The Science of Malaria Eradication

Scientific Organizers:
Pedro L. Alonso
Chetan E. Chitnis
Lee Hall

Organized in collaboration with:
MESA – Malaria Eradication Scientific Alliance

Part of the Keystone Symposia Global Health Series supported by the Bill & Melinda Gates Foundation

February 2–7, 2014
Fiesta Americana
Mérida, Yucatán, México

Visit **keystonesymposia.org/14F1** to view the meeting program online.

Twitter hashtag for this meeting: **#KSmalaria**

Unless otherwise noted, the information in this book is current as of **January 14, 2014**. If you registered after this date, your name is included in an online list accessed from attendees' Keystone Symposia accounts.

Please be advised that no video equipment, cameras, audio equipment or any other type of recording device will be allowed in the meeting room or poster sessions. Full meeting policies are on page 81.

KEYSTONE SYMPOSIA™
on Molecular and Cellular Biology
Accelerating Life Science Discovery

Keystone Symposia is a 501(c)(3) nonprofit organization directed and supported by the scientific community.

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Welcome

Dear Keystone Symposia Meeting Attendee,

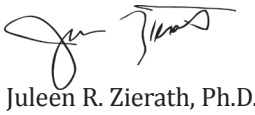
Thank you for joining us as we convene the Keystone Symposia conference on *The Science of Malaria Eradication.* We're sure you will enjoy the days you spend here in Mérida absorbing the latest and most exciting research in the company of the like-minded – both those you may know very well and those you will meet for the first time.

This is one of 58 conferences Keystone Symposia has scheduled for the 2013-2014 meeting season. Not included in that number is Keystone Symposia's first-ever virtual event – on "HIV/AIDS: Strategies for an Endgame" – in December 2013, a milestone for the organization. While more of these online events will bring science to a broader global audience, nothing can quite replicate the value of a face-to-face meeting like this one, and we hope you will make the most of it.

Along these lines, please take advantage of the newly enhanced and redesigned Keystone Symposia mobile app to connect with colleagues and make new connections. New this year, you will be able to read poster and speaker abstracts on the app, as well as send messages directly to specific participants. You can also take notes on the sessions and abstracts, "favorite" sessions you don't want to miss, and learn more about the local area. If you haven't already, be sure to upload your photo and profile to the app so that other attendees can more easily recognize you.

Please complete the survey when you receive the link just after the conference concludes. Your input is extremely valuable to assist us in continuously enhancing the scientific content and format of our meetings. We sincerely hope you enjoy this Keystone Symposia conference and return for many more.

Best wishes,



Juleen R. Zierath, Ph.D.
Professor of Molecular Medicine and Surgery, Karolinska Institutet
Chair of the Board, Keystone Symposia

Dear Meeting Participants,

Thank you for choosing to attend. Our highest priority is to provide the most stimulating meeting programs and environment for sharing data, generating ideas, starting collaborations, and maybe launching life-long collegial relationships. In doing these things, we also strive to add value to the training of the next generation of scientists. In spite of the continuing worldwide economic troubles, which may affect some scientists' ability to attend, we are gratified that many do continue to engage in this vital face-to-face debate of the scientific challenges facing the world.

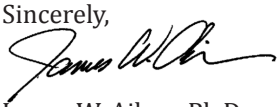
Our meeting participation is also becoming more global in reach. In 2013, participants came from 92 countries, including 19 African, 14 South or Latin American, and 25 Asian or Asia Pacific countries. Eleven years ago, the year before I joined Keystone Symposia, participants came from 64 countries. During those years, the number of participants from the USA increased by about 5%, while non-USA participation increased by 80%. In 2012, 43% of all attendees came from outside the USA and in 2013 non-USA attendance was closer to 46%. These simple numbers just hint at the intricacy of the present era of science globalization. We will continue to expand our global programs; in 2013 we held our first two conferences in South America (Rio de Janeiro and Ouro Preto, Brazil).

Dr. David Woodland has completed his second year as Chief Scientific Officer. Woody has moved quickly to ensure the continuing high quality of the conferences. Quality in programming is highly dependent on feedback from attendees, so please be generous with comments, either good or bad. The CSO, Scientific Advisory Board, and Scientific Organizers integrate feedback to generate a portfolio of annual meetings that we hope will energize the scientific community.

We greatly value the financial support of corporations, foundations, governments and individuals. Keystone Symposia does not have an endowment, so this continuing diverse base of support on an annual basis is vital. Through generous donations, we are able to defer some of the expenses of many deserving early-career scientists and also offset many of the costs we would otherwise have to pass on to attendees.

I hope that your experience at this conference is valuable and memorable and that you will spread the word to others who might benefit from what you learn.

Sincerely,



James W. Aiken, Ph.D.
President and Chief Executive Officer, Keystone Symposia

Meeting Format

The conference program has been designed around Keystone Symposia's mission: to accelerate life science discovery by providing a forum to present top-quality science, foster new collaborations and help prepare the next generation of life scientists.

Poster Abstract Sessions

Poster sessions play host to some of the most dynamic interactions that take place at our conferences and are not to be missed. Abstracts have been numbered by session: abstracts presented during Poster Session 1 are numbered in the 1000s, Poster Session 2 in the 2000s, etc. Scientific organizers have selected short talks for plenary sessions and sometimes workshops from submitted poster abstracts. These oral poster abstract presentations may or may not fall on the same day as the presenter's poster session. If you are a presenter, please check the index to find your abstract number; your abstract will appear in the corresponding poster abstract section of the book. (*Note: Plenary session speakers are numbered in the hundreds: day one speakers are the 100s, day two speakers are the 200s, etc. Speaker abstracts are located before the poster abstracts in this book.*) To make the most of the formal poster sessions, we encourage you to preview posters during the time slots marked for informal poster abstract viewing.

Enjoying the Location

Please be aware of your environment as you plan your free-time activities. If you are at a high-altitude meeting, we urge you to rest on your first day and drink plenty of water. Check the bulletin board for group outings and other activities and discounts that Keystone Symposia and venue staff may have arranged.

Meals

The meals included in your registration vary by site. Check the program for meals marked "On Your Own" and plan accordingly. Meals listed with a time and place are provided as part of your registration. Some attendees choose to make a meal out of "Lite Bites."

Abstract Books and Online Resources

With the anticipation that digital delivery of conference materials will eventually supplant print, Keystone Symposia staff is working to provide you with multi-platform access to all conference information. If you find you prefer the digital formats, feel free to return this printed abstract book to the registration desk.

In further efforts to cut back on waste, we have also replaced the notepads provided in the past with extra note-taking pages in the back of this book. Our staff has also been working hard to consolidate the abstract book to reduce the total number of pages. We anticipate this will save roughly 400,000 sheets of paper this meeting season!

Digital Abstract Book from Your Account

You may download a PDF of this book from your Account on our secure website beginning seven days before the meeting and for up to 30 days after the meeting. Your Account page also contains other useful content such as printable invoices and invitation letters, your profile with mail/email preferences, and much more. If you have questions about accessing your Account, don't hesitate to ask one of our on-site staff at the registration desk.

Keystone Symposia Mobile App

Our redesigned and enhanced mobile app can be used on phones, tablets and laptops. If you have not already done so, please download the app by scanning the QR code or visiting **http://ks.eventmobi.com**. Creating an EventMobi account within the app will also allow you to personalize your participant profile by uploading a photo and adding biography information, as well as take notes and save a customized personal agenda for the week.

Social Media Networks

Join us on the following social media platforms to stay informed, interact with other participants, and post your own photos, videos and text about your conference experience:

Facebook – facebook.com/KeystoneSymposia
LinkedIn – linkd.in/0x70RJ
Twitter – twitter.com/KeystoneSymp (Twitter hashtag for this meeting: **#KSmalaria**)
YouTube – youtube.com/KeystoneSymposia

Download the meeting app!

We Welcome Your Feedback

Please be sure to give us your feedback by completing the survey that will be emailed to you at the conclusion of the meeting. Your input is very valuable to us as we plan future meetings.

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Twitter hashtag for this meeting: **#KSmalaria**

This Keystone Symposia meeting provides a comprehensive look at the cutting edge of the science of malaria eradication as it advances. For the first time since the paradigm shift from malaria control to the interruption of transmission, research, development, innovation and lessons learned will all be captured. The central goal of the meeting is to provide a unique and needed space for malaria eradication scientists to share new information and advance the scientific debate. As the field develops and results emerge, so too will the questions which need to be answered. The meeting facilities cross-fertilization between disciplines, which all have a role in advancing the science of malaria eradication.

In an environment conducive to creative thinking, an anticipated outcome of the meeting is the generation of ideas and the next priorities for the scientific community to tackle. Other disease eradication efforts, past and present, have taught us the critical role of research and development. The publication of the malaria eradication research agenda (malERA) in 2011 laid the foundation for this R&D effort. This meeting serves as a significant milestone in the continual development of this research agenda. By showcasing new evidence, emerging data and new challenges, the meeting aims to catalyze ideas across multiple disciplines as well as new research activities in the field.

Steering Committee of MESA:

***Pedro Alonso**, Barcelona Institute for Global Health (ISGlobal)*
***Fred Binka**, School of Public Health, University of Ghana*
***Graham Brown**, Nossal Institute for Global Health, University of Melbourne*
***Chetan Chitnis**, International Centre for Genetic Engineering and Biotechnology*
***Jessica Milman**, Bill & Melinda Gates Foundation*
***Rob Newman**, Global Malaria Programme, World Health Organization*
***Jetsumon Prachumsri**, Mahidol Vivax Research Center, University of Mahidol*
***Regina Rabinovich**, Harvard School of Public Health*
***David Schellenberg**, London School of Hygiene and Tropical Medicine*
***Marcel Tanner**, Swiss Tropical and Public Health Institute*

SUNDAY, FEBRUARY 2

16:00–20:00	Yucatán Foyer	Arrival and Registration
18:00–20:00	CIS Terrace	Welcome Mixer

MONDAY, FEBRUARY 3

08:00–09:00	Salón Yucatán 2-4	Breakfast
09:00–9:45	**Salón Yucatán 1**	**Opening Remarks** **Pedro L. Alonso**, Barcelona Institute for Global Health (ISGlobal), Spain **Chetan E. Chitnis**, International Centre for Genetic Engineering and Biotechnology, India **Lee Hall**, NIAID, National Institutes of Health, USA
9:45–11:30	**Salón Yucatán 1**	**Different Strategies for Disease Eradication** ***Lee Hall**, NIAID, National Institutes of Health, USA **Dyann F. Wirth**, Harvard School of Public Health, USA (0101) *The Parasite Population in Control, Elimination and Eradication*
	Foyer	Coffee Break
		Frank O. Richards, Carter Center, USA (0102) *Pragmatic Approaches:* *Where to Start with Elimination – Different Strategic Lessons that Can Be Learned from NTD Programs* **Alyssa E. Barry**, Walter and Eliza Hall Institute, Australia (1005) *Short Talk: Contrasting Population Biology of Plasmodium falciparum and Plasmodium vivax in Papua New Guinea: Implications for Malaria Control* **Euzebiusz Jamrozi**, Monash University, Australia (2014) *Short Talk: Bioethics of Malaria Elimination*
11:30–13:00	Salón Yucatán 2-4	Poster Setup
13:00–22:00	Salón Yucatán 2-4	Poster Viewing
		On Own for Lunch and Recreation
16:00–16:30	Foyer	Coffee Available
16:30–17:00	Foyer	Group Photo

MONDAY, FEBRUARY 3 (continued)

17:00–19:00 **Salón Yucatán 1** **Reducing Vectorial Capacity**

***Marcel Tanner**, Swiss Tropical and Public Health Institute, Switzerland
Jetsumon S. Prachumsri, Mahidol University, Thailand (0103)
Inhibition of Malaria Parasite Development in Different Vectors
Anthony A. James, University of California, Irvine, USA (0104)
Genetic Approaches for Controlling Transmission of Mosquito-Borne Diseases: Focus on Malaria
Marcelo Jacobs-Lorena, Johns Hopkins Bloomberg School of Public Health, USA (0105)
Fighting Malaria with Engineered Symbiotic Bacteria from Vector Mosquitoes
Austin Burt, Imperial College London, UK
Short Talk: Self-Sustaining Strategies for Reducing Malaria Transmission Using Homing Endonuclease Genes (HEGs)

19:00–20:00 Salón Yucatán 2-4 Social Hour with Lite Bites

19:30–22:00 **Salón Yucatán 2-4** **Poster Session 1**

Poster sessions provide exciting opportunities for engagement between all levels of investigators. Pages 43–50 contain the abstracts featured at this evening's poster session (abstract numbers 1001–1032).

TUESDAY, FEBRUARY 4

08:00–09:00 Salón Yucatán 2-4 Breakfast

09:00–12:15 **Salón Yucatán 1** **Drugs and Drug-Based Strategies for Eradication**

***Pedro L. Alonso**, Barcelona Institute for Global Health (ISGlobal), Spain
Elizabeth A. Winzeler, University of California, San Diego, School of Medicine, USA (0201)
Using Phenotypic Screening and Forward Genetics to Find Targets for a Malaria Elimination Agenda
Timothy N.C. Wells, Medicines for Malaria Venture, Switzerland (0202)
Discovery and Development of New Medicines for Eradication: Integrating with Translational Medicine

Foyer Coffee Break

Marcus V. G. Lacerda, Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Brazil (0203)
Drugs for Plasmodium vivax in the Context of Eradication
Frédéric Ariey, Institut Pasteur, France (0204)
A Molecular Marker of Artemisinin-Resistant Plasmodium falciparum Malaria
Chanaki Amaratunga, NIAID, National Institutes of Health, USA (1032)
Short Talk: In vitro Correlates of Artemisinin-Resistant P. falciparum Parasite Subpopulations in Western Cambodia
Ingrid Chen, University of California, San Francisco, USA (1012)
Short Talk: Low-Dose Primaquine to Reduce the Transmission of Plasmodium falciparum Malaria: A Roadmap Update

*Session Chair; ( ) = abstract number

TUESDAY, FEBRUARY 4 (continued)

12:15–13:00	Salón Yucatán 2-4	Poster Setup
13:00–22:00	Salón Yucatán 2-4	Poster Viewing
		On Own for Lunch and Recreation
14:30–16:30	**Salón Yucatán 1**	**Workshop**
16:30–17:00	Foyer	Coffee Available
17:00–19:00	**Salón Yucatán 1**	**Health Systems Research**

***N. Regina Rabinovich**, Harvard School of Public Health, USA

David L. Smith, Johns Hopkins Bloomberg School of Public Health, USA (0205)
How Stable Is Elimination?

Thomas A. Smith, Swiss Tropical and Public Health Institute, Switzerland (0206)
Dynamics of Malaria Infection: Implications for Elimination

Felipe De Jesus Colón González, Abdus Salam International Centre for Theoretical Physics, Italy (1018)
Short Talk: A Regional-Scale, High-Resolution Dynamical Model for Malaria

Sian E. Clarke, London School of Hygiene and Tropical Medicine, UK (1016)
Short Talk: Intermittent Parasite Clearance in Schools in Mali: Impact on Malaria, Anaemia and Cognition

19:00–20:00	Salón Yucatán 2-4	Social Hour with Lite Bites
19:30–22:00	**Salón Yucatán 2-4**	**Poster Session 2**

Poster sessions provide exciting opportunities for engagement between all levels of investigators. Pages 51–59 contain the abstracts featured at this evening's poster session (abstract numbers 2001–2035).

