologies and novel approaches to better understand the fundamental biology of the malaria parasite and mechanisms of drug resistance. The group's current efforts seek to determine both the number and identity of genes expressed by the parasite in response to drug treatment and to evaluate the role of these genes for parasite survival. The long-term goal of this work is to understand basic molecular mechanisms in protozoan parasites with the goal of discovering and applying preventive and therapeutic interventions against infection. Professor Wirth's research activities are made possible through collaborative research partnerships with investigators, universities, and clinical centers in Africa, Asia, and South America.

Together with partners in the malaria community, she is involved in a new university-wide effort called Defeating Malaria: From the Genes to the Globe, to produce, transmit, and translate knowledge to support the control and ultimate eradication of malaria. This initiative is being spearheaded by the Harvard School of Public Health in collaboration with the Harvard Global Health Institute, and it is being launched in partnership with the United Nations Special Envoy for Malaria.

She is Past President of the American Society of Tropical Medicine and Hygiene; a member of the Board of Directors of the Burroughs-Wellcome Fund and the Board of the Marine Biological Laboratory; she is also a member of The Institute of Medicine of the National Academy of Sciences and a Fellow of the American Academy of Microbiology.

POSTER ABSTRACTS

Poster #1
Effectiveness of Larviciding for Malaria Control in Urban Dar es Salaam, Tanzania
Presenter: Mathieu Maheu-Giroux
Co-author: Marcia Castro

Background: The use of larval source management has been neglected by contemporary malaria control programs in sub-Saharan Africa despite historical success. Larviciding, in particular, could be effective in urban areas where transmission is focal and access to *Anopheles* breeding habitats is generally easier than in rural settings. **Methods:** Larviciding was implemented in 3 out of 15 targeted wards of Dar es Salaam after two years of baseline data collection. The intervention was subsequently scaled up to 9 wards a year later and, to all 15 targeted wards in 2008. Cluster sampling of malaria prevalence and socio-demographic characteristics was carried out during 6 survey rounds (2004-2008). Bayesian random effects logistic regression models were used to quantify the effect of the intervention on malaria prevalence. **Results:** After adjustment for confounders, the odds of individuals living in areas treated with larviciding being infected with malaria were 21% lower (Odds Ratio=0.79; 95% Credible Intervals: 0.66-0.93) than those who lived in areas not treated. The larviciding intervention was most effective during dry seasons and had synergistic effects with other protective measures. **Conclusion:** A large-scale community-based larviciding intervention significantly reduced the prevalence of malaria infection in urban Dar es Salaam.

Poster #2
A Randomized Trial on the Impact of Text Message Reminders on Adherence to Antimalarial Treatment
Presenter: Julia Goldberg
Co-author: Günther Fink

Background: Due to massive international efforts, artemisinin based combination therapies (ACTs) for malaria are widely available. However, low adherence to the three-day ACT regimens increases the likelihood that ACT resistance will emerge. **Methods:** We conducted a randomized trial to assess the impact of reminders on adherence to ACT regimens. 1792 study participants were invited to enroll in the text message system. Of 1140 subjects

successfully registered in the text message system, 554 subjects were randomly selected for treatment group and 586 subjects were randomized to the control group. Patients in the treatment were further randomized with equal probability to receive either short or long messages. **Findings:** Only 58% of adults and 71% of child patients reported completing the treatment as prescribed. The short reminder message increased the odds of adherence by 32.8% (95% CI [0.967, 1.824], p-value 0.078), while the effect of the long message was not statistically significant. The effect of the short message was largest for children under 18, with an estimated increase in the odds of adherence of 108% (95% CI [1.087, 3.960], p-value 0.027).