WEDNESDAY, FEBRUARY 5

08:00–09:00	Salón Yucatán 2-4	Breakfast
09:00–12:15	**Salón Yucatán 1**	**Vaccines for Eradication**
		***Chetan E. Chitnis**, International Centre for Genetic Engineering and Biotechnology, India
		Stephen L. Hoffman, Sanaria, USA (0301) *Plans for Development of the PfSPZ Vaccine for Use in Malaria Elimination*
		Patrick E. Duffy, NIAID, National Institutes of Health, USA (0302) *Transmission-Blocking Vaccine and Assay Development*
	Foyer	Coffee Break
		David Kaslow, PATH Malaria Vaccine Initiative, USA (0303) *Talk Title to be Determined*
		Carlota Dobaño, Barcelona Centre for International Health Research (CRESIB), Spain (0304) *Approaches and Challenges in Profiling Immune Responses to the RTS/s Vaccine Candidate*
		Veronique Beiss, Fraunhofer IME, Germany (1007) *Short Talk: Evaluating PfGap50 as a Component of Novel Recombinant Subunit Vaccines Derived from Plants*
		Daria Nikolaeva, National Institutes of Health/University of Oxford, UK (3003) *Short Talk: Functional Characterization of Novel Plasmodium falciparum Transmission-Blocking Vaccine Targets*
12:15–13:00	Salón Yucatán 2-4	Poster Setup
13:00–22:00	Salón Yucatán 2-4	Poster Viewing
		On Own for Lunch and Recreation
16:30–17:00	Foyer	Coffee Available
17:00–19:15	**Salón Yucatán 1**	**Measurement of Transmission**
		***Dyann F. Wirth**, Harvard School of Public Health, USA
		Richard W. Steketee, PATH – MACEPA, Malaria Control Program, USA (0305) *Measuring Malaria Transmission in a Program Context in Sub-Saharan Africa*
		Ivo Mueller, Walter and Eliza Hall Institute, Australia (0306) *Determining Transmission of P. vivax and P. falciparum in Three Non-African Settings*
		Sarah K. Volkman, Harvard School of Public Health, USA (0307) *Using Genomics to Understand Malaria Transmission toward Elimination and Eradication*
		Ana Maria Fonseca, Barcelona Centre for International Health Research (CRESIB), Spain (2002) *Short Talk: Dissecting VAR2CSA to Develop a Pregnancy-Specific Serologic Assay to Quantify Malaria Transmission Intensity*
		David M. Newman, University of Exeter, UK (3002) *Short Talk: The Use of Haemozoin as a Diagnostic Biomarker at Different Stages in the Lifecycle of Plasmodium falciparum*

WEDNESDAY, FEBRUARY 5 (continued)

19:15–20:15	Salón Yucatán 2-4	Social Hour with Lite Bites
19:30–22:00	**Salón Yucatán 2-4**	**Poster Session 3** *Poster sessions provide exciting opportunities for engagement between all levels of investigators. Pages 60–69 contain the abstracts featured at this evening's poster session (abstract numbers 3001–3040).*

THURSDAY, FEBRUARY 6

08:00–09:00	Salón Yucatán 2-4	Breakfast
09:00–12:00	**Salón Yucatán 1**	**Parasite-Host Interactions** ***Jetsumon S. Prachumsri**, Mahidol University, Thailand **Robert E. Sinden**, Imperial College London, UK (0401) *Identifying Biological Challenges: Trojan Horses of the Parasite Life Cycle* **Hernando del Portillo Obando**, Barcelona Centre for International Health Research (CRESIB), Spain (0402) *Reticulocyte-Derived Exosomes: An Intercellular Communicator in Plasmodium vivax Malaria?*
	Foyer	Coffee Break **Oliver Billker**, Wellcome Trust Sanger Institute, UK (0403) *Signaling Pathways for Development of Transmission Stages* **Gabriele Pradel**, RWTH Aachen University, Germany (3011) *Short Talk: The Role of the Perforin-Like Protein PPLP2 during Egress of Malaria Gametocytes from the Red Blood Cell* **Abhinav Sinha**, R D Gardi Medical College, India (3020) *Short Talk: Identification of a Gene that Is Essential for Commitment to Gametocytogenesis in Malaria Parasites*
		On Own for Lunch and Recreation
16:00–16:30	Foyer	Coffee Available

THURSDAY, FEBRUARY 6 (continued)

16:30–18:15 **Salón Yucatán 1** **Surveillance for Elimination**

***Ivo Mueller**, Walter and Eliza Hall Institute, Australia
Richard W. Steketee, PATH – MACEPA, Malaria Control Program, USA
Talk Title to be Determined
Justin M. Cohen, Clinton Health Access Initiative (CHAI), USA (0404)
Defining Operational Surveillance Strategies for Malaria Elimination Programs
Marcel Tanner, Swiss Tropical and Public Health Institute, Switzerland (0405)
Surveillance and Response: The Challenges for Science and Elimination Actions

17:45–18:45 **Salón Yucatán 1** **Keynote Address**

Peter C. Agre, Johns Hopkins Malaria Research Institute, USA (0406)
Opening Doors Worldwide through Medical Science

18:45–19:00 **Salón Yucatán 1** **Concluding Remarks**

Pedro L. Alonso, Barcelona Institute for Global Health (ISGlobal), Spain
Chetan E. Chitnis, International Centre for Genetic Engineering and Biotechnology, India
Lee Hall, NIAID, National Institutes of Health, USA

19:00–20:00 Salón Yucatán 2-4 Social Hour with Lite Bites

20:00–23:00 Salón Yucatán 2-4 Entertainment

FRIDAY, FEBRUARY 7 DEPARTURE

*Session Chair; ( ) = abstract number

Thank you...

...to all our donors supporting this meeting. Their generosity and dedication to the mission of collaborative science distinguish them as valuable members of the Keystone Symposia community.

This meeting is organized in collaboration with:
MESA – Malaria Eradication Scientific Alliance

The meeting is part of the Keystone Symposia Global Health Series, supported by the Bill & Melinda Gates Foundation.

Additional support for this meeting provided by:

National Institute of Allergy and Infectious Diseases,*
Grant No. 1R13AI110077-01

In-kind marketing/advertising support provided by:

Malaria Nexus

**The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.*

Scholarship and Travel Award Recognition

Congratulations

The following participants were awarded financial aid to attend this meeting. Be sure to stop by their poster sessions to see the abstracts that earned their merit-based support. Poster numbers are listed in parentheses, with the first digit indicating the corresponding poster session. Visit ***keystonesymposia.org/financialaid*** *for more information on Keystone Symposia's scholarship and travel award opportunities.*

Early-Career Investigator Travel Award Recipient

Made possible by National Institute of General Medical Sciences (NIGMS) Ancillary Training Program funding

Maria Belen Cassera, Virginia Polytechnic Institute and State University, USA (1011)

Keystone Symposia Future of Science Fund* Scholarship Recipients

Chanaki Amaratunga, NIAID, National Institutes of Health, USA (1032)

Sara E. Canavati de la Torre, Malaria Consortium, Cambodia (1003)

Felipe De Jesus Colón González, Abdus Salam International Centre for Theoretical Physics, Italy (1018)

Ana Maria Fonseca, Barcelona Centre for International Health Research (CRESIB), Spain (2002)

Leanne J. Robinson, PNG Institute of Medical Research, Papua New Guinea (3015)

Abhinav Sinha, R D Gardi Medical College, India (3020)

MESA – Malaria Eradication Scientific Alliance Scholarship Recipients

Nicanor T. Obaldia, Harvard School of Public Health, USA (3005)

Min Wang, Beijing Technology and Business University, China

National Institute of Allergy and Infectious Diseases (NIAID) Scholarship Recipients

Josselin Carolina Corzo-Gómez, Instituto Nacional de Salud Pública, Mexico (1020)

Alison Isaacs, Institut Pasteur, France (2013)

Dennis Massue, National Institute for Medical Research, Tanzania (2027)

*To learn more about the Keystone Symposia Future of Science Fund, see page 26 or visit **keystonesymposia.org/FSF**; ( ) = abstract number

Keystone Symposia Global Health Travel Award Recipients

Made possible by funding from the Bill & Melinda Gates Foundation

George Olusegun Ademowo, Institute for Advanced Medical Research and Training, Nigeria

Vincent Amarh, University of Edinburgh, UK

Marcele Fontenelle Bastos, Universidade Estadual de Campinas, Brazil (1001)

Lilian L. Bueno, Universidade Federal de Minas Gerais, Brazil (1010)

Mahamadou Diakite, Malaria Research and Training Center, Mali (1025)

Nancy Odurowah Duah, Noguchi Memorial Institute for Medical Research, Ghana

Alex Eapen, Indian Council of Medical Research, India (1028)

Esraa Mohammed Osman Ahmed Ismail, University of Khartoum, Sudan

Shaifali Jain, International Centre for Genetic Engineering and Biotechnology, India

Aditya Nath Jha, Centre for Cellular and Molecular Biology, India (2008)

Francis T. Kimani, Kenya Medical Research Institute, KEMRI, Kenya (2018)

Ayokulehin Muse Kosoko, University of Ibadan, Nigeria

Judith Nekesa Mangeni, Moi University, Kenya (2026)

Nancy Stephen Matowo, Ifakara Health Institute, Tanzania (2028)

Viswanathan Arun Nagaraj, Indian Institute of Science, India (3001)

Isabel Cristina Naranjo Prado, Unicamp, Brazil (3014)

Dickson Shey Nsagha, University of Buea, Cameroon (3004)

Titilope Modupe Okuboyejo, Covenant University, Nigeria (3006)

Adebola Emmanuel Orimadegun, College of Medicine, University of Ibadan, Nigeria

Segun Isaac Oyedeji, Bells University of Technology, Nigeria

Alok Kumar Pandey, International Centre for Genetic Engineering and Biotechnology Delhi, India

Exequiel O. Porta, Rosario Chemistry Institute, Argentinean National Research Council, Argentina

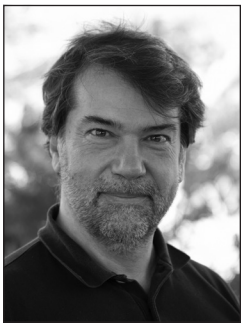
Tajali Sahar, International Centre for Genetic Engineering and Biotechnology, India

Abayomi Olusola Sijuade, Ekiti State University, Nigeria

Judith Koryo Stephens, University of Ghana, Ghana

Surangi Gayanitha Yasawardene, University of Sri Jayewardenepura, Sri Lanka

We also thank the Bill & Melinda Gates Foundation for funding a number of registrations for investigators from Latin America who would not otherwise have been able to participate in the conference.



Pedro L. Alonso, M.D., Ph.D. currently Director of ISGlobal, Head of the International Health and Tropical Medicine Unit of the Hospital Clínic of Barcelona, Professor at the University of Barcelona and President of the Governing Board of the Manhiça Foundation/Manhiça Health Research Centre, CISM (Mozambique).

Some of Professor Alonso's most relevant work has been carried out in the field of malaria and has led to the development and testing of new tools for preventing and treating this disease. He conducted the first trials to show the impact of insecticide-treated nets in the reduction of all-cause mortality (*Lancet* 1991) as well as phase 2b trials of the first malaria vaccine candidate (RTS,S) in Africa (*Lancet* 1994) and the first proof-of-concept trials of RTS,S in African children and infants (*Lancet* 2004 and 2007). He is the lead author on papers showing the safety and efficacy of iron supplementation in young infants in malaria-endemic areas (*Lancet* 1997) and demonstrated the first proof of concept of intermittent preventive treatment as a malaria control tool in infants (*Lancet* 2001). He has published over 300 papers in peer-reviewed journals.

Professor Alonso spearheaded the creation of the Manhiça Health Research Centre in Mozambique, now one of the leading research infrastructures in Africa. Currently, he chairs the Steering Committee of the *Global Technical Strategy for Malaria Control and Elimination 2016-2025* led by WHO, serves as a board member of the Medicines for Malaria Venture, and is a member of the *WHO Malaria Policy Advisory Committee.* Professor Alonso chaired the *Malaria Eradication Research Agenda (MalERA) Steering Committee* and today chairs the *Malaria Eradication Scientific Alliance (MESA) Steering Committee,* an alliance that addresses the knowledge gaps by catalyzing research, examining evidence and monitoring progress.

His current and future research focuses in malaria include: (i) design and testing of innovative tools and strategies for malaria elimination in sub-Saharan Africa, Central America and Papua New Guinea; (ii) strengthening research in P.vivax from *in vitro* cell culture, to epidemiology and transmission; (iii) factors affecting acquisition of immunity and identification of biomarkers associated with induced immunity; (iv) studies in controlled human malaria infection by sporozoite injection; and (v) effectiveness and impact of the malaria vaccine RTS,S.

Chetan E. Chitnis, Ph.D. is Principal Investigator at the International Centre for Genetic Engineering and Biotechnology in India working on malaria vaccine and drug development research. In particular, he focuses on receptor-ligand interactions involved in erythrocyte invasion, receptor ligand interactions involved in cytoadherence, and malaria vaccine development.

Prior to his current position, he was a Fogarty International Fellow at the National Institutes of Health in Bethesda, Maryland from 1991 to 1996. Dr. Chitnis received his undergraduate degree in physics from the Indian Institute of Technology, a Master's degree in physics from Rice University and a Ph.D. in biophysics from the University of California, Berkeley. A Fellow of the Indian Academy of Sciences, he has received a wide range of awards including the Infosys Prize in Life Sciences in 2011 and the MOT Iyengar Award for Research on Malaria in 2000.

Lee Hall, M.D., Ph.D. is Chief of the Parasitology and International Programs Branch (PIPB) in the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. In 2005, Dr. Hall was promoted to Chief of PIPB where he oversees multiple programs involving grants and contracts that support basic, translational and clinical research and development in parasitology and vectors responsible for transmission of parasites. In 1991, after having completed an infectious diseases fellowship at NIAID and Yale University, Dr. Hall returned as a Medical Officer and Host Immunity Program Officer in PIPB. In the ensuing years he developed a new program focused on vaccine research and development for parasitic diseases, and in 2000, he was promoted to Chief of the Malaria Vaccine Development Section. In that capacity he provided oversight and direction for a program of research grants, contracts and collaborative agreements ranging from basic immunologic research, target identification and validation to translational research and development activities to clinical evaluation of promising vaccine candidates domestically and overseas. He has also served on numerous committees for federal and international activities involving vaccine R&D and global health, and has chaired and participated in numerous scientific symposia on vaccine R&D and tropical infectious diseases at national and international meetings. He received his A.B. from Harvard College and his M.D. and Ph.D. in immunology from the New York University School of Medicine. He completed his residency in Internal Medicine at the Johns Hopkins Hospital, and infectious diseases subspecialty training at the NIH and Yale University School of Medicine.

Keystone Symposia on Molecular and Cellular Biology

About Keystone Symposia

Keystone Symposia on Molecular and Cellular Biology is a 501(c)(3) nonprofit organization headquartered in Silverthorne, Colorado, USA that convenes open, peer-reviewed conferences across a broad range of the life sciences. Our mission is to accelerate life science discovery by providing a forum to present top-quality science, foster new collaborations and help prepare the next generation of life scientists. Approximately 50–60 conferences take place each year. More than half the symposia are held in mountain venues across the American and Canadian West, with the remainder primarily in North American cities and various global locations. We have now convened conferences on five continents: Africa, Asia, Australia, Europe and North America. The first in South America was held in Ouro Preto, Brazil in May 2013.

Keystone Symposia receives revenue from two sources: registration fees (approximately 65-70%) and generous support from corporations, foundations, government entities and individuals (approximately 30-35%). This support provides funding for scholarships as well as speaker travel expenses (subsidies are based on economy-rate travel and no honoraria are paid), allowing registration fees to be kept as low as possible. Many speakers forego expense reimbursement to provide more funds for scholarships.

Under the direction of Chief Executive Officer James Aiken, Chief Scientific Officer David Woodland and an advisory Board of Directors, a staff of approximately 40 full-time, part-time or seasonal employees handles all aspects of administration, meeting management/logistics, attendee services, fundraising and marketing.

How Keystone Symposia Conferences Are Programmed

All Keystone Symposia conferences are developed through a rigorous peer-review system that involves the coordinated efforts of a Scientific Advisory Board (SAB) comprised of more than 70 leading scientists from academia, industry and government worldwide, more than 100 programming consultants and the Keystone Symposia staff.

Meeting development starts more than two years in advance through teleconference and online discussion forums involving SAB members and ad-hoc programming consultants. This process generates information on trending scientific areas and new meeting ideas. The SAB then convenes in Keystone, Colorado in January and uses the online-generated information to identify conference topics, suggest potential scientific organizers, make recommendations regarding meeting content and identify meetings that could be held jointly. Based on the recommendations of the SAB, Keystone Symposia staff solicits conference organizers and helps them prepare programs for peer review. The staff also receives 12-15 additional organizer-initiated proposals during this time.

The SAB meets again in June to review all submitted meeting proposals (both solicited and unsolicited), recommend whether proposals should be accepted or rejected and provide constructive

Keystone Symposia's History

Founded in 1972 in Los Angeles as the ICN-UCLA Symposium on Molecular Biology by Professor C. Fred Fox, the organization evolved into UCLA Symposia before relocating to Silverthorne, Colorado in 1990. At that time we became a free-standing division of a nonprofit called The Keystone Center and were renamed Keystone Symposia on Molecular and Cellular Biology. We separated from The Keystone Center and became an entirely independent nonprofit in a phased transition beginning in 1995 and ending in 1997.

Attendees at the first Keystone Symposia meeting in Squaw Valley in 1972.

Notable Milestones

1972: Keystone Symposia was founded as the ICN-UCLA Symposium on Molecular Biology and held an initial conference on membrane research in Squaw Valley, California, March 13-17, 1972.

1984: Keystone Symposia convened the first-ever open, international meeting on AIDS in 1984, which was widely credited with catalyzing a consensus that AIDS was caused by a retrovirus now known as the Human Immunodeficiency Virus.

1990: Under the chairmanship of first Dr. Pedro Cuatracasas (then President of the Parke Davis Research Laboratories) followed by Professor Ralph Bradshaw (then at the University of California, Irvine), Keystone Symposia relocated to Silverthorne, Colorado, became a division of The Keystone Center and was renamed Keystone Symposia on Molecular and Cellular Biology.

1995: Under the Board leadership of Professor Dennis Cunningham of the University of California, Irvine, Keystone Symposia began a phased transition to separate from The Keystone Center.

1997: Under the chairmanship of Professor Edward A. Dennis of the University of California, San Diego, this separation was completed and Keystone Symposia became a completely independent nonprofit 501(c)(3) organization.

(continued on next page)

2001: We held our first conference outside of the US in Canada ("Hematopoiesis" in Whistler, British Columbia, Canada) and also launched our formal diversity initiatives, supported first by a grant from the David and Lucile Packard Foundation and later by another from the Alfred P. Sloan Foundation.

2003: Dr. James W. Aiken assumed the new position of Chief Executive Officer.

2005: Keystone Symposia's first conference in Asia convened ("Stem Cells, Senescence and Cancer" in Singapore).

2006: We held our first conference in Europe ("Multi-Protein Complexes Involved in Cell Regulation" in Cambridge, UK) and also launched the Keystone Symposia Global Health Series, supported by the Bill & Melinda Gates Foundation, which also funds Global Health Travel Awards to enable developing-country investigators to attend meetings in this Series.

2007: Keystone Symposia's first conference in Africa and the first Global Health Series meeting convened ("Challenges of Global Vaccine Development" in Cape Town, South Africa).

2009: We organized our first conference in Australia ("Telomere Biology and DNA Repair" in Ashmore).

2010: Keystone Symposia received a five-year, US$1.37 million MARC (Minority Access to Research Careers) grant from the National Institute of General Medical Sciences of the US National Institutes of Health to help fund expanding diversity initiatives.

2011: Dr. David L. Woodland ("Woody") joined Keystone Symposia as Chief Scientific Officer.


Dr. David Woodland

2013: Keystone Symposia convened its first conference in South America ("The Innate Immune Response in the Pathogenesis of Infectious Disease" in Ouro Preto, Brazil).

feedback to organizers to improve programs. The SAB also reviews the entire meeting portfolio to determine whether any additional meetings need to be "fast-tracked" to fill gaps in the portfolio. While the key focus of the SAB is the quality of the scientific content, considerable attention is paid to speaker diversity in the programs, including gender, stage of career, ethnicity, affiliation and geographical distribution. Particular attention is also given to reducing the number of repeating speakers if a similar conference has recently been held. Finally, efforts are made to ensure appropriate representation of basic, clinical and industry research in the programs, depending on the scientific topic. Organizers submit revised meeting programs by September and October, allowing Keystone Symposia staff to start inviting speakers well over a year in advance of the conference season.

To ensure the best-quality science unencumbered by commercial interests, Keystone Symposia does not accept any requests to speak on the programs. Similarly, corporate sponsors do not receive speaking slots and are not given preference when organizers invite speakers. Even in cases where nonprofit foundations and publishers sponsor sessions or speakers, the organizers always select the associated speakers and topics.

Like the SAB members and ad-hoc programming consultants, scientific organizers serve in an entirely volunteer capacity with only their travel, lodging and registration expenses paid. Organizers fine-tune their programs and select speakers, using guidelines from Keystone Symposia to encourage fresh and diverse participation. A number of slots in each session are left open for late-breaking developments to be later filled by short talks that the organizers select from submitted abstracts.

Keystone Symposia chooses conference venues that are able to accommodate the expected number of participants, provide cost-effective facilities and offer an atmosphere conducive to information exchange and informal networking. Keystone Symposia staff negotiate discounted lodging rates, and every attempt is made to select sites that are environmentally conscientious.

Keystone Symposia Diversity Initiatives

Keystone Symposia strives to engage conference attendees with many different experiences and backgrounds – e.g., different research interests and work environments, career stages and cultures. Diverse experiences and backgrounds provide the lens through which we discern and conceive of research questions. By including a rich variety of perspectives, we ensure that the best research questions and problem-solving approaches are represented at the conferences.

We are dedicated to increasing the number of scientists from designated underrepresented backgrounds and female scientists as organizers, speakers and attendees. Scholarships and highly interactive poster sessions encourage the participation of students and postdoctoral fellows, who typically account for 40% of

(continued on next page)

Keystone Symposia Diversity Initiatives (continued)

attendees each year. The Keystone Symposia Global Health Travel Awards make possible the participation of investigators from developing countries in meetings of the Keystone Symposia Global Health Series.

Through a range of initiatives in diversity, we actively promote participation of UR (underrepresented) investigators. Overseen by our Director of Diversity in Life Science Programs, with input from scientists on the Diversity Advisory Committee, these initiatives include:

Underrepresented Trainee Scholarships – We award up to $1,200 for UR graduate students and postdoctoral fellows of US citizenship or permanent residency to attend a Keystone Symposia conference. Submission of an abstract is required, and selection is based on the quality of the abstract. These competitive Scholarships are made possible in part by Keystone Symposia's NIH MARC grant and Keystone Symposia funds. Applications are reviewed by meeting organizers. Visit **keystonesymposia.org/URScholarship** to learn more.

ABRCMS Scholarships – Each year during the Annual Biomedical Research Conference for Minority Students (ABRCMS), managed by the American Society for Microbiology, Keystone Symposia awards scholarships to two students presenting research at the conference.

Early-Career Investigator Travel Awards – We award up to $1,950 for UR scientists who are assistant professors or industry scientists at equivalent levels with US citizenship or permanent residency to attend a Keystone Symposia meeting. The application requires the candidate to identify a specific question he/she is researching which might be addressed by attending a particular meeting. It also requires a commitment to mentoring a student (undergraduate, graduate, postdoc) from an underrepresented background in a laboratory around career development and positioning issues for a minimum of one year. These competitive Awards are made possible by Keystone Symposia's NIH MARC grant and Biogen Idec. Applications are reviewed and ranked by meeting organizers. Visit **keystonesymposia.org/EarlyCareerAward**.

Keystone Symposia Fellows Program – Keystone Symposia accepts on average five early-career scientists annually who are committed to a research career and to enhancing diversity in the life sciences by increasing participation of designated UR scientist populations. The Keystone Symposia Fellows Program provides an opportunity to engage in the Keystone Symposia program development process and gain insight into the inner workings of the life science community. Fellows interact at the highest levels with renowned scientists, engaging via teleconferences and face-to-face participation in the meetings of our Scientific Advisory Board and Fellows Circle. This program is funded by Keystone Symposia's NIH MARC grant. Visit **keystonesymposia.org/Fellows** to learn more, apply or read about past and current Fellows.

Peer-to-Peer Program – Participants from underrepresented backgrounds are invited by email before a conference begins to meet with each other at a specified time and place during the conference to share research backgrounds and have names and faces to connect with throughout the conference. If attendees have not self-identified as being members of a federally designated UR population, they will not be sent an email invitation.

Biogen Idec Mentoring Program – Keystone Symposia collaborates with Biogen Idec in offering formal mentoring sessions to scientists from UR backgrounds at selected Keystone Symposia meetings. These sessions are facilitated by scientists from Biogen Idec.

Strategic and Deliberate Outreach – Keystone Symposia's Director of Diversity in Life Science Programs, Chief Scientific Officer and other staff members present at conferences such as ABRCMS, Understanding Interventions Conference, The Leadership Alliance National Symposium, SACNAS (Society for the Advancement of Chicanos and Native Americans in Science) Annual Conference and Biogen Idec's Pathways to Success Conference and at molecular and cellular biology conferences, universities and medical schools nationwide. Ongoing collaborations to promote early-career investigator development and diversity enhancement include work with Brown University, Harvard University, The Leadership Alliance, The Endocrine Society, Biogen Idec, Novartis Institutes for BioMedical Research and the American Physician Scientist Association (APSA).

Evaluation Research – A key component of Keystone Symposia's portfolio of initiatives in diversity is the ongoing evaluation, review and revision of programmatic offerings. Initiatives are evaluated on a regular basis utilizing feedback of participants, expert observers and the Director, Diversity in Life Science Programs. Recent peer-reviewed articles on initiatives have appeared in *Trends in Biochemical Sciences,* August 2013 and *Trends in Molecular Medicine,* December 2012.

Our Director of Diversity in Life Science Programs, ***Laina King, Ph.D.****, welcomes your input and can be reached at* ***lainak@keystonesymposia.org*** *or* ***1.970.262.1230 ext. 137****.*

If you are interested in supporting these Programs, please contact Dr. Laina King or Dr. Christopher Atwood, Director of Development, at ***chrisatwood@keystonesymposia.org*** *or* ***1.970.262.1230 ext. 124****.*

To learn more about Keystone Symposia's Diversity in Life Science Program initiatives and their evolution, visit ***keystonesymposia.org/diversity*** *and* ***keystonesymposia.org/timeline****.*

To find out ways you can help foster diversity in the life sciences, visit ***keystonesymposia.org/diversityhelp****.*

Thank you

To fulfill our nonprofit scientific mission, Keystone Symposia relies on significant financial commitment from government, foundation and industry donors as well as generous support from individuals. Gifts to the discretionary Directors' Fund ensure Keystone Symposia's ability to provide sufficient program support for meetings on a greater variety of scientific topics than would be possible if gifts were restricted to specific meetings in each case. All contributions are vital to the fulfillment of our mission — catalyzing collaborations to accelerate discoveries and helping to prepare and position the next generation of leading life scientists.

To all of our faithful supporters:
Thank you for your generous commitment to Keystone Symposia.

If your organization is interested in making a donation to Keystone Symposia, please contact our Development Director, Dr. Christopher Atwood, at ***chrisatwood@keystonesymposia.org*** *or* ***1.970.262.1474****. You can also visit* ***keystonesymposia.org/corporategiving*** *for more information.*

If you are interested in making a personal donation to the Future of Science Fund, please visit our secure individual donor platform at ***keystonesymposia.org/FSF****.*

To explore personal bequests and other planned gift vehicles, please visit ***ksgift.org*** *or contact Christopher Atwood.*

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Donors of $50,000 or above. We are very grateful for this extraordinary commitment to our mission to connect the scientific community and accelerate discoveries that benefit the world community. Special thanks to these organizations for consistent, annual Benefactor-level support.

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Support for Keystone Symposia Diversity in Life Science Programs

We are grateful for this valuable support directed at increasing the participation of underrepresented scientists among meeting leaders and attendees, thereby enhancing diversity in the life science research community. Read more about our Diversity in Life Science programs on page 17.

Alfred P. Sloan Foundation
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NIGMS Minority Access to Research Careers (MARC)*

**Funding for Keystone Symposia's Diversity Program is made possible in part by award number 5T36GM089175-04 from the National Institute of General Medical Sciences (NIGMS) Minority Access to Research Careers (MARC) Ancillary Training Activities Program. The content is solely the responsibility of Keystone Symposia on Molecular and Cellular Biology and does not necessarily represent the official views of the National Institute of General Medical Sciences or the National Institutes of Health.*

US Federal Grant Funding

Keystone Symposia truly appreciates the support received from various institutes of the National Institutes of Health and from the National Science Foundation. This support primarily funds scholarships for graduate students and postdoctoral fellows to attend our conferences. US federal grant support for the 2014 meeting series was generously provided by:

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We would like to thank our conference assistants for their contributions to this meeting. These individuals assist the scientific organizers and Keystone Symposia's onsite staff throughout the meeting. They also compile a meeting summary for submission to our government financial supporters.

Beatriz Galatas, Barcelona Institute for Global Health (ISGlobal), Spain

Armando Menezes-Neto, Instituto René Rachou/FIOCRUZ, Brazil

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These generous alumni of previous meetings and others with a passion for ensuring a future of scientific discovery that benefits humankind have made gifts during the last 12 months to support the Keystone Symposia Future of Science Fund. Through their generosity, we are able to provide scholarships and travel awards to the next generation of biomedical and life scientists, whose education and careers are enhanced by the opportunity to attend meetings and interact with the world's leading senior scientists.

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If you would like to discuss individual giving opportunities, please contact the Development Director, Christopher Atwood, at **1.970.262.1474** or **chrisatwood@keystonesymposia.org.**

Keystone Symposia Future of Science Fund

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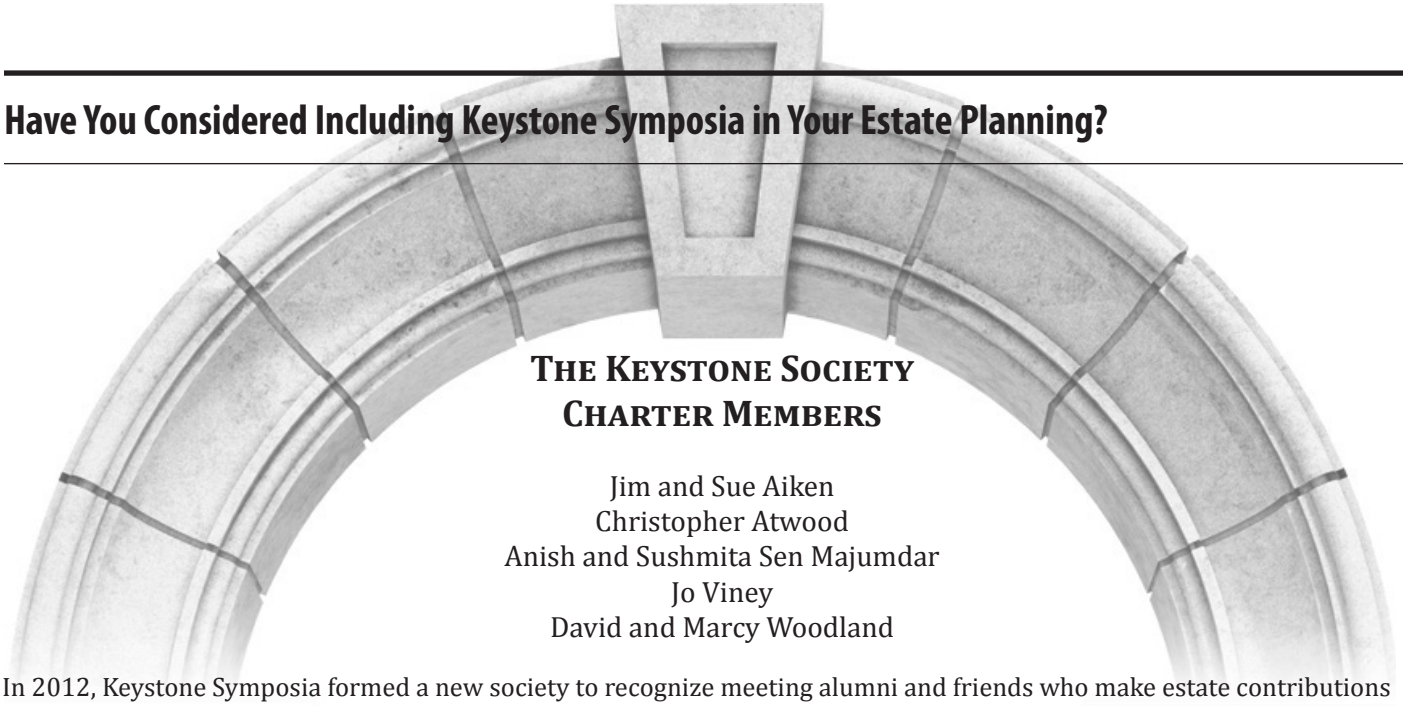

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0101: Wirth

The Parasite Population in Malaria Control, Elimination and Eradication

Dyann F. Wirth
Harvard School of Public Health and The Broad Institute of MIT, Cambridge, MA, USA

Our goal is to understand threats to the malaria elimination/eradication agenda. As effective control measures are deployed, parasite populations change due to selective pressure (e.g. as applied by drugs and vaccines) and to local population bottlenecks. We have developed population biology tools that permit effective, efficient monitoring of parasite transmission and population dynamics through simple genetic testing of parasites sampled from the population. The breakthrough has been a rapid technical advance in genome sequencing and genotyping, which allows us to directly sequence parasites from infected humans and evaluate the number and types of parasites present. As transmission intensity declines, we can observe predictable changes: a decline in the number of parasite types in each infection (complexity of infection, COI), a rise in prevalence of certain parasite types, and an increase in linkage disequilibrium. Coupled with novel modeling methods, these technologies will help assess intervention strategies critical to successful malaria eradication. Recognizing that *P. falciparum* is not the whole story of malaria, we have developed a parallel set of tools to conduct similar studies in *P. vivax*, including validation in a field setting. In addition, we report follow up work identifying specific markers as diagnostic of selective pressures on the parasite. We have used the new plethora of sequence data to discover genetic loci under natural selection in the parasite, including variants associated with drug resistance (particularly for artemisinin and partner drugs) and those potentially related to other biological processes that impact transmission including gametocyte carriage or gametocytogenesis.

Taken together, this set of tools should allow us to map, in real time, changes in parasite transmission as interventions are introduced using material sampled from a small number of patients. The approach should allow the tracking of progress to reduced transmission but importantly should be able to rapidly detect increased transmission, perhaps as an early warning sign of intervention failure. This information will be particularly valuable in settings undergoing dynamic changes in transmission and should be amenable to worldwide deployment.

The Wirth laboratory has received funding for malaria research from the following organizations: The Bill and Melinda Gates Foundation, Sanofi-Aventis U.S., Inc, NIH/NIAID, and Exxon Mobil.

0102: Richards

Pragmatic Approaches:
Where to Start with Elimination – Different Strategic Lessons that Can Be Learned from NTD Programs

Frank O. Richards
The Carter Center, Malaria Program, Atlanta, GA, USA

Eradication has remained an important concept in the field of global health, with its sights set on bringing the global prevalence of diseases such as polio, guinea worm (dracunculiasis), and malaria to zero. Elimination, or 'getting to zero' at local, national or regional levels, is a more confusing term that should define (or begin to define) the stepwise march towards "getting to zero" globally. Cleary defining what we mean by elimination is very important, as the term is frequently used imprecisely ('elimination as a public health problem', and 'virtual elimination' are examples).