Poster #3
Cost Effectiveness of Insecticide Treated Wall Liner for Malaria Prevention in Rural Western Kenya
Presenter: Elizabeth Glaser
Co-authors: Donald Shepard, Aggrey Kihombo, George Olang, Nabie Bayoh, Meghna Desai, Frank Odhiambo, John Gimnig, Mary J Hamel, Angelique Kanyange Rwiyereka, Vincent Were, Peter Otieno, Kayla Laserson, and Simon Kariuki

Insecticide treated nets (ITNs) and other strategies have reduced the burden of malaria, yet it remains a major cause of morbidity and mortality across sub-Saharan Africa. We assessed the cost-effectiveness of a new malaria prevention tool, insecticide treated wall liner (ITWL). Efficacy is based on a 6-month cluster randomized trial by Gimnig et al of 1,592 children (6 months-11 years) in 12 rural villages in Kenya during 2010. Control villages had only ITNs; experimental villages had ITNs and ITWL. The cost-effectiveness analysis considered unit costs and quantities of each input, demographic records, and literature. Adjusted protective efficacy of ITWL: 38% (95% CI: 23%-50%), 1.1 infection averted per child year. ITWL's incremental cost: US$64.23 per person covered; ITWL's projected factory price (44.9%), shipping (5.1%), management (24.5%), installation materials (0.4%), local transportation (13.9%), and labor (11.1%). ITWL cost-effectiveness: Assuming cost per discounted life-year gained (DLYG) at 3 months is US$4,837, if ITWL endures 4 years (manufacturer projected life), cost per DLYG is US$482. Interventions with cost-effectiveness ratios below a country's GDP are considered highly cost-effective, therefore if ITWL remains effective for at least 2.2 years, at a cost per DLYG of US$795, (Kenya GDP per capita 2010), ITWL is considered highly cost-effective.

Poster #4
Evolution and Malaria: A Battle for Survival
Presenter: Megan L. Srinivas

The emergence of rapidly evolving malaria parasites has exacerbated the epidemic to greater heights than ever before. The factors instigating the development of drug resistance are still unknown. This investigation aimed to understand factors influencing the evolution of drug resistance in the malaria parasite. Interviews were conducted in August 2008 with 79 individuals, 38 from the Amazon Basin and 41 from the North Coast of Peru. Each individual orally completed two surveys in Spanish, the first regarding his/her malarial experiences during 2002-2007 (Period I) and the second regarding his/her malarial experiences during 2007-2008 (Period II). Treatment type, efficacy, compliance, distribution, and prevention measures were compared between locations and time periods. These factors were analyzed to determine correlations to rates of malaria infection and species prevalence. It was found that the rate of malaria has significantly increased between the time periods and that drug-resistant forms of *P. falciparum* and *P. vivax* are present. The data suggested that chloroquine and primaquine are no longer sufficiently effective treatments in these regions, but it was discovered that chloroquine may be an effective prophylaxis against *P. falciparum*. Additionally, it was found that treatment cycle compliance and use of prevention techniques (specifically bednets) decrease the proliferation of drug resistance.

Poster #5
Catching *Plasmodium falciparum* between a Rock and a Hard Place: Suppressing Anti-malarial Drug Resistance with Antagonistic Inhibitors
Presenter: Leila Ross
Co-authors: Amanda Lukens, Francisco Javier Gamo Benito, Maria Jose Lafuente-Monasterio, Onkar M.P. SIngh, Dyann F. Wirth, and Roger C. Wiegand

Managing drug resistance is a core problem in anti-malarial drug therapy. Combination therapy is a key tool for delaying the development and spread of resistant parasites. A novel combination strategy is 'targeting resistance.' A primary drug inhibits a wild-type target, and a partner drug inhibits the most likely drug-resistance mechanism for that target. The pyrimidine biosynthetic pathway was used as a test case. Selection of parasites resistant

to either alkylthiophene- or triazolopyrimidine- based Dihydroorotate Dehydrogenase (DHODH) inhibitors resulted in mutations in DHODH: E182D, F227I, or L531F. We screened a library of DHODH inhibitors, which yielded several compounds ten- to one-hundred-fold more potent against the mutant parasites. Drug resistance selections on the DHODH E182D mutant parasite resulted in a second mutation in codon 182, and the altered codon resulted in a reversion to the wild-type protein sequence. Dual selection with wild-type DHODH inhibitors and mutant inhibitors largely failed to produce drug-resistant parasites. 'Targeting resistance' traps malaria escape from the primary drug which results in increased sensitivity to the partner drug. For the pyrimidine biosynthetic pathway and perhaps other pathways, the fitness costs of becoming resistant to multiple inhibitors may provide a path for suppressing drug resistance.