With a definition of 'getting to zero' in mind for either eradication or elimination terms, this presentation will focus on lessons learned in three Neglected Tropical Disease (NTD) Programs: Guinea worm eradication (GWE), Lymphatic Filariasis Elimination (LFE), and Onchocerciasis Elimination in the Region of the Americas (OEPA). Among the different NTD strategies to be explored are the use of village based workers (GWE), the strategy of mass drug administration to prevent humans from infecting mosquitoes (LFE), and the problem of the long tail (OEPA and GWE).

0104: Prachumsri

Inhibition of Malaria Parasite Development in Different Vectors

Jetsumon S. Prachumsri
Mahidol Vivax Research Center, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Transmission of malaria is complicated due to co-evolution of parasites and their vectors. All four human malaria species and *P. knowlesi*, a monkey malaria parasite endemic in some countries, have the ability to maintain transmission in different mosquito vectors. Thus a single tool to block transmission may not be universally applicable in all areas. Knowledge of vectors species specific to each location will improve the evaluation of control measures and elimination strategies. Evaluation of different tools used to inhibit parasite development in different vectors from Africa and Asia will be compared and discussed.

0104: James

Genetic Approaches for Controlling Transmission of Mosquito-Borne Diseases: Focus on Malaria

Anthony A. James
Department of Microbiology and Molecular Genetics, School of Medicine, University of California, Irvine, CA, USA

Genetics-based approaches have been proposed to control transmission of vector-borne pathogens. Strategies for both population suppression and population replacement of mosquitoes have benefitted from the development of transgenesis, site-specific recombination and targeted effector molecules. Advances in the development of vector-based genetic control strategies for preventing malaria parasite transmission have resulted in tools that in laboratory trials either suppress completely mosquito populations or render them incapable of transmitting the pathogens. The latest research will be presented on the development of a flightless-female strain for population suppression, a parasite resistance gene and DNA insulator activity for preventing the transmission of the human malaria parasite, *Plasmodium falciparum* by the Asian vector mosquito, *Anopheles stephensi*. Models and outcomes for the effective practical use of these strains will be presented.

0105: Jacobs-Lorena

Fighting Malaria with Engineered Symbiotic Bacteria from Vector Mosquitoes

Sibao Wang and Marcelo Jacobs-Lorena
Johns Hopkins School of Public Health and Malaria Research Institute, Baltimore, MD, USA

The unbearable burden of malaria demands the urgent development of novel approaches to fight this deadly disease.

Technical advances in vector biology have allowed the development of a new strategy to combat malaria, by genetically modifying the mosquito to reduce its vectorial competence. However, one crucial unresolved aspect of this approach is how to introduce transgenes into wild mosquito populations ("genetic drive"). Several strategies have been proposed, but a number of technical hurdles have yet to be overcome.

We are exploring an alternative approach based on the fact that the mosquito, as all higher organisms, carries a microbiota in its midgut. Rather than genetically modifying mosquitoes, our strategy is to genetically modify symbiotic bacteria for delivering anti-malarial effector molecules into the mosquito midgut (paratransgenesis). It is in the midgut that the most vulnerable stages of *Plasmodium* development in the mosquito take place. We have shown that the bacterium *Pantoae agglomerans* engineered to express and secrete anti-*Plasmodium* effector molecules strongly inhibits *Plasmodium* development in the mosquito by up to 98%.

Recently, we have identified another mosquito symbiotic bacterium of the genus *Serratia* that is transmitted both vertically from female to larval progeny and horizontally from male to female during mating. These transmission properties suggest that it should be possible to introduce recombinant *Serratia* into mosquito populations in the field for the purpose of malaria control. This approach is 'low-tech' and does not involve the introduction of a new species of bacteria, since *Serratia* is a natural component of the African mosquito microbiota.

Transgenesis and paratransgenesis are complementary approaches that once perfected, may be used simultaneously for maximum effectiveness.

Funded by NIH AI88033

0201: Winzeler

Using Phenotypic Screening and Forward Genetics to Find Targets for a Malaria Elimination Agenda

Elizabeth A. Winzeler
Department of Pediatrics, Division of Pharmacology and Drug Discovery, University of California San Diego School of Medicine, La Jolla, CA, USA

To eliminate malaria, broadly acting medicines must be developed that cure the symptomatic asexual blood stage, clear the preceding liver stage infection that can cause relapses and block parasite transmission to mosquitoes. Radical cure activity is especially important for Plasmodium vivax, which forms hypnozoites that can persist for years before reinitiating development and triggering blood stage infection. Primaquine is the only licensed antimalarial capable of eliminating the hypnozoite reservoir and delivering a radical cure. However, side-effects and weak activity against blood stages preclude widespread use of primaquine. Since primaquine's target and mechanism of action are not known, the search for novel radical cure drugs has been limited to related analogs. To overcome this, we are using a chemical genomics approach. Chemical libraries are first subjected to a variety of phenotypic screens, including ones that measure inhibition of parasite growth in hepatocytes, assess activity against gametocytes, and detect stalled blood stage replication. Small molecules that fulfill these criteria may be used as leads for drug discovery, or may also be used as probes to find chemically validated targets. Here, parasites are grown in sublethal concentrations of compound until they acquire genetic modifications that allow them to overcome the inhibitory effect of the compound. The identity of the genetic change is revealed by full genome sequencing, which in many cases reveals the target. A variety of novel targets have been discovered using this approach, opening up new avenues of target-based discovery to identify drugs with an ideal activity profile for the prevention, treatment and elimination of malaria.

0202: Wells

Discovery and Development of New Medicines for Eradication: Integrating with Translational Medicine

Timothy N.C. Wells, Jeremy N. Burrows Stephan Duparc and Joerg J Möhrle
Medicines for Malaria Venture, Geneva, Switzerland

Recent developments in screening and access to diversity collections have led to the identification of many new chemical series active against malaria erythrocyte stages in vitro. However, the eradication agenda requires molecules to have activity against other stages of the pathogen lifecycle: specifically transmission blocking, relapse prevention and chemoprotection. As the new generation of compounds has transitioned into clinical studies, we have developed a platform for determining the 'fingerprint' of each compound at each stage of the parasite life cycle. These fingerprints were initially based on standardized cell biology assays. This enables clear identification and prioritization of molecules based on their fit to target candidate profiles. These initial fingerprints can be refined with animal data from blood stage, transmission blocking, and hepatic assays, and also propensity to resistance generation. The most important development in the last few years is the integration of translational medicine approaches to rapidly and simply determining the characteristics of our key compounds in humans. Examples include the blood and sporozoite challenge models in human volunteers, as well as SMFA assays for transmission blocking. All these data then can be used in the modeling and simulation of the activities of potential new combinations before key (and expensive) phase IIb combination studies start. Finally, questions of safety in human subjects is often overlooked in eradication agenda discussions: early determination of key safety parameters such as QTc prologation and hepatic safety in volunteers is critical. Eradication discussions often suggest giving therapeutic regimens to asymptomatic carriers or even non-infected subjects, where clearly the benefit:risk ratio will need to be higher. The next ten years should see the registration of new classes of medicines against malaria; by making the appropriate decisions now, we can ensure that we maximize their potential use for malaria eradication.

Burrows JN, et al., Designing the next generation of medicines for malaria control and eradication Malar J. 2013 Jun 6;12:187.

This work was supported primarily by grants from the Bill and Melinda Gates Foundation, UK DIFD and specifically Wellcome Trust

0203: Lacerda

Drugs for *Plasmodium vivax* in the Context of Eradication

Marcus V. G. Lacerda
Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Manaus, Amazonas, Brazil

In the context of malaria control, antimalarial drugs have always been the cornerstone tool. The conceptual shift from control to elimination/eradication keeps the same rationale. Major advances were achieved in the past decades regarding the development and distribution of antimalarials in most of the endemic areas. The response to worldwide *P. falciparum* chloroquine resistance was the development of Artemisinin-based Combination Therapy (ACT), and in order to block transmission, there is good evidence that primaquine in a single low dose is able to kill gametocytes and contribute to decrease transmission. However, the *P. vivax* problem was not tackled likewise. *P. vivax* choloroquine resistance still poses a major problem in some areas, and knowledge on ACT efficacy in these areas is still scarce. To complicate matters, the only anti-hipnozoite available drug, primaquine, is one of the most toxic antimalarials in specific populations, such as the G6PD deficient, leading to severe hemolysis; resistance seems to be increasing all over; and the ideal 14-day regimen offers very low compliance. The new anti-relapse 8-aminoquinoline drug under current clinical development, tafenoquine, will probably solve the compliance problem, since a single oral dose could be as effective as the 14-day primaquine regimen, however G6PD deficiency will still pose a major problem in the context of massive use of this drug.

0204: Ariey

A Molecular Marker of Artemisinin-Resistant *Plasmodium falciparum* Malaria

Frédéric Ariey
Institut Pasteur, Paris, France

Plasmodium falciparum resistance to artemisinin derivatives in Southeast Asia threatens malaria control and elimination activities worldwide. To monitor the spread of artemisinin-resistance, a molecular marker is urgently needed. Based on a whole-genome sequencing of an artemisinin-resistant parasite line from Africa and clinical parasite isolates from Cambodia, we associate mutations in the PF3D7_1343700 kelch propeller domain ('K13-propeller') with artemisinin resistance in vitro and in vivo. K13-propeller polymorphism constitutes a useful molecular marker for large-scale surveillance efforts to contain artemisinin resistance in the Greater Mekong Subregion and prevent its global spread. The use of this marker in the light of malaria elimination strategy will be discussed.

0205: Smith

How Stable Is Elimination?

David L. Smith
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Malaria transmission experienced massive changes dramatically during the 20th century. The range of malaria contracted massively, due partly to the Global Malaria Eradication Programme (1955-1969). As the GMEP ended and funding for interventions was lost, some countries experienced massive resurgence of malaria. Analysis of these historical patterns suggests that elimination is highly stable once achieved: it is a "sticky" state. Understanding why malaria elimination was stable in some countries but not in others is important for the current long-term plan to eradicate malaria.

The health system plays a major role in detecting and containing malaria outbreaks and in keeping a country free of malaria. Where malaria is endemic even at low levels, clinical immunity can develop and help the pathogen to persist in transmission hotspots. Once malaria is gone and immunity has waned, the health system can play a much larger role in controlling transmission. Changing immunity and improved health systems can keep malaria out of places where it was once highly endemic. This phenomenon provides one potential explanation for why malaria elimination is "sticky," and it provides justification for the policy of spatially progressive malaria elimination.

0206: Smith

Dynamics of Malaria Infection: Implications for Elimination

Thomas A. Smith
Swiss Tropical and Public Health Institute, Basel, Switzerland

Both successful and failed programs for disease eradication hold important lessons for malaria, in particular regarding prioritisation of geographical areas for intervention. However, the existence of partial immunity to malaria (both *P. falciparum* and *P. vivax*) leads to fundamental differences in transmission dynamics from those of viruses that induce life-long immunity. In particular, malaria is generally an endemic, rather than an epidemic infection and there are no good estimates of the minimum population size for persistence of either of the main human malarias. The dynamics of loss of immunity and of evolutionary changes induced by interventions are poorly understood, but are critical for the outcome of long term strategies against the disease. One implication is that it is crucial to plan effective surveillance-response strategies for areas where transmission has been interrupted.

0301: Hoffman

Plans for Development of the PfSPZ Vaccine for Use in Malaria Elimination

Stephen L. Hoffman
Sanaria, Rockville, MD, USA

The term, Vaccine that Interrupts Malaria Transmission (VIMT) was introduced by the Malaria Eradication Research Agenda (malERA) initiative [malERA Consultative Group on Vaccines. A research agenda for malaria eradication: vaccines. *PLoS Med.* **8**, e1000398 (2011)]. An ideal VIMT would induce protective immune responses against all stages of the parasite life cycle. However, the ideal single stage VIMT would prevent infection at the pre-erythrocytic stage of the parasite life cycle, thereby preventing erythrocytic stage infection and all parasite-caused disease and transmission of the parasite from humans to mosquitoes. The PfSPZ Vaccine is a pre-erythrocytic stage vaccine and the malaria vaccine closest to being able to be used as a VIMT. It was recently reported to be safe and to completely protect six of six volunteers who received the highest dosage administered in a clinical trial from *Plasmodium falciparum* (Pf) infection. Clinical trials at 8 sites in Africa, Europe, and the United States will begin in late 2013 and the first half of 2014. These trials are designed to establish reproducibility of the safety and efficacy results of the first clinical trial, establish an immunization regimen that provides durable protection against all Pf strains with the least number of doses and least quantity of vaccine, identify an immunological test that predicts protection, and begin the implementation research needed to pave the way for mass administration campaigns. We have set an ambitious 4-year timeline for moving through the stages of clinical development to pivotal phase 3 clinical trials and then to licensure and demonstration of the capacity of the vaccine to eliminate *Plasmodium falciparum* from a population of greater than 200,000 individuals. The plans for doing so, including the challenges we face, our strategies for overcoming them, and the roles of the numerous international partners involved in the process will be discussed.

0302: Duffy

Transmission-Blocking Vaccine and Assay Development

Patrick E. Duffy
NIAID, National Institutes of Health, Bethesda, MD, USA

Malaria transmission-blocking vaccines were conceived in the 1970s, and a number of candidate vaccine antigens identified in the 1980s and 1990s. However, the poor immunogenicity of candidate antigens, and cumbersome nature of functional assays, has slowed further development. We have pursued protein-protein conjugation as a strategy to enhance immunogenicity while maintaining vaccine safety. In Phase 1 trials, four doses of recombinant Pfs25 antigen chemically conjugated to recombinant ExoProtein A, induced measurable transmission-blocking activity in malaria-naïve vaccinees in USA. This vaccine (Pfs25-EPA/Alhydrogel) is now being tested for safety and immunogenicity in malaria-experienced adults in Mali, using a similar regimen. In parallel, we are comparing membrane feeding assays to direct skin feeding assays on vaccines and nonvaccinees, in order to inform the optimal format for measuring efficacy in future trials. Our results thus far using samples from semi-immune adult Malians indicate that "transmission reducing activity" measured using the standard membrane feeding assay (SMFA) in USA may correspond to "transmission blocking activity" using direct membrane feeding assay (DMFA) in Mali. The SMFA uses laboratory lines of parasites and mosquitoes, and typically achieves much higher oocyst burdens in comparison to DMFA, for which we use freshly collected parasite/gametocyte isolates that are fed to recently derived colony of locally caught mosquitoes in Mali.

Funding – Division of Intramural Research, NIAID, NIH; Malaria Vaccine Initiative at PATH

0303: Kaslow

Abstract not available at the time of printing.

0304: Dobaño

Approaches and Challenges in Profiling Immune Responses to the RTS/s Vaccine Candidate

Carlota Dobaño
Barcelona Centre for International Health Research (CRESIB), Spain

RTS,S is the most advanced malaria vaccine candidate in clinical development, currently in last stages of a phase 3 trial for licensure in 11 African countries. Vaccine efficacy against clinical malaria has ranged from about 55% in children to 30% in infants over a follow up period of 12 months. Many gaps of knowledge remain as to the protective mechanisms of the vaccine and the longevity of the immune response elicited. Understanding its mode of action is needed for the rational development of second generation more potent vaccines.

Investigators from 7 African research centers in collaboration with European partner institutions, GSK and PATH-MVI are conducting a comprehensive immunology study ancillary to the phase 3 trial to profile immune responses to RTS,S in well-characterized serum/plasma and cell samples in different age cohorts and malaria transmission settings.

We aim to (i) define the initial protective immune responses targeting the circumsporozoite antigen upon vaccination with RTS,S and (ii) assess naturally acquired humoral and cellular immunity to blood stage parasites that may modulate vaccine outcomes. Specifically, we will characterize the magnitude of the antibody response and supporting B- and T helper cells (T_{FH}-like and T_H2), as well as T_H1 responses that may contribute to protection via effector functions such as cytotoxicity or secretion of cytokines. Multiparameter flow cytometry, luminex and transcriptional analyses are used to profile cellular immune responses in vaccinated and protected children. We are also performing non-biased antibody profiling via protein array and qualitative and functional analyses of immunoglobulins.

The RV144 HIV vaccine two-stage approach is being adapted, starting with a pilot study to downselect and prioritize immunological variables, before conducting the main immune correlates studies. Additionally, a systems biology approach will be adopted to integrate the data and identify signatures associated with vaccination and protective immunity.

Identifying the immune correlates of protection of RTS,S will greatly facilitate the development of more efficacious and long-lasting vaccines for malaria eradication.

Grant funding acknowledgement. PATH-MVI (CTA, 7760), NIH (R01 AI095789 and U19 RFA-EI-09-040), EU FP7 (SGR 934), FIS-ISCIII (PI11/00423), Fundación Ramon Areces and AGAUR (Malaria Immunopathology Program).