Poster #6
Utilizing Direct Patient Samples for Antimalarial Resistance GWAS in *P. falciparum*
Presenter: Daria Van Tyne
Co-authors: Daniel Park, Clarissa Valim, Amanda Lukens, Rachel Daniels, Stephen Schaffner, Hsiao-Han Chang, Kevin Galinsky, Daouda Ndiaye, Souleymane Mboup, Roger Wiegand, Daniel Neafsey, Daniel Hart, Sarah Volkman, Pardis Sabeti, and Dyann Wirth

Plasmodium falciparum malaria's rapid adaptation to new drugs allows it to remain one of the most devastating infectious diseases of humans. Understanding the genetic basis of these adaptations is critical to successful intervention. Association studies are an established tool for discovering the genetic mechanisms contributing to variation in drug responses. However, recent malaria-based GWAS have either had limited sample sizes due to the laborious nature of parasite culture adaptation or limited phenotype heritability due to the use of clinical phenotypes when avoiding culture adaptation. Here, we present a GWAS based on direct patient samples, utilizing ex vivo drug phenotypes and whole genome sequence of *P. falciparum*-enriched DNA using a hybrid-selection technique. This approach avoids both culture adaptation and clinical phenotypes and simplifies the process of performing a well-powered GWAS. We adapted recent mixed-model GWAS tools, such as EMMA and GCTA, and selection tools, such as iHS and XP-EHH, to study the heritability of drug response phenotypes and identify known and

novel loci associated with drug resistance at genome-wide significance. This demonstrates a highly scalable type of GWAS for antimalarial response, one that does not require time-intensive culture adaptation processes yet still utilizes an ex vivo drug phenotype that is less influenced by host or environmental factors than clinical phenotypes.

Poster #7
Functional Characterization of a Novel Protein Required for *Plasmodium falciparum* Replication, MOP1
Presenter: Sabrina Absalo
Co-authors: Lauren Pepper, Matthias Marti, Manoj Duraisingh, Susan Lindquist, and Jeffrey D. Dvorin

The egress of mature *Plasmodium falciparum* parasites from host red blood cells is an essential yet incompletely understood process. Our studies on PfCDPK5, a calcium-dependent protein kinase, highlighted the key role of the calcium-mediated signal in *P. falciparum* egress. However, its molecular mechanism remains largely unknown. To discover novel protein candidates critical for the PfCDPK5-signaling pathway, we screened for proteins that interact with PfCDPK5 using a yeast two-hybrid assay. We used the catalytic domain from PkCDPK5, the *P. knowlesi* ortholog of PfCDPK5, as bait and a *P. knowlesi* cDNA library as prey. With this assay, we identified a conserved *Plasmodium* protein of unknown function, PKH_071430. We successfully fused a hemagglutinin epitope tag and destabilizing domain to the carboxy-terminus of the *P. falciparum* ortholog that we named MOP1 for Merozoite Organizing Protein-1. The timing of MOP1 expression during the intra-erythrocytic life cycle by immunoblot analysis showed a peak of expression in the schizont stage and a knockdown of 80% following the removal of the stabilizing ligand Shield1. Following knockdown of MOP1, the transgenic parasites have a 90% growth defect over two asexual life cycles. Ongoing studies are focused on elucidating the molecular function of MOP1 and its potential interaction with PfCDPK5.

Poster #8
Multiple Independent Evolutions of Chloroquine Drug Resistant Malaria in the Pacific, 1969 - 1987
Presenter: Abigail MacFadden
Co-authors: Alysa Pomer, Rita Spathis, Chim W. Chan, and J. Koji Lum

Plasmodium falciparum is the parasite associated with the most lethal form of

malaria. Chloroquine drug resistance in *P. falciparum* first appeared in the Western Pacific in 1974. Resistance is directly associated with a gene called pfcrt found in parasite DNA. In contrast, mitochondrial DNA (mtDNA) measures population change over time without connection to a particular trait; thus, mtDNA serves as a neutral marker. We are assessing the connection between the neutral marker (mtDNA) and drug resistance marker (pfcrt) within *P. falciparum* DNA. To do this, we are looking at populations from the highland of Papua New Guinea and nearby islands of the Western Pacific, representing the time period 1969 to 1987. Using approximately 600 DNA samples, we are assessing the correlation between specific loci on mtDNA and the pfcrt mutation associated with drug resistance.