0305: Steketee

Measuring Malaria Transmission Reduction in a Program Context in Sub-Saharan Africa

Richard W. Steketee, Science Director, Malaria Control Program and MACEPA, PATH, Seattle WA, USA

In the past decade, remarkable change in malaria control and transmission has been documented in many (but not all) African nations and some countries are moving toward elimination. The malaria control community has long measured and tracked malaria transmission using a variety of methods from the highest to the lowest transmission areas. For program action across the spectrum of transmission between humans and mosquitoes, the balance between accurate measurement, sufficient detail to inform program decisions, and ease and simplicity of information collection, analysis and interpretation has always been challenging. A summary of historic and current efforts to measure parasites within and moving between people and mosquitoes will be provided with an emphasis on how the approaches and emphasis change as transmission intensity changes. The program decision needs for routine systems and for special studies to track transmission reduction will be discussed. Finally, the detection and verification of "zero" infection and transmission will be discussed in terms of tools and sampling methods that will allow the designation of malaria-free areas.

0306: Mueller

Determining Transmission of *P. vivax* and *P. falciparum* in Three Non-African Settings

Ivo Mueller, Jetsumon Prachumsri, Leanne Robinson, Andrea Kuehn, Marcus Lacerda, Inoni Betuela, Ingrid Felger
Walter and Eliza Hall Institute, Australia

In order to re-orient a malaria control program from reducing the burden of disease towards the interruption of local transmission, it is essential to have an in-depth understanding of patterns and determinant of transmission. In particular it is essential to accurately measure transmission and efficiently identify areas with residual vs. no transmission. Traditionally, transmission is determined using direct entomological measures. However, the EIR is very difficult to measure in low transmission setting. Surrogate epidemiological measure (e.g incidence, prevalence are thus often used.

In a series of cross-sectional and cohort studies in PNG, Thailand and Brazil we are determining presence of asexual and sexual parasites using qPCR/qRT-PCR-based methods to study the temporal patterns of parasitaemia and gametocytaemia. In PNG, the children acquired upto 3-time as many genetically distinct *P. vivax* than *P. falciparum* blood-stages. Relapsed from long-lasting liverstages accounted for up to 80% of *P. vivax* blood-stages infection, >50% of clinical episodes and are likely to contribute substantially to transmission. In a cross-sectional survey, half of people of all ages with PCR-detectable falciparum and vivax infection were also positive by qRT-PCR for gametocytes. The density of blood-stage parasitaemia was the most important predictor of gametocyte prevalence and densities. Comparable studies are ongoing in Thailand and Brazil are initial results will be presented. Although the degree infectivity of PCR-only positive infections is yet to be fully investigated, these results highlight that low-level asymptomatic infection may be in important source of transmission.

0307: Volkman

Using Genomics to Understand Malaria Transmission toward Elimination and Eradication

Sarah K. Volkman
Harvard School of Public Health, Boston, MA, USA

Malaria is an important human disease and the target of a global eradication campaign. Critical for the success of efforts to eliminate the malaria parasite will involve leveraging new technologies and informatics advancements in parasite population genomics to both identify genetic loci under selection and to find variants associated with key clinical phenotypes such as drug resistance. We have developed genotyping strategies including the development of a molecular barcode for both *Plasmodium falciparum* and *Plasmodium vivax* parasites based upon single nucleotide polymorphisms (SNPs) with a high minor allele frequency. These molecular barcode tools have been instrumental in revealing dramatic changes in parasite population structure coincident with application of increased malaria interventions or declining clinical cases in a number of malaria endemic countries including Senegal and Panama. I will discuss the development and rationale for use of these genotyping approaches as a possible way to measure transmission dynamics and present data supporting the hypothesis that changing parasite population structure can signal a reduction in malaria transmission as a consequence of successful malaria control and elimination efforts. Development of population genetics based strategies are being applied to malaria to both identify genetic loci as key targets of interventions as well as to develop monitoring and surveillance strategies that are crucial for the successful elimination and eradication of malaria.

0401: Sinden

Identifying Biological Challenges: Trojan Horses of the Parasite Life Cycle

Robert E. Sinden
Imperial College London, UK

Trojan horses are potentially available to all adversaries, both those available to the malarial parasites of man on the one side, and on the other those available to man in his attempts to eliminate the parasites will be discussed in this presentation.

The parasites: - Any parasite stage or strategy, whose biological significance remains unrecognised (e.g. the hypnozoite), provide unique potential for a pathogens' ability to avoid eradication. If our efforts are not to be undermined, the biological strategies employed by every life stage must be fully understood from the molecular to the population level. Are there yet further surprises for us in the *Plasmodium* biology? Do we fully understand the journey of the sporozoite from the mosquito salivary gland to the hepatocyte?

At the population level unidentified parasite reservoirs - found in both the vertebrate and the insect hosts, have prompted widespread efforts to develop methods to identify asymptomatic infections/infectious reservoirs in the human host, the utility of these endeavours will be discussed. We have not embraced the idea that the identification and targeting of infected vectors with the same enthusiasm as the asymptomatic human - 'Why not?' Do we need to identify more clearly the small populations of parasites mediating transmission across the dry season? Where such bottlenecks populations are located and how they are dispersed between their vertebrate and invertebrate hosts may prove to be critical factors in the success/failure of our attempts at elimination and eradication.

The human population: - We have uncovered many of the 'Trojan' strategies used by *Plasmodium*, thus potentially undermining their utility to the parasites. In implementing eradication and elimination campaigns we should focus our resources on the weakest points in the parasite transmission cycle, and in so doing introduce Trojan Horses of our own. Our potential to design such strategies requires we identify and apply novel tools and novel strategies that the target parasite or vector life stages/molecules have not experienced in the course of their evolution. To be used efficiently these must then be tested in assays with the potential to examine the impact of the interventions at every point in the parasite life cycle. Then, when used we cannot then forget that their novelty will be lost unless every witness to their existence has been killed.

0402: del Portillo Obando

Reticulocyte-Derived Exosomes: An Intercellular Communicator in *Plasmodium vivax* Malaria?

Lorena Martin-Jaular, Armando de Menezes, Marta Monguió, Aleix Elizalde-Torrent, Marco Fernández, Carmen Fernandez-Becerra, Maria Montoya, Francesc E. Borrás and Hernando del Portillo Obando*
Barcelona Centre for International Health Research (CRESIB)

Exosomes are 30-100-nm membrane vesicles of endocytic origin. Recently, we have described the isolation and characterization of exosomes from reticulocytes, rex, of BALB/c mice infected with the P. yoelii 17X strain (rexPy). Remarkably, subcutaneous immunization of mice with purified rexPy+CpG induced protection and subsequent long-lasting sterile protection in 83% of the animals lethally challenged. We have now determined the molecular composition of these vesicles and found the presence of parasite proteins and yet uncharacterized small RNAs. Moreover, we found that subcutaneous administration of exosomes determines their initial fate to draining lymph nodes. Nevertheless, the spleen plays an essential role since protection does not occur in splenectomised mice. In addition, we are determining the cellular response to rexPy in terms of their capture, ability to stimulate immune cells and capacity to promote the appearance of memory cells in the spleen. In order to translate these results to humans, experiments of the capturing of human exosomes from vivax infections (rexPv) by human splenocytes and their stimulation were performed. Last, we are determining the molecular composition of exosomes obtained from plasma of patients actively infected with Plasmodium vivax. Results will discuss the potential use of rex for advancing the science of malaria eradication.

Funded by by the European Community's Seventh Framework Programme (grant agreement N° 242095) and by the Ministerio Español de Economia y Competitividad (SAF2012-35133), Spain

0403: Billker

Signaling Pathways for Development of Transmission Stages

Oliver Billker
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Sexual development in P. berghei is tightly regulated through transcription, translation and signal transduction. To gain insights into these different aspects of regulation, we need to ask which parasite genes and proteins are required for transmission and how the diverse layers of their control are integrated. Using a family of putative transcriptional regulators with AP2 domains as an example, I will demonstrate how gene targeting vectors freely available from the PlasmoGEM resource (http://plasmogem.sanger.ac.uk/) have facilitated a phenotypic screen of individual cloned mutants that revealed at least five ApiAP2 genes with different stage specific essential functions for gametocyte development and ookinete formation. Gene knock out and tagging vectors from the PlasmoGEM resource integrate into the P. berghei genome with high efficiency due to their relatively long homology arms, and they do not give rise to resistance unless integrated. It is therefore now possible to generate mixed pools of dozens of loss-of-function mutants in a single mouse and monitor the growth of each mutant individually using barcode sequencing. This not only allows large numbers of parasites to be screened in parallel for growth phenotypes in vivo, it also enables screens for gene-gene or gene-environment interactions. Using an example of an unexpected interaction between protein kinase genes, I will demonstrate how reverse genetic screening with PlasmoGEM vectors gives rise to new hypotheses regarding the regulation of calcium dependent signalling pathways downstream of a cyclic GMP dependent protein kinase, PKG, which we recently found controls gametocyte activation and ookinete gliding in addition to schizont rupture.

0404: Cohen

Defining Operational Surveillance Strategies for Malaria Elimination Programs

Justin M. Cohen
Clinton Health Access Initiative (CHAI), USA

National malaria programs must build strong surveillance systems to target limited resources, eliminate malaria, and prevent reestablishment. A key operational difference between a program that aims to eliminate endemic transmission and one that aims only to control the burden of disease involves surveillance strengthening: elimination programs must transition from aggregate to individual-based reporting, and they should complement passive infection identification with active strategies. Nevertheless, passive surveillance comprises the backbone of an elimination program. The probability that a given infection will be transmitted depends upon not only mosquito-related factors but also the strength of the health system: the higher the fraction of incident infections rapidly treated with effective drugs, the lower the probability of onwards transmission. Quantitative evaluation with decision trees reveals that improving the fraction of infected individuals who seek treatment, receive effective drugs, and adhere to their regimen could play a critical role in facilitating elimination feasibility.

Active surveillance is considered an essential complement to passive approaches, but the form such operational activities should take is poorly defined. Programs must consider what passive threshold triggers investigation, how large that investigation should be, which individuals should be tested, and what responsive actions should be conducted. Regardless of whether infections are identified actively or passively, effective programs require operational approaches to analyzing risk on an ongoing basis and designing strategies that account for parasite movement. Simply categorizing cases as local versus imported is insufficient to elucidate the drivers of malaria transmission. For example, draining the infectious reservoir in a place that imports large numbers of new infections will be a Sisyphean endeavor. By building surveillance systems that evaluate both transmission risk and parasite pathways, malaria programs can define smart, cost-effective strategies to eliminate malaria sustainably.

0405: Tanner

Surveillance and Response: The Challenges for Science and Elimination Actions

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Surveillance and response represent the final crucial steps in achieving effective elimination of malaria as well recognized in many of the ongoing malaria control and elimination programs. Introducing surveillance-response approaches represents a paradigm shift from maintaining comprehensive monitoring and evaluation (M&E) activities to focusing on the approaches that rapidly detect remaining / reemerging pockets or "hot spots" of transmission and allow swift public health action with well-tailored integrated response packages to interrupt transmission and thus, eliminate malaria transmission in those pockets/hot spots. The key feature of the surveillance response systems/approaches is that they are based on the concept of collecting minimal essential data in space and time to identify pockets of transmission or reintroduction. Surveillance-response is clearly different from "classical" M&E that aims at collecting all maximally possible data/indicators that leads often to information overflow and no/little feedback to program operations and hence no rapid effective public health action. The presentation will outline and discuss the progress made so far in developing effective surveillance-response system as well as the underlying research priorities such as the (i) dynamic detection and mapping of transmission, particularly low level transmission, also using e-/m-health; (ii) near real-time capture of population dynamics; (iii) modeling to establish the minimal essential databases/-sets and indicators to be collected in space and time; (iv) design of effective response packages tailored to different transmission settings and levels; and (v) comprehensive validation of approaches and response packages with regards to effectiveness within elimination programs. Surveillance-response systems integrated into the respective national health system will form the crucial cornerstone for any effective and integrated use of old and new control/elimination tools and, thus, for any successful malaria elimination program.

0406: Agre

Opening Doors Worldwide through Medical Science

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A major challenge faced by the United States, and other developed nations, is the unfavorable image we often project to the people of the developing world. When questioned, polls reveal that only a small fraction of individuals will view the U.S. favorably. This contrasts strikingly with how the same individuals respond when questioned about U.S. science and technology. Indeed, advances in science and technology are widely admired and may even open doors to hostile regimes. Advances in nanotechnology, microelectronics, computer software, agricultural sciences, and materials engineering are greatly desired. But more often it is the medical sciences that are universally embraced, since it is communicable diseases, such as malaria, that still restrict economic advancements throughout the developing world. To illustrate this, the speaker will present examples of individuals he encountered and events he experienced in which science opened doors worldwide. The greater lesson is that our science should not be restricted only to laboratories and classrooms.

1001 Improving Host Tolerance to Pathogens: The Role of Pressurized Oxygen in Cerebral Malaria

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Despite decades of research, cerebral malaria (CM) remains one of the most serious complications of *Plasmodium falciparum* infection, mainly in Sub-Saharan Africa, where, despite effective antiparasitic treatment, a significant proportion of individuals still succumb to CM and survivors develop long-term neurological sequelae. Although not completely understood, CM pathogenesis is marked by uncontrolled production of cytokines, coagulopathy and oxidative stress. These features affect cerebral microcirculation, endothelial cell integrity, leading to blood-brain barrier dysfunction, convulsions, coma and death. Hyperbaric oxygen (HBO) therapy has been successfully used in patients with numerous brain disorders such as stroke, migraine and atherosclerosis and recent studies demonstrate its efficacy in ameliorating several parameters related to ischemic process. Indeed, we have recently shown protective effects induced by HBO against experimental cerebral malaria (ECM) reducing expression of TNF-α, IFN-γ and IL-10 mRNA levels and preventing the breakdown of the blood-brain barrier. Here, using several approaches, we provide first evidence that pressurized oxygen modulates ICAM-1 and nitric oxide expression levels, alter oxidative stress, improves microcirculatory blood-brain flow, inhibits leukocyte adhesion into the cerebral microvasculature and reduces parasite load in the brain. Finally, because of the pressurized oxygen effects on several host parameters implicated in malaria severity, and the fact that HBO does not interfere directly on parasite development, we believe that HBO could act as an effective adjunct therapy by improving host tolerance to pathogens.

1002 Mechanochemical Synthesis of Trimethoprim-copper and its Antimalarial and Safety Evaluation in mice

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Combating malaria especially in the sub-Saharan Africa is identified by the World Health Organization (WHO) and United Nations in the Millennium Development Goals as an objective. Antimalarial medicines are central to any strategy for effective reduction of mortality related to malaria. Efficacy and safety of antimalarial medicines, as measured by their quality, are therefore essential in mitigating morbidity and reducing deaths. The mechanochemical synthesis and characterization of trimethoprim - copper complex and its antimalarial efficacy on *Plasmodium berghei* infected mice and toxicity evaluation are described. Derivatization of trimethoprim with copper enhanced the activity of the drug by significantly ($p< 0.05$) improving the suppression of parasitemia in established infection when compared with the controls. Trimethoprim-copper complex demonstrated to be more efficacious than pure trimethoprim while chloroquine was most efficacious in malaria parasite clearance. Administration of trimethoprim, trimethoprim-copper complex and chloroquine to mice for seven days caused significant reduction ($p<0.05$) in the activities of alanine and aspartate aminotransferases, alkaline phosphatase and lactate dehyrogenase in the liver, kidney and small intestine when compared with the control while there was a corresponding significant elevation in their plasma activities. Also there was a significant decrease ($p<0.05$) in the levels of PCV, Hb, RBC and lymphocytes and a significant increase ($p<0.05$) in WBC and neutrophil concentrations across all the treatment groups when compared with control. The result indicates that coordination of copper to trimethoprim by mechanical induction improved its antimalarial activity while the alterations in the investigated biochemical parameters suggest functional and structural toxicity. Thus, trimethoprim-copper complex may not be completely safe as antimalarial oral remedy.

1003 Understanding the Feasibility and Potential Impact of Screening for Asymptomatic Malaria in Households Where a Febrile Case of Malaria Has Been Reported in a Malaria Elimination Setting in Pailin Province, Western Cambodia

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Background: There is a need to strengthen active detection and response systems to all malaria cases in pre-elimination settings. In Cambodia, although several pilot focused screening and treatment attempts were conducted during the containment project, there is still a need to better understand the mechanisms by which reactive case detection strategies contribute to reduce and sustain transmission below the critical level in these settings.
Objectives: The long-term overarching goal of the project is to generate the necessary information to develop an interventional tool consisting of screening households with a malaria case and eliminating the asymptomatic reservoir.
Methodology: Data being captured may explain how foci of asymptomatic parasitaemia changes according to specific risk factors. Identified cases are being geo-referenced to assess the potential spatio-temporal relationship of asymptomatic cases following the detection of an index symptomatic case. A full assessment of the logistics, resources and personnel required to conduct this activity is being conducted to inform the potential feasibility of future scale-up of ADAT exercises in Cambodia.
Results: Since July 2013, 118 index households and 50 control households have been screened for malaria parasites. Preliminary results from this study will be presented and will therefore provide evidence on whether ADAT activities are operationally feasible and effective as an active case detection activity in an area where pre-elimination conditions already exist and a malaria alert system is fully functional.
Discussion and recommendations: This study will serve as the basis to evaluate a novel strategy to reduce the malaria reservoir and prevent malaria episodes amongst individuals harboring malaria parasites. This information will be a very valuable addition if not essential to the strategy to eliminate *P. falciparum* & *P. vivax* infections by 2015 and 2020, respectively.

1004 Evaluation of Field Feeding Assays In Preparation for Testing Transmission Blocking Vaccines In Mali

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Transmission blocking vaccine (TBV) is an integral part in malaria control and eradication. Methods to evaluate TBV efficacy is a critical element in TBV development. Feeding assays where laboratory-reared mosquitoes were fed with malaria-infected blood, together with vaccine-induced antibodies, have been used to evaluate efficacy of the vaccine to block parasite development in mosquito midgut. The current study aims to develop and standardize these methods in preparation of a Phase 1b trial in Malian Malaria endemic area testing a candidate TBV made with a surface protein Pfs25 of *Plasmodium falciparum* ookinete stage. Direct Skin Feeds (DSF), where mosquitoes were allowed to feed directly on volunteer's leg, and Direct Membrane Feeds (DMF), where mosquitoes were feed on blood collected from volunteers and place in an artificial membrane feeder. Volunteers were consented and recruited on site based on blood smears reading results for gametocytes and trophozoites. Lab-reared mosquitoes were tested and free of known transovarially transmissible rivuses. DSF procedure and safety: Over 140 DSF conducted, each used ~60 lab reared mosquitoes. The feeding rate is 95%, meaning each DSF volunteer received 50 bites. The procedure is well tolerated. The DSF participants are actively followed 24 hours post feed and passively followed 2 weeks post feeds. There was no DSF related adverse events. Mosquito infectivity by various feeding methods: The mosquito infection rate is the highest by DSF. Blood process for DMFA resulted in some loss of infectiousness of the parasite to mosquitoes, which may be improved by controlling processing temperature and minimizing the the processing duration. There are natually existing transmission blocking activity in volunteer's plasma, because replacing the autologous plasma with a serum from a malaria-naive serum pool retores parasite infectivity to mosquitoes. In conclusion, DSF is safe and better suited for evaluation of transmission blocking vaccine in malaria-endemic areas.
Grant/NIH/ Project Insurance: FWA #00005897

1005 Contrasting population biology of *Plasmodium falciparum* and *Plasmodium vivax* in Papua New Guinea: Implications for malaria control

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Knowledge of the genetic structure of target parasite populations can play a critical role in focusing antimalarial interventions to areas where they will have the greatest impact[1]. Our research on the highly endemic north coast of Papua New Guinea (PNG) shows that prior to the intensification of malaria control efforts, the Plasmodium falciparum population was organised into discrete subpopulations[2] whereas Plasmodium vivax populations were more diverse and less structured[3,4]. We are now gaining insight into patterns of population structure across a broader geographic range, and investigating the impact of intensified malaria control. Furthermore, high-resolution molecular tools are being developed to differentiate between local populations. These will be used to identify isolated parasite populations and routes of transmission, to monitor control efforts, and to identify the origins of outbreaks and imported infections in areas targeted for elimination. This research will be valuable to design strategies for malaria control and to progress towards elimination of malaria in the region.

1. Arnott et al. (2012) Malaria J. 11:14
2. Schultz et al. (2010) Malaria J. 9: 336
3. Koepfli et al. (2013) PLoS ONE 18;8(6)
4. Jennison et al. In preparation

This research was supported by Project Grants 488221 and 1003825 from the National Health and Medical Research Council of Australia.

1006 Development of Antimalarial Compounds with New Mechanisms of Action using Next-Generation Synthesis

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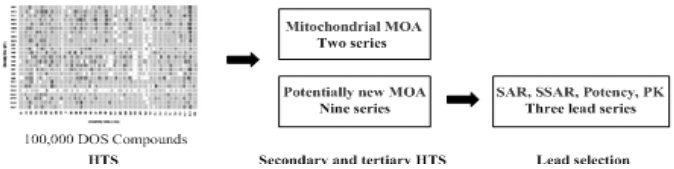
Malaria is one of the most deadly infectious diseases with approximately one third of the world's population at risk and mortality estimated at 781 thousand deaths per year.[1] Given that resistance to currently available therapeutics is an increasing problem, there is a pressing need for the discovery of new classes of compounds not related to existing pharmacophores, but with unique core structures more likely to have novel mechanisms of action. We have reported the preparation of a screening collection of 100,000 diverse small molecules using a diversity oriented synthesis (DOS) strategy; combining the complexity of natural products and the efficiency of high-throughput synthesis.[2] The performance of this collection in the phenotypic screening of *Plasmodium falciparum* blood-stage parasites will be discussed. Our goal is to discover antimalarials with new mechanisms of action (MOA) and screening hits were grouped into three categories based on counterscreening studies. Potent antimalarials were discovered with suspected known mitochondrial targets as well as potentially novel MOA. Medicinal chemistry studies have been initiated on three series from the latter category, which have attractive potency, SAR, SSAR and pharmacokinetic properties.



References
1) World Health Organization, Geneva, *World Malaria Report*, 2010.
2) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D. t.; Liu, H.; Lowe, J. T.; Marie, J. C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B. C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y. L.; Fass, D. M.; Reis, S. A.; Zhao, W. N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. An aldol-based build/couple/pair strategy for the synthesis of medium- and large-sized rings: discovery of macrocyclic histone deacetylase inhibitors. J. Am. Chem. Soc. 2010, 132, 16962-16976.

1007 Evaluating PfGap50 as a component of novel recombinant subunit vaccines derived from plants

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One key objective in the Fraunhofer Foundation project "Innovative technologies to manufacture ground-breaking biopharmaceutical products in microbes and plants" is the development and production of novel malaria vaccines using plant-based systems. Plants are ideal production platforms because their quality control and subcellular targeting capabilities allow the efficient production of novel multi-stage and -component subunit vaccines in the optimal biochemical environment. We have thus produced PfGap50 variants targeted to different compartments by transient expression in *N benthamiana* leaves.

The 44.6-kDa transmembrane protein PfGAP50 of *Plasmodium falciparum* has previously been described as part of the inner membrane complex, anchoring the actin-myosin motor of the invasive stages. Recently, we showed that during gametogenesis in the mosquito midgut, PfGAP50 relocates from the inner membrane complex to the plasma membrane. Here it functions as a receptor for the complement regulatory protein FactorH, which the newly formed gametes bind from the blood meal to evade lysis by human complement. Because antibodies against PfGAP50 can activate the classical and the alternative complement pathway, the transmembrane protein represents a promising novel candidate for transmission blocking vaccines.

We have successfully produced His-tagged variants of PfGap50 in plants, targeted to the ER, the apoplast and the plastids. The corresponding yields were 60 mg/kg (ER), 80 mg/kg (apoplast) and 120 mg/kg (plastids). All three proteins could be harvested 5 dpi and were extracted by blending with two volumes of PBS containing 2 µM $CoSO_4$ and 0,5 M NaCl. After centrifugation to remove debris, the proteins were purified by Ni^{2+} IMAC, reaching 85% purity. The ER and plastid variants were dialyzed against PBS, tested for their ability to bind Factor H and used for immunization of rabbits. Resulting sera will then be tested for transmission-blocking activity using a standard membrane feeding assay.

Our results demonstrate that functional PfGap50 can be produced efficiently in plants, further adding to our portfolio of *Plasmodium* spp. antigens that can be used to develop the next generation of combination vaccines against malaria.

1008 Cyclic peptides mimicking FK506 as selective *Plasmodium falciparum* inhibitors

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FKBP35 is the only immunophilin FK506-binding protein type present in *Plasmodium falciparum*. This protein is very well represented in the human body, with 14 homologs, and in other organisms. The *Plasmodium* protein itself contains an FK506 binding domain (FKBD), a tetratricopeptide repeat domain that is presumably involved in protein–protein interactions, and a calmodulin-binding site. Human FKBPs can contain one or more FKBDs, sometimes in combination with tetratricopeptide repeat and/or other domains.

The FKBD has peptidyl-prolyl *cis-trans* isomerase (PPIase) activity and a substrate for this enzymatic reaction is the peptide ALPF. Proline, with its unusual cyclical structure, is responsible for the conformer stabilization in the *cis*- form, in contrast with the energetic preference for the *trans*- conformation in peptide bonds not containing proline. FK506 (Tacrolimus) has antimalarial activity and it is a macrolactone produced by the bacterium *Streptomyces tsukubaensis* with a structure reminiscent of a cyclic peptide and containing a proline-mimicking piperidine group.
This study investigates the capacity of cyclic peptides selective for *P. falciparum* FKBP35 to mimic the natural ligand FK506. The databases include several amino acids structure lengths, from a minimum of 4 up to 7.
The compounds were designed, selected using a pharmacophoric screening, and simulated *in silico* against *P. falciparum* FK506 binding domain and all the 22 human FKBDs. The best hits were then tested *in vitro* for antimalarial activity and for *Pf*FKBD binding using a thermal melt binding assay and a spectrophotometric PPIase enzyme inhibition test.

1009 Identification of a novel selective inhibitor of *Plasmodium falciparum* histone deacetylase 1

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Histone deacetylase (HDAC) inhibitors have been demonstrated to be effective inhibitors of drug resistant *P. falciparum*. The approved drug suberanilohydroxamic acid (SAHA) and experimental drugs belinostat and panobinostat all kill the parasites *in vitro*. Unfortunately these compounds were designed as inhibitors of the human isoform and therefore have off target effects on the host. We used high-throughput docking methods to identify possible new inhibitors for *P. falciparum* HDAC1. Here we report three new HDAC1 inhibitors. All three compounds kill *P. falciparum* 3D7 in the low nanomolar range *in vitro* (EC_{50}'s 142-745 nM). We used the HDAC enzyme assay to assess their activity against the *P. falciparum* HDAC1 and human HDAC1 proteins. All three compounds inhibited the *P. falciparum* HDAC1 in the low miromolar range (IC_{50}'s 2.9 micromolar, 1.8 micromolar and 4.6 micromolar). While two of the compounds had similar activity for the human HDAC1 (IC_{50}'s 2.8 micromolar and 0.6 micromolar), one of the compounds inhibited the *P. falciparum* HDAC1 with an IC_{50} of 4.6 micromolar but did not inhibit the human form (IC_{50} > 10 mM). Here we present a novel compound with selective activity for the *P. falciparum* HDAC1. This demonstrates that designing specific *P. falciparum* HDAC1 inhibitors is possible and provides a possible new lead compound for the treatment of drug resistant strains.

1010 Apoptosis of $CD4^+$ T Cells in Malaria Infection Caused by *Plasmodium vivax*

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Malaria is considered an important public health problem in Latin America countries being the *Plasmodium vivax* the main causative agent of the disease in Brazil. Lymphocytopenia, reduction of lymphocytes number, has been reported in subjects with malaria episode, and during the treatment the levels of these cells are normalized. Despite the lymphocytopenia is well established in the literature, the mechanism involved on it is not still understood. Some studies suggest that the reduction in T lymphocytes is due to the reallocation of these cells to inflammatory sites followed by reemergence of these cells during the treatment. Other studies considered the apoptosis mediated by Fas/FasL system as the causative of the observed effect. Our hypothesis is that the apoptosis occurs in $CD4^+$ T cells and contributes, at least in part, to the lymphocytopenia. Thus, the aim of this study was to investigate the occurrence of apoptosis in $CD4^+$ T cells and their pathways in subjects naturally infected with *P. vivax* from a Brazilian endemic area (Porto Velho – RO). The immunophenotyping was performed with peripheral mononuclear cells (PBMC) from 20 infected subjects and 11 healthy donnors using staining with Annexina-V and Propidium Iodide (PI) and anti-CD4 antibody. The data acquisition was made using Flow Cytometry. PCR array (RT^2 Profiler PCR Array – Human Apoptosis) was performed to investigate 84 genes involved in different apoptosis pathways, using cDNA from $CD4^+$ T cells. *P. vivax* infected subjects showed higher percentage of $CD4^+$ T cells in early (Annexina-V^+) and late (Annexina-V^+/PI^+) apoptosis when compared to non-infected individuals ($p<0,0001$). It was observed significant differences in gene expression of BCL-2, TNF receptors and caspases family's. Our data show that *P. vivax* infection induces apoptosis in $CD4^+$ T cells from human host. It is important to highlight that this study is the first one to evaluate the signaling pathways of apoptosis in $CD4^+$ T cells in malaria caused by *P. vivax*.

Key-words: Malaria; *Plasmodium vivax*; Apoptosis
Financial support: CAPES; CNPq; FAPEMIG

1011 Identifying the mechanism of action among compounds of the Malaria Box using anti-apicoplast and gametocytocidal screening

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Artemisinin-based combination therapies are currently the preferred first-line antimalarial against *Plasmodium falciparum* (the deadliest of the five species that infect humans). However, the rapid development of resistance to the partner drug and the recent artemisinin resistance demonstrated in the Cambodia–Thailand border area vindicates the constant need for development of new drugs against different targets to expand our repertoire of antimalarials that can be used in combination therapies and has highlighted the relevance of more effective transmission-blocking drugs.
We screened 400 compounds from the Malaria Box, which is available to the scientific community through Medicine for Malaria Venture, using apicoplast-targeting and gametocytocidal phenotypic assays to identify their potential mechanism of action. We identified only one compound that specifically targeted the apicoplast in the malaria parasites and another twelve compounds that were active against late-stage gametocytes with half-minimum inhibitory concentration values below 1 μM. During our screening, we stressed the identification of compounds showing activity against both asexual and sexual intraerythrocytic stages, which allowed us to identify promising lead compounds.
Our continuing efforts to identify the molecular target(s) of these compounds will reveal cellular functions that are essential in both asexual and gametocyte stages; thus, more effective drugs can be developed to both cure malaria and stop its transmission.

Funding provided by the Fralin Life Science Institute, Jeffress Memorial Trust of Virginia (J-1058), and Virginia's Commonwealth Health Research Board (208-03-12) to M.B.C.

1012 Low-dose primaquine to reduce the transmission of *Plasmodium falciparum* malaria: a roadmap update

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As the only commercially available drug capable of clearing mature *Plasmodium falciparum* gametocytes, primaquine offers a unique ability to stop malaria transmission from humans to mosquitoes. Despite its potential role in malaria control and elimination, the widespread adoption of primaquine has been limited due to its hemolytic effects in G6PD-deficient individuals. While hemolysis is understood to be dose dependent, there are limited data to support the safety and efficacy of current WHO recommendations to give, in conjunction with an artemisinin-based combination therapy, single dose primaquine (0.25 mg/kg) to all *P. falciparum* cases in areas threatened by artemisinin resistance or approaching malaria elimination.

In March 2012, a group of experts from academia, industry, non-governmental organizations, malaria programs, and donors convened to discuss existing data on the use of primaquine as a malaria transmission blocker. The meeting served to identify hurdles and to propose a roadmap to establish whether low-dose primaquine can be safely and effectively deployed to block *P. falciparum* malaria transmission in sub-Saharan Africa.

Since then, much knowledge has been gained on the pharmacokinetics, safety, and efficacy of low-dose primaquine. In late 2013 and early 2014, the group of experts will reconvene to discuss roadmap progress and update knowledge gaps to determine if and how low-dose primaquine can be implemented as a malaria transmission blocker. We will provide an update of ongoing and planned primaquine studies with a focus on study design and endpoints. We will highlight existing gaps and welcome discussion and seek advice from experts.

We thank the Bill & Melinda Gates Foundation for financial support (Award A115501).

1013 Anti-malarial efficacy of ZRC032a and ZRC032d in *Plasmodium berghei* infected mouse model

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The control of malaria is challenged by drug resistance leading to the requirement of new antimalarial drugs. Calpain, a cysteine protease family, which is a central mediator for essential parasitic activities, is a potential drug target for malaria parasite. Calpain inhibitor, *N*-Acetyl-L-leucyl-L-leucyl-L-norleucinal (ALLN), is proposed to inhibit parasite proliferation by suppressing haemoglobin degradation. In a previous study, thirty two ALLN derivatives were synthesized and evaluated anti-malarial activity *in vitro*. ZRC032a and ZRC032d among the ALLN derivatives showed excellent anti-malarial activity.
In this study, the two ALLN derivatives were evaluated for anti-malarial efficacy in *Plasmodium berghei* infected mouse model. ICR mice (n = 8) were infected with 10^6 *P. berghei*-infected erythrocytes by ip injection. After parasitemia reaches 5-10%, ZRC032a and ZRC032d were injected once daily for 4 days at 0.5 and 10 mg/kg dose. Chloroquine was used as a positive control and iv injection of chloroquine was performed under the same
Our results showed that ZRC032a and ZRC032d exhibited excellent anti-malarial efficacy in *P. berghei* infected mice with high survival and low parasitemia. Therefore, these results indicated that the two derivatives could be new candidates for anti-malarial drugs.
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. NRF-2010-0020801).