Preliminary analysis comparing the data from mtDNA markers and pfcrt indicates low correlation between the neutral and the drug resistant markers. Low correlation indicates that chloroquine drug resistant *P. falciparum* evolved independently multiple times in this region, specifically within population of low exposure and low acquired immunity. Thus, we can expect drug resistance to develop not in the malaria endemic areas, but in the periphery.

Poster #9
Discovering A New Antimalarial Target: Prolyl tRNA Synthetase is the Target of Halofuginone
Presenter: Jonathan Herman
Co-authors: Lauren Pepper, Joseph F. Cortese, Kevin Galinsky, Tracey Keller, Malcolm Whitman, William Sullivan, Susan Lindquist, Ralph Mazitschek, and Dyann Wirth

Many current anti-malarial drugs work within the same biological pathways leading to shared resistance mechanism. We have taken the methodology of chemogenomics to identify potential antimalarials that target novel pathways. Understanding the anti-plasmodial mechanism of halofuginone (HFG), a febrifuginone analogue, informs our understanding of parasite biology and directs the future creation of novel therapies. To interrogate mechanism, we selected parasites that are resistant to halofuginone and then used whole genome sequencing to identify the causative mutation (SNPs) and developed high resolution melting (HRM) genotyping assays to follow up those most promising. We found two nonsynonomous mutations in the

active site of the cytoplasmic prolyl-tRNA synthetase (PfcPRS) in independent selections. Using a heterologous S. cerevisiae model, we have confirmed the sufficiency of PfcPRS to confer sensitivity to halofuginone. In addition, the two nonsynonous SNPs abrogate sensitivity to halofuginone. Amino acid deprivation of *P. falciparum* activates the amino acid starvation response (AASR) a highly conserved stress pathway that inhibits cell-wide translation. To determine the involvement of AASR, we then performed western blot analysis of the phosphorylation of eukaryotic initiation factor 2 Î± (eIF2Î±) in the presence or absence of excess proline. We have found that halofuginone and febrifugine block *P. falciparum* proline metabolism. Treatment of parasites with halofuginone and febrifugine also results in increased phosphorylation of a *P. falciparum* eIF2Î± analogue. Furthermore, proline supplementation in the media decreases sensitivity to halofuginone in a dose-dependent fashion. In a similar dose dependent manner, the phosphorylation of eIF2Î± is dependent on the level of exogenous proline in the presence of halofuginone. Overall, these results demonstrate halofuginone-induced proline starvation via an interaction with PfcPRS leads to translational inhibition. Thus we posit that the potential of amino acid supply and aminoacyl tRNA synthetases as a new promising and potential target for chemotherapeutic intervention.

Poster #10
Parasite calcineurin is a critical regulator of invasion of erythrocytes by *Plasmodium falciparum*
Presenter: Aditya S. Paul
Co-authors: Aziz L. Kosber, and Manoj T. Duraisingh

Proliferation of the *Plasmodium falciparum* within erythrocytes requires egress of the merozoite forms of the parasite from infected erythrocytes and their invasion into uninfected erythrocytes. The phosphatase calcineurin mediates critical signal transduction processes in other eukaryotes in response to increases in cytosolic calcium levels typically accompanying stressful stimuli. Considering the strong upregulation in transcription of the parasites ortholog of the calcineurin near the time of egress and invasion, we tested if calcineurin regulates these processes. We found that inducible knockdown of the regulatory subunit of calcineurin, CnB, reduces the bulk rate of proliferation by up to ~70%. This phenotype is explained completely by a defect in the invasion of erythrocyte, specifically in the ability of the merozoite to form functional links between itself and the uninfected

erythrocyte. We complemented knockdown of CnB with specific chemical inhibition of calcineurin-phosphatase activity, and found that in static culture conditions, the nearly complete inhibition of calcineurin only partially reduces re-invasion (~50-70%). By contrast, with vigorous shaking, inhibition of calcineurin reduces invasion by up to ~97%. We currently favor a model whereby calcineurin promotes robust invasion by the parasite through the development of strong links with the erythrocyte to resist shear forces arising from bloodflow.