1014 Homology modeling of *Plasmodium falciparum* calpain active form and covalent docking study for the anti-malarial drug discovery

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Malaria causes estimated 2-3 million deaths annually, and most deaths by malaria are caused by *Plasmodium falciparum* which is one of the 5 species of malaria parasites. Although there are several anti-malarial agents such as Chloroquine, discovery of novel anti-malarial drugs is strongly needed due to the increasing resistance of malaria parasites to available drugs. Since the *Plasmodium falciparum* calpain (*Pf*-calpain) is believed to be an essential mediator of merozoite invasion, it could be a promising target for the discovery of new anti-malarial drugs.
Pf-calpain is a cysteine protease which might have an alternative Ca^{2+}-independent regulatory mechanism. Based on the enzymatic assay, it is found that *Pf*-calpain can be active only with the catalytic subdomain IIa. The multiple sequence alignment shows that the catalytic subdomain IIa of *Pf*-calpain contains all residues necessary for the catalytic triad (Cys-His-Asn) formation. Our homology modeling study suggests that the subdomain IIa of *Pf*-calpain makes the active site holding the catalytic triad residues in their appropriate orientation for catalysis. The mutation study further supports that those residues are functional to have the enzymatic activity of *Pf*-calpain.
In order to discover the potent *Pf*-calpain inhibitors, several dipeptidyl amide analogs were designed and synthesized based on the covalent inhibitor ALLN. Among them, some compounds show strong anti-malarial activities. Using our homology model, we carried out the covalent docking study of the compounds. The docking results along with our homology model could provide useful information for discovery of new anti-malarial drugs.

1015 FightMalaria@Home – finding novel targets for antimalarial compounds

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New antimalarial drugs against novel targets are urgently needed as *Plasmodium falciparum* continues to evolve resistance to available medication. Over 3 million compounds have been screened against malaria and over 20,000 have been shown to kill the parasite in whole organism growth assays. To identify potential targets for these hit antimalarial compounds we are docking each compound against the 1400 models of suitable proteins from the *Plasmodium falciparum* 3D7 genome. To complete the 190m docking calculations, we have distributed these to over 20,000 volunteer computers in 135 countries using BOINC. The first results, using the MMV MalariaBox collection of 400 hit compounds, are reported here. For each ligand we present the top 20 most likely receptors based on normalised Z-scores. To facilitate prioritisation we include the laboratory EC50, pEC50, estimated binding energy and estimated ligand efficiency. In addition we provide the BLAST scores against both the human genome (to identify proteins with poor homology to host proteins) and PDB structural database. Similarly, we present the top 20 ligands for each protein receptor model tested. Using this data we have found three novel histone deacetylase (HDAC) inhibitors from *in vitro* validation studies for the top 20 docking hits. All data will be freely available through our website (http://bioinfo-casl.ucd.ie/fmah/). This data should provide novel targets for future drug discovery efforts, with the added benefit that each of the ligands used in this study is already able to effectively kill *Plasmodium falciparum*.
The goal is to find novel targets that have not been inhibited by established antimalarial drugs.

1016 Intermittent parasite clearance in schools in Mali: Impact on malaria, anaemia, and cognition

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Historically malaria eradication was associated with increased literacy and years of schooling in Mexico, Brazil and Sri Lanka; and similar gains might be expected with renewed elimination efforts. Recent randomized trials also provide evidence that malaria prevention in schoolchildren can improve cognition and school performance.

A cluster-randomized controlled trial was conducted in 80 primary schools in Sikasso Mali. Children in intervention schools received malaria prevention education to promote net use, together with a single round of intermittent parasite clearance (treatment dose given irrespective of infection status) given at end of the transmission season in November 2011. Marked reductions in malaria parasitaemia and gametocyte carriage were seen at follow-up in February 2012 in intervention compared to control schools. The effect was sustained until May 2012, and associated with a 10-fold reduction in gametocyte prevalence at the beginning of the next transmission season. Parasite clearance was also associated with a decrease in anaemia (OR=0.56, 95% CI 0.39-0.78, p=0.001), and increase in sustained attention ($p<0.001$).

These results add to a growing body of evidence that asymptomatic malaria infection impairs cognitive performance in schoolchildren. Intermittent parasite clearance in schools has potential as a cost-effective strategy to improve the health and education performance of school-aged children. The approach is particularly suited to areas of seasonal transmission where a single annual treatment can be given at the end of the transmission season. The role that malaria control in schools can play in transmission reduction and the potential effect of malaria elimination on cognitive development and education in malaria-endemic areas will be discussed

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WITHDRAWN

1018 A regional-scale, high resolution dynamical model for malaria

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Malaria transmission models are useful tools for understanding the epidemiology of the disease, as well as for the development Early Warning Systems (EWS) in affected regions. Dynamical models explicitly model the key equations describing the disease dynamics. Unlike statistical models, dynamical models are not confounded by sparse or short data records. Weather factors such as temperature and precipitation regulate many key cycles of the malaria system, and thus they should be incorporated into the malaria models. Vector-host dynamics is also key for determining disease occurrence in a given area. Therefore, vector-host interations should be incorporated in the models to effectively differentiate between peri-urban and rural malaria. These vector-host interactions have been rarely considered in previous malaria modelling attempts.
Here, we introduce a new open source high resolytion O(10km) dynamical malaria model (VECTRI) that represents the effect modification of temperature on key cycles of the malaria system such as the larvae growth, sporogonic and gonotrophic cycles via dynamical equations. The model explicitly resolves these cycles dividing them into discrete fractional bins depending on the local air and water temperatures. The model also includes a simple surface hydrology model that provides a calculation for the potential breeding sites provided by temporary water bodies and ponds. Moreover, the model explicitly allows for vector-host interactions accounting for population density in the calculation of transmission probabilities. This novel feature of VECTRI enables the model to differentiate between urban, peri-urban and rural environments. Additionally, it permits the future incorporation of intervention measures and transnational migration into the modelling framework. We then interface the VECTRI model with two state-of-the-art weather prediction systems to develop a pilot Malaria EWS for Africa at a O(25 km) resolution. The EWS provides forecasts of malaria prevalence and intensity up to three months in advance and has shown skill two to three months ahead.

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WITHDRAWN

1020 Molecular polymorphism of *mdr1* and *dhfr* in *Plasmodium vivax* from Mexico and Nicaragua

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Plasmodium vivax is the main species causing malaria in the Mesoamerican region. Clinical studies and *in vitro* assays to detect drug resistant parasites in the region are complicated and too expensive. To advance toward malaria elimination and contribute to the molecular surveillance of drug resistance, *P. vivax* dihydrofolate reductase (*pvdhfr*) and multidrug resistance 1 (*pvmdr1*) gene polymorphism was analyzed.

Parasites from southern Mexico and Nicaragua were obtained from affected patients. Total genomic DNA was extracted and used to amplify *pvdhfr and pvmdr1 genes, and gene fragments were sequenced*. All Mexican parasites had *pvdhfr* and *pvmdr1* sequences similar to that of Salvador I; for *pvmdr1* only one synonymous mutation was present at codon 529 (frequency of 95.7%). While, in *pvdhfr,* 18.5% of the Nicaraguan parasites had a synonymous mutation at codon 206 and 12.5% had an insert TSGGDN at codon 310, the latter was only present in samples from the pacific coast and were previously reported in parasites from Papua New Guinea. For *pvmdr1,* non-synonymous mutations were detected at codons 500 D/N (22.4%), 958 T/M (100%), 976 Y/F (83%), 1076 F/L (100%) and two synonymous mutations at codons 529 (A/G) and 1021 (C/T).
There were important differences in *pvdhfr and pvmdr1* polymorphism among sub-regions and the importance for drug resistance and parasite relationships will be discussed. No polymorphisms associated to pyrimethamine resistance were detected.

This work was supported by CONACyT- CB-2009-01 -0131247

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WITHDRAWN

1022 Playing to learn malaria prevention and control: the case of Malaball board-game

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Malaria is Africa's leading cause of child mortality and accounting for about 90% of global malaria deaths. Most public health promotion campaigns to combat malaria in Africa use the mass media which often tend to be expensive as they are tailor-made for specific communities and are not interactive. Often campaigns cannot be repeated as they are expensive and again are not transferable. People soon forget the messages as the campaigns are not repeated and that makes the campaign ineffective.
Games have been used successfully in health promotions and they have proved to be effective in engaging the target audience and also help the people to remember the messages as they play the games repeatedly. Malaball is a board-game developed and intended to be used in health promotion campaigns of malaria prevention and control in Ghana. The board-game was developed to be interactive using football as a metaphor, as the game is very popular amongst both genders in Ghana.
The aim of the project is to design and develop an affective and effective interactive communication tool to be used in the education of malaria prevention and control. Prototyping the board-game on public health students, the feedback themes was 'entertaining way' 'visual method', 'interactive' and 'informative'. It was found that the game engages its audience, provides fun and makes the malaria prevention and control education easier to understand and practical.

1023 A Simple Sample Preparation Device for Improvement in RDT Performance for the Detection of Malaria

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The advent of point of care (POC) diagnostic tools has changed the face of malaria eradication programs in low-resource areas, often plagued by poverty, absent or intermittent electricity, hot and humid environmental conditions as well as a lack of skilled clinicians. Rapid diagnostic tests (RDTs) were developed to circumvent these challenges in the form of a rapid, low-cost, easy to use test. Despite their many advantages, diagnosing asymptomatic carriers (≤200 parasites/µL) presents a major hurdle for complete malaria eradication. The World Health Organization (WHO) annually reviews all malaria RDTs manufactured for diagnostic use, and sets the limit of detection for these tests at 100 parasites/µL. There are an estimated 200 types of tests manufactured, and less than 10% of those tests are effective at detecting 200 parasites/µL parasite densities. Poor manufacturing standards and storage conditions render many brands inoperable and unreliable. We have recently reported the creation of a low-resource extraction cassette that can extract, purify and concentrate the most common sub-Saharan malarial biomarker, *Plasmodium falciparum* Histidine Rich Protein II (*pf*HRPII), from a blood sample, in less than 30 minutes. By preloading a series of aqueous buffer solutions separated by oil surface tension valves into a single length of tubing, we were able to purify the protein biomarker from asymptomatic blood samples with greater than 50% efficiency by processing biomarker bound magnetic particles through the cassette using a handheld magnet. When the extraction cassette was coupled to commercially available RDTs, a marked increase in performance of the tests was observed. Regardless of the WHO detection score, we found all brands to be improved within asymptomatic levels of infection--a regime of diagnosis that RDTs have traditionally been unable to detect. Both the visual signal and limit of detection were enhanced at least 4-fold, with two brands having a limit of detection of 3 parasites/µL. The ability to transform RDTs from a confirmative test to a quantitative one would be invaluable for malaria eradication campaigns.

1024 Vectored antibody gene delivery protects mice against sporozoite challenge

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Plasmodium sporozoites can be neutralized *in vitro* by monoclonal antibodies (MAb) against the circumsporozoite protein (CSP). Passively transferred MAb against *P. falciparum* CSP can block liver invasion by sporozoites of a transgenic rodent parasite that expresses *P. falciparum* CSP (Pb-Pf), preventing infection in mice. Despite this, attempts at targeting CSP for a vaccine have fallen short of expectations, in part due to inability to induce durable high-titer antibodies. A single un-neutralized sporozoite can initiate infection, necessitating sustained high-titer neutralizing antibodies for lasting protection.

Recently, David Baltimore's laboratory developed an adeno-associated virus type 8 (AAV8) platform that efficiently delivers pre-formed MAb genes *in vivo* and directs sustained, high-level MAb production. With the Baltimore lab, we have adopted that technology to express humanized MAbs against the central repeat region of the CSP protein of *P. falciparum* in mice. Mice developed high titer human IgG antibodies as early as 1 week post transduction and levels have remained constant for more than 20 weeks at 200 to 1000 µg of IgG/ml. In 70 percent of mice transduced with CSP MAb humanized 2A10 (h2A10), and challenged intravenously with 10^4 Pb-Pf sporozoites, parasite liver burden was reduced to below the level of detection. h2A10-transduced mice challenged by infected mosquito bite displayed a statistically significant delay in time to patency, and in a separate experiment, 70 percent of mice were sterilely protected. Examination of antibody levels in individual mice revealed that all mice with human IgG concentrations above 1mg/mL were completely protected. This suggests that exceeding this antibody threshold results in consistent sterile protection and establishes that vectored MAb gene delivery has the potential to be an effective form of malaria control.

1025 Relationship between malaria incidence and IgG levels to Plasmodium falciparum merozoite antigens in Malian children: impact of hemoglobins S and C

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Heterozygous hemoglobin (Hb) AS (sickle-cell trait) and HbAC are hypothesized to protect against Plasmodium falciparum malaria in part by enhancing naturally-acquired immunity to this disease. To investigate this hypothesis, we compared antibody levels to four merozoite antigens from the P. falciparum 3D7 clone (apical membrane antigen 1, AMA1-3D7; merozoite surface protein 1, MSP1-3D7; 175 kDa erythrocyte-binding antigen, EBA175-3D7; and merozoite surface protein 2, MSP2-3D7) in a cohort of 103 HbAA, 73 HbAS and 30 HbAC children aged 3 to 11 years in a malaria-endemic area of Mali. In the 2009 transmission season we found that HbAS, but not HbAC, significantly reduced the risk of malaria compared to HbAA. IgG levels to MSP1 and MSP2 at the start of this transmission season inversely correlated with malaria incidence after adjusting for age and Hb type. However, HbAS children had significantly lower IgG levels to EBA175 and MSP2 compared to HbAA children. On the other hand, HbAC children had similar IgG levels to all four antigens. The parasite growth-inhibitory activity of purified IgG samples did not differ significantly by Hb type. Changes in antigen-specific IgG levels during the 2009 transmission and 2010 dry seasons also did not differ by Hb type, and none of these IgG levels dropped significantly during the dry season. These data suggest that sickle-cell trait does not reduce the risk of malaria by enhancing the acquisition of IgG responses to merozoite antigens.

1026 Reducing malaria transmission, targeting Plasmodium falciparum gametocytes in the human host

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Background: Transmission-reducing interventions are now key elements in the malaria control and elimination agenda. However, little is known about the immune responses directed at circulating *P. falciparum* gametocytes in humans, knowledge of which would be useful in the development of intervention strategies to reduce and block malaria transmission.
Methods: Consequently, antibody responses to surface antigens of *P. falciparum* gametocyte-infected RBCs (GSA) were determined in plasma samples from malaria asymptomatic Ghanaian school children between the ages of 5-17 years. These children were screened for malaria parasites and treated with dihydro-artemisinin piperaquine if positive, one week after first sample collection, and followed up weekly for one month. Gametocytes were produced from a laboratory adapted parasite line, 3D7 and a recent patient isolate from Kenya (HL1204).
Results: From a cohort of 113 children, all the children harboured plasma antibody responses that recognized GSA on a proportion of mature gametocyte-infected RBCs of 3D7 by flow cytometry. However, 56% of the children exhibited strong antibody responses to GSA (immune response above the median within the cohort per sampling time) by both the proportion of mature gametocytes bound to antibodies and the intensity of the antibody binding to GSA. Longitudinal data provided an additional 10% developing strong GSA responses during the 1 month follow-up. There were some children with antibody responses fluctuating around the median immune response within the cohort. Children with GSA antibodies present at enrolment, were less likely to develop new gametocytaemia at subsequent visits (odds ratio = 0.29, 95% CI 0.06 - 1.05; P = 0.034). 3D7a is a laboratory adapted parasite line so a selection of positive plasma samples was tested against mature gametocyte preparations from HL1204 and strong plasma antibody binding was again shown. No binding to the surface of RBCs infected with immature gametocytes of HL1204 was detected.
Conclusion: A proportion of malaria infected asymptomatic children harbour plasma antibodies which were strongly recognized by antigens on the surface of mature gametocyte-infected RBCs. Strong plasma antibody responses may contribute to the control of gametocytaemia *in vivo*. Ghanaian GSA responses recognized antigens on both 3D7 and an east African parasite line, suggesting these are relatively conserved.

1027 Residual transmission, a challenge for malaria elimination

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Scaling up of insecticide treated nets (ITNs) and expanding indoor residual spraying programs (IRS) have contributed to a substantial malaria decline. Although with a maximum coverage of ITNs and IRS even greater gains could be achieved (including malaria elimination in a number of countries and regions), malaria transmission will persist in some regions. This so-called residual transmission is due to the fraction of the vector population not affected by the classic vector control tools. Indeed, IRS only affects indoor resting mosquitoes and ITNs only target night-biting mosquitoes. Moreover vectors with zoophilic tendencies will be less exposed to ITNs. Although the relative importance of residual transmission might be low, it will compromise malaria elimination.
In our presentation, we will show that even before widespread use of vector control measures, a heterogeneity in behaviour between and within malaria vector species was present. Moreover, several studies have shown that this behaviour can be genetically determined. Because of the heterogeneity in behaviour, mosquitoes have different opportunities to escape from the killing or excito-repellent action of insecticides used in ITNs or IRS. Different shifts in vector species or vector behaviour observed after widespread use of ITNs or IRS will be discussed. Therefore, further reduction of malaria will only be feasible if the protection gap is closed by implementing additional effective vector control tools.
One of the proposed additional vector control tools is the widespread use of topical repellents which is currently evaluated in Cambodia (MalaResT project). Preliminary results will be presented of the entomological surveys carried out in this project. For DEET and picaridin repellents, a heterogeneity in repellent sensitivity was observed between wild southeast Asian vector species. This heterogeneity in sensitivity might result in a geographically heterogeneous epidemiological impact of repellent use for malaria control.

1028 Epidemiology and transmission of persistent malaria in Chennai-a metropolitan city in India

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Malaria is indeed a serious public health problem, causing high morbidity and mortality in the Indian subcontinent. Chennai city is endemic for malaria and the transmission is perennial with a peak between July and October. During the last two decades, the city alone contributed 45.3 to 78.8% of total cases annually to the malaria burden in Tamil Nadu state. *Plasmodium vivax is* the predominant parasite species accounting for 93.6 to 99.8% of the prevalence in Chennai. *Anopheles stephensi*, the vector responsible for malaria transmission in the city, breeds mainly in clean/clear water such as overhead tanks, wells, cisterns besides, roof gutters, curing pits in construction sites, fountains and ornamental tanks. Despite the routine anti malaria operations carried out by the programme since the initiation of Urban Malaria Scheme (UMS) in 1973, malaria still remains to be a persistent problem due to multifaceted reasons. The present system of malaria control envisaged is unlikely to eliminate malaria due to rapid rate of urbanization and other socio-ecological reasons. The eco-epidemiology project as part of Center for the Study of Complex Malaria in India initiated includes (1) community study to determine the prevalence and incidence of asymptomatic and symptomatic malaria;(2) clinic study to investigate the disease outcome in infected individuals and monitoring for continued and emerging drug resistance. The study confirmed the diagnosis of malaria parasites by PCR, is 3.5 times more compared to conventional microscopy and 8 times more in asymptomatic carriers indicating higher rate of sub patent parasitemia revealing there is underestimation of disease prevalence.

1029 The structure of the cyclic guanosine monophosphate-dependent protein kinase (PKG) from Plasmodium falciparum

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Plasmodium cGMP-dependent protein kinase (PKG) is the mediator of the second messenger cGMP, and has been implicated essential roles in gametogenesis and blood stage schizogony (in *P. falciparum*) as well as in ookinete differentiation and liver stage schizogony (in *P. berghei*). It is known to be the target of tri-substituted pyrroles and tri-substituted piperazines, both of which have been used as chemical probes to help establish PKG's functions in malaria parasites. We present the first ever crystallographic structure of PKG from *P. falciparum* and *P. vivax*, which also happens to be the first PKG structure from any organism. These structures reveal for the first time the auto-inhibited conformation of PKG. One of our crystal structures contains a tri-substituted piperazine, namely Compound 2, and confirms that the inhibitor targets the hydrophobic pocket presented by the parasite enzyme's threonine gatekeeper. Our structures enable us to present a hypothesis about the previously unknown mechanism of activation of PKG. Furthermore, it provides the basis for structure-guided discovery of inhibitors of a potential target of transmission blocking.

1030 Inducing potent humoral and cellular responses to multiple sporozoite and liver-stage malaria antigens using pDNA

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Current evidence suggests a vaccine candidate that elicits humoral and cellular responses to multiple sporozoite and liver-stage antigens may be able to confer protection against *P. falciparum (Pf)* malaria. Here, we report the preclinical assessment of a DNA vaccine approach that targets four *Pf* antigens: CSP, LSA1, TRAP, and CelTOS (MAV4). Synthetic DNA sequences were designed and delivered using electroporation (EP). In mice, DNA+EP delivery induced IFNγ production as measured by ELISpot (3172 SFU), and antibodies to all antigens (OD=1 >1,000). Antigen-specific responses were found in both the CD4+ (1.5%) and CD8+ (2.9%) splenic T-cell compartments. Further, hepatic CD8+ T cells produced CSP- (0.6%) and LSA1- (1.5%) specific IFNγ. A chimeric *Pf-P. berghei (Pb)* CSP sporozoite challenge model, a *Pb* sporozoite that contains the N-terminus of *Pf* CSP, was used to evaluate if immune responses induced by the *Pf* CSP component of MAV4 could decrease liver-stage parasite burden. Immunization with the synthetic pDNA *Pf* CSP resulted in a significant 26-fold decrease in liver *Pb-Pf* levels 40 hours after challenge. In Rhesus macaques, MAV4 elicited antibodies to all antigens (OD=1 > 500), cellular responses by IFNγ ELISpot (2035 SFU), and in both the CD4+ (0.6%) and CD8+ (0.7%) T-cell compartments. Notably, the majority of antigen-specific CD8+ T cells were Granzyme B+ (0.7%) and T-bet+ (0.5%), suggesting the potential for cytotoxic and effector functions. In conclusion, DNA+EP delivery elicits strong immune responses against multiple malaria antigens and merits further study in clinical trials.

1031 Malaria Eradication and Health System Strengthening: Impact of Enhanced Surveillance with Available Technologies

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Health Systems Strengthening (HSS) has received increasing attention as a pivotal step to reduce malaria morbidity and mortality by reaching universal coverage and sustaining achievements in the pre-elimination/eradication stage.
HSS refers to activities and initiatives that improve health systems of countries, by acting on one or more of the system building blocks: service delivery, health workforce, information, medical products, financing and leadership/governance. The ultimate goal is to achieve more equitable and sustainable health services and health outcomes. In particular, strengthening disease surveillance at local and national levels has been identified as an urgent priority by WHO malaria programme. Ironically, current evidence shows malaria surveillance systems are weakest where malaria burden is greatest. Elimination and eradication goals therefore require effective surveillance strategies to monitor progress.
Fionet™ (Fio Corporation, Toronto, Canada) uses readily available technologies (RDTs, mobile telephone networks, and cloud computing) to deliver HSS. At Point-of-Care (POC), Deki Readers™ provide health care workers (HCW) with highly accurate diagnosis and case management guidelines, timely feedback on performance as well as the ability to report data in almost real-time. At higher levels in the health care system, by logging into Spiri™ health program managers are able to remotely monitor qualitative and quantitative field activities by health workers (diagnostics and case management), identify areas for improvement, and perform data-based resource allocation decisions.
Field studies using components of Fionet have shown high diagnostic performance of Deki Reader in automating interpretation of mRDTs, equivalent to experts, and high degree of usability by intended users. Collection and transmission of patient information has been done by all users, transmitting it to a central database hosted in a cloud information system using local cell phone networks. Over 95% of records reach the database in less than 24 hours.
Larger deployments of Fionet in Sub-Saharan Africa have demonstrated the ability of the system to perform disease surveillance, improve monitoring & evaluation of programs, and provide remote quality control of diagnostics being performed at POC. Furthermore, Spiri has allowed program managers to make information based adjustments to the program (re-training of HCW, allocation of resources, supply-chain process, etc) and improve on case management. Fionet has been shown to be highly cost-efficient in malaria control programs using mathematical modelling.
Scale-up deployment of Fionet is being planned in many countries, regions, districts and sub-district levels where enhanced efficiencies of the system would have the greatest impact. The ability of the system to provide benefits in multiple other health programs besides malaria using the same infra-structure makes Flonet a powerful tool for HSS.

1032 In-vitro susceptibility of artemisinin-resistant P. falciparum parasite subpopulations in western Cambodia

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Artemisinin-based combination therapies are recommended for treating Plasmodium falciparum malaria worldwide. However, artemisinin (ART) resistance is entrenched in Western Cambodia, observed as a long parasite clearance half-life (HL) in patients treated with ARTs. Whole-genome sequence data identified three subpopulations (KH2, KH3 and KH4) associated with longer HL compared to KH1 subpopulation in Pursat province, Cambodia. A novel in-vitro assay (ring-stage survival assay, $RSA^{0\text{-}3h}$) detects artemisinin resistance in parasite isolates from malaria patients in Cambodia.

To explore the molecular basis of artemisinin resistance in KH2, KH3 and KH4 subpopulations, we culture-adapted 10 parasite isolates from each KH group and compared them in the $RSA^{0\text{-}3h}$. We show for the first time a significant correlation between HL and an in-vitro ($RSA^{0\text{-}3h}$ survival rate) parameter of ART resistance ($r=0.59$, $P<0.0001$). $RSA^{0\text{-}3h}$ survival rates and HLs differed between KH groups (Kruskal-Wallis test, $P=0.001$ and $P=0.04$, respectively). $RSA^{0\text{-}3h}$ survival rates increased in the order KH1 < KH4 < KH3 < KH2 with median survival rates of 0.7%, 3.0%, 18% and 24%, respectively. Non-synonymous SNPs in genes previously implicated in ART resistance segregated poorly or not at all among the KH groups, indicating they are not reliable markers of ART resistance.

These data suggest that genetic determinants of ART resistance may differ between the KH2, KH3 and KH4 subpopulations. Updated progress on identifying these genetic determinants will be presented.

2001 The P-type ATPase, PfATP4, mediates resistance to both aminopyrazole and spiroindolone antimalarials

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Due to the spread of resistance, antimalarials with novel mechanisms of action are needed. The aminopyrazoles were identified in a cellular antiparasitic screen and have potent activity against *Plasmodium falciparum* blood-stage parasites. To investigate their mechanism of action we pressured parasites until they acquired low-level resistance to a representative member of the aminopyrazole series, GNF8874. Whole genome sequencing of three resistant lines showed that each had acquired independent mutations in a P-type cation-transporter ATPase, PfATP4 (PF3D7_1211900), a gene implicated in resistance to another, structurally unrelated, class of antimalarials called the spiroindolones. GNF8874-resistant lines exhibited cross-resistance to the spiroindolones and transgenic parasite lines harboring mutations in *pfatp4* showed resistance to both GNF8874 and representative spiroindolones. Like the spiroindolones, GNF8874 inhibits parasite transmission to mosquitoes and disrupts intracellular sodium homeostasis, further validating PfATP4 as a membrane-spanning sodium transporter. Additional chemotypes were identified that exhibit cross-resistance with the GNF8874 resistant parasite lines demonstrating that PfATP4 plays a critical role in cellular processes. Our data show that PfATP4 can be inhibited by several distinct antimalarial pharmacophores and supports the recent observations that PfATP4 is a critical drug target.

Funding provided by the NIH (R01 AI090141 and F32AI102567)

2002 Dissecting VAR2CSA to develop a pregnancy-specific serologic assay to quantify malaria transmission intensity

Fonseca AM, Campo J, Gonzalez R, Maculuve S, Sevene E, Mwangoka G, Mombo-Ngoma G, Kariuki S, Massougbodji A, Ramharter M, Tuike-Ndam N, Cot M, Macete E, Alonso P, Menéndez C, Mayor A
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The current focus on malaria elimination requires new metrics for malaria transmission intensity (MTI). We hypothesized that measurement of antibodies against *P. falciparum* VAR2CSA that binds to placental chondroitin sulphate A may allow to assess parasite exposure during pregnancy and estimate MTI. To address this, we have explored the value of VAR2CSA synthetic peptides to measure pregnancy-specific antibodies using a Luminex-based assay. Peptides were selected after alignment of 18 VAR2CSA full length sequences from *P. falciparum* isolates of different geographic origins (Asia, Africa, Central and South America) and stratification by their polymorphism level. 46 peptides ranging from 35-65AA (5 peptides from DBL1x domain, 4 DBL2x, 6 DBL3x, 6 DBL4ε, 5 DBL5ε, 4 DBL6ε and 16 from Inter-domain regions), covering both conserved and semi-conserved regions of the protein, were used to measure antibody response in a plasma pool from 28 Mozambican hyperimmune pregnant women. Preliminary results showed medium-high seroreactivity (antibody levels above 10000 MFIs using 1:50 plasma dilution) against 78.3% (36/46) of peptides (3 from DBL1x, 4 DBL2x, 5 DBL3x, 6 DBL4ε, 4 DBL5ε, 3 DBL6ε and 11 from ID regions). These results indicate that VAR2CSA peptides used are target of antibody responses that could be included into a pregnancy-specific serology test. However, further selection of peptides need to be performed based on their pregnancy-specific recognition and longevity of antibody responses.

Funding: Malaria Eradication Scientific Alliance, Portuguese Foundation for Science and Technology, EDCTP, AECID, Spanish Ministry of Health

2003 Human immunization with *P. falciparum* sporozoites under chloroquine prophylaxis induces functional antibodies that inhibit hepatocyte infection

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Long-lasting and sterile protective immunity against *Plasmodium falciparum* can be achieved by exposure of malaria-naïve human volunteers under chloroquine prophylaxis to infected mosquito bites (CPS-immunization). Protection by CPS-immunization is predominantly mediated by immune responses directed against sporozoite/liver-stage parasites.

We recently found that $CD4^+$ T-cells with a cytotoxic phenotype correlate with CPS-induced protection. These might eliminate infected hepatocytes and thereby prevent symptomatic blood-stage infection. However, this cellular immune response is not present in all protected volunteers, indicating that other immune effector mechanisms contribute to protection. Antibodies targeting the sporozoites might prevent traversal and invasion of hepatocytes, and thus lower parasite liver load. In the present study, we explored the capacity of CPS-induced antibodies to inhibit sporozoite functionality. To this end, *in vitro* traversal experiments of human hepatocytes and *in vivo* mosquito bite challenge experiments in the human liver-uPA-SCID mouse model were performed, using IgG purified from plasma samples obtained in two clinical CPS-immunization trials.

We demonstrate for the first time that CPS-immunization induces functional antibodies against the malaria parasite, which are able to inhibit parasite traversal *in vitro* and prevent infection after passive immunization *in vivo*.

2004 Ivermectin for Malaria Elimination

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Our data collected from laboratory and field experiments in Senegal, Liberia and Burkina Faso have demonstrated that mass drug administrations (MDA) of ivermectin (IVM) to villagers during the malaria transmission season temporarily disrupts *Plasmodium* transmission by directly and indirectly affecting most variables that define vectorial capacity. Mosquito-affecting concentrations of IVM circulate in human blood for a least 1 week post-MDA and are ingested by human-biting *Anopheles* vectors. Most importantly, IVM significantly reduces the daily probability of *An. gambiae* s.l. survival by >-10% for approximately 1 week post-MDA. In the field, these effects reduce the local *An. gambiae* parity rate by approximately -20-40%, and thus cause a shift in the vector population structure for 2-4 weeks after the MDA. We are also assessing and will present near infrared spectroscopy data as an additional tool to measure mosquito population age structure changes over time. Our data demonstrate that sub-lethal concentrations of IVM significantly inhibit sporogonic development in surviving mosquitoes, however, there are interesting differences in the data obtained from lab, semi-field and field experiments. The combination of effects reduces the vectorial capacity of malaria vectors by about -98% in the week following the MDA, which returns to pre-treatment levels over the next several weeks. This effect translates into significant (>60%) reductions of sporozoite transmission in treated villages that lasts for more than two weeks post-MDA. IVM MDA satisfy the three main challenges the malERA Consultive Group on Vector Control identified to develop vector-targeted interventions that would support elimination and eradication goals. We hypothesize that repeated MDA over the course of malaria transmission seasons would significantly reduce new parasite infections, and it could be an especially safe and effective transmission-blocking additive to chemoprevention strategies against asexual forms to foster local malaria parasite elimination.

2005 Trimethoprim Sulfamethoxazole (TMP-SMX), but not Lopinavir/ritonavir (LPV/RTV), Kills Plasmodium knowlesi Liver Stage Parasites

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Introduction: HIV and malaria overlap geographically, and impact of HIV drugs on malaria requires further investigation. We have previously shown that the HIV protease inhibitor LPV/RTV and the antibiotic TMP-SMX inhibit Plasmodium liver stages in vivo in rodent models and in vitro with P. falciparum. Since clinically relevant levels are better achieved in the non-human-primate model, we investigated the antimalarial activity of LPV/RTV and TMP-SMX on Plasmodium knowlesi liver stages in rhesus macaques.
Methods: To ensure drug steady state drug and 100% infection, rhesus (Macaca mulatta) monkeys were dosed starting 2 days prior to and 5 days after infection with 2500 cryopreserved, purified P. knowlesi H strain sporozoites IV. Pharmacokinetic modeling dosing used in this experiment predicted all drugs would be reduced to non-active levels prior to parasite emergence from the liver. PCR was used for detection of parasites in blood (sensitivity 4.24 x 10 e-5 parasite/µl). Prolonged time to PCR detection of parasites in blood was used to gauge liver stage parasite killing.

Results: Parasites were detected by PCR in controls on D5 and 6, and on D10 and 11 in TMP-SMX treated animals. LPV/RTV had no effect on pre-patent period. (Pooled analysis Chi square test, $p<0.05$).

Conclusions: TMP-SMX prolonged time to PCR detection of parasites in blood, reflecting a reduction of liver stage parasite burden. In contrast, LPV/RTV did not inhibit liver stage parasites. Because drugs that inhibit the liver stages target parasites when they are present in lower numbers, clinical studies are warranted to investigate these findings.

2006 Testing the hypothesis that *Plasmodium vivax* ookinete protein and rRNA SSU 18S variation is associated to *Anopheles* species compatibility in Mesoamerica

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To direct vector control strategies is necessary to determine Anopheles species participation in malaria transmission. *Anopheles albimanus* and *An. pseudopunctipennis* are the main malaria vectors of *Plasmodium vivax* in the Mesoamerican region. Previously, Pvs25 and Pvs28 protein polymorphism has been associated to mosquito susceptibility in southern Mexico; Pvs25 130Ile and rRNA 18S Sal I type have been associated to *An. albimanus* susceptibility, and the circumsporozoite protein repeat (CSPr) vk247, Pvs25 130Thr to *An. pseudopunctipennis* susceptibility. To search and test molecular markers associated to *P. vivax* vector transmission. In this work, groups of parasites from southern Chiapas, Mexico that produced different mosquito infectivity pattern were analyzed for 18S SSU rRNA