Poster #11
Chemogenomic Approach to Identify and Validate the Target of a Diversity-Oriented Synthesis Probe
Presenter: Amanda K. Lukens
Co-authors: Richard W. Heidebrecht, Jr., Carol Mulrooney, Jennifer A. Beaudoin, Eamon Comer, Kevin Galinsky, Justin Dick, Michael Foley, Benito Munoz, Roger Wiegand, and Dyann F. Wirth

The availability of complete genome sequences of different *Plasmodium* species and comparative bioinformatics have divulged several metabolic pathways for antimalarial drug discovery and genome-wide methods for target identification and understanding mechanisms of resistance. We have adopted a chemogenomics approach for identifying highly potent bioactives that can be powerful probes of parasite-specific biological processes. Here we present studies of a novel probe from the Diversity-Oriented Synthesis Informer Set (DOS-IS) library with sub-nanomolar activity against the parasite in phenotypic whole cell assays. The DOS-IS is a representative collection of the >100k DOS compounds that have been synthesized at the Broad Institute. Compounds that are derived for DOS pathways aim to cover chemical space extending beyond the common confinements set by "drug-like" parameters, which is characteristic for traditional MedChem libraries and limits the diversity of represented compounds. We successfully applied an intermittent selection protocol to isolate Dd2 parasites that were 100-fold less sensitive to lead compounds in order to investigate the mode of action and molecular target of the DOS probe. To identify the genetic changes that confer resistance, we employed a whole-genome sequencing approach comparing the resistant mutants to the Dd2 parental line. These studies have led to the identification of target mutations in the Qi site of cytochrome b. The DOS mutants remain fully sensitive to atovaquone, suggesting that cross-resistance to both Qi and Qo site inhibitors might be

challenging for the parasite and represent a promising avenue for the development of combination therapies. Further studies to determine the effects of targeting multiple active sites in a single enzyme and the ability of the parasite to develop dual resistance are underway.

Poster #12
Effect of Indoor Residual spraying for Malaria Control
Presenter: Nkechi Onwuka
Co-authors: John Boney, Nneka Obi, Biodun Salako, and Alexi Matousek

Malaria is a preventable disease that is transmitted by the female anopheles mosquito. Indoor spraying of DDT has been found to be a particularly effective vector control that can stop the spread of this disease. However DDT is listed by the WHO as moderately hazardous and can have potentially harmful effects, especially among pregnant women and newborns. Although DDT is an effective in controlling malaria, its use should not be discontinued. However the human and environmental impacts can not be ignored. It should be used sparingly, and alternative means of control should be encouraged.An estimated 660,000 malaria deaths occurred in 2010 and an estimated 80% of these deaths occurred in just 14 countries, mainly Africa. DDT (dichlorodiphenyltrichloroethane) is an odorless insecticide which is effective in killing malaria vector but with potential toxic effects. There has been ongoing controversy on the use of DDT for vector control . Presently, three schools of thought exist; those who are against the use and production of DDT primarily because of environmental and human health concerns; those who accept the need for a strong control method to curtail the spread of malaria while recognizing the inherent dangers, and those who are pro-DDT, who argue that proper and safe-guarded use of the chemical is invaluable in saving lives .The aim of our project is to further explore these issues.

Poster #13
Diversity Driven Immune Evasion: A New Paradigm for Malaria Vaccine Development
Presenter: Amy Kristine Bei
Co-authors: Ababacar Diouf, Rachel F. Daniels, Samuel E. Moretz, Kazutoyo Miura, Sarah Volkman, Ambroise D. Ahouidi, Daouda Ndiaye, Tandakha Dieye, Souleymane Mboup, Carole A. Long, and Dyann F. Wirth

The proposed research will interrogate the impact of diversity on the develop

ment of protective immune responses over time and with multiple exposures. I hypothesize that polymorphic alleles of blood stage antigens play a major role in immune evasion, potentially compromising the development of natural or vaccine induced protective immunity. To address this hypothesis, I will identify novel targets of invasion inhibitory immune responses by utilizing genomic approaches, measure the acquisition of humoral immune responses to these targets over time in a West African longitudinal cohort, and assess the effector function of the naturally acquired IgG in growth inhibition assays (GIA) in the face of such diversity. Using a translational approach, I will monitor both the diversity of the parasite infections and the development of immunity in real-time in both the individual and in the population, creating a history of the progression of infection. The goal of my study is to precisely determine the molecular and immunologic role of naturally arising polymorphisms in important blood stage vaccine candidate antigens, and the impact these polymorphisms have on the development of protective immunity, so that a diversity-transcendent vaccine can be developed.

Poster #14

Fatty Acid Metabolism in *Plasmodium falciparum*: Characterization of the Acyl-CoA Synthetase Gene Family

Presenter: Allison Demas
Co-authors: Pamela Magistrado, Ulf Ribacke, Jean-Francois Blain, Sarah Volkman, Roger Wiegand, and Dyann Wirth

Malaria poses a significant public health threat, and better understanding of the causative agent, *Plasmodium*, will help identify new targets for interventions. Recent work in the Wirth lab has identified an expansion of the Acyl-CoA Synthetase (ACS) gene family in *Plasmodium falciparum*, the most deadly of the five human-infecting malaria parasites. Furthermore, members of this gene family are under recent positive selection in the parasite, indicating that modifications to these genes are an important adaptive response to selective pressure exerted by the human host and/or mosquito vector. The conserved members of this gene family are predicted to activate exogenous fatty acids and play an important role in fatty acid scavenging in the parasite, while function of the expanded paralogs remains unknown. The overall goal of this study is to characterize the ACS gene family in *P. falciparum* using genetic and biochemical approaches, and to understand how these enzymes mediate fatty acid metabolism in the cell. New knowledge of the regulatory role of these enzymes will be used to

determine the importance of fatty acid metabolism in post-translational protein acylation and the role of fatty acid metabolism in key parasite virulence phenotypes. The characterization of the ACS gene family will also reveal the potential of ACS inhibitors or other novel intervention strategies to aid in malaria eradication efforts.

Poster #15
Targeting reproduction in *Anopheles gambiae* for vector control
Presenter: Flaminia Catteruccia
Co-authors: Francesco Baldini, Evdoxia Kakani, Perinne Marcenac, Sara N. Mitchell, William R. Shaw, Andrea Smidler, Adam South, and Flaminia Catteruccia

Among the biological features that render *An. gambiae* the most efficient vectors for human malaria is their high reproductive rate, ensured by a single and potentially vulnerable copulation event. Targeting reproductive biology is therefore a promising strategy for future vector control. Our group studies reproduction from pre-mating behavior through to egg-laying. Pre-mating chemical cues, such as cuticular hydrocarbons, may play a role in mate recognition and choice, with our analysis suggesting differences between the chemical profiles of mated and virgin females. Post-mating, sperm is stored and we have identified a network of proteins that ensure sperm viability for a female's lifetime. Seminal secretions are also metabolized, coinciding with major behavioral and physiological changes in the female. Our temporal transcriptomics implicates a number of metabolic pathways triggered by mating. Steroid hormones transferred from the male may also have a role in inducing this transcriptional response, and we have identified a link between steroid hormones transfer and increased egg development. Currently we are delineating the hormone synthesis pathway in male accessory glands. Through embryo injection we have also targeted male fertility, creating spermless males, albeit inefficiently; transgenic technologies offer opportunities to produce larger numbers of infertile males. This multifaceted approach to studying reproductive success in *Anopheles* mosquitoes will help to reduce the burden of malaria in the future via novel and targeted vector control strategies.

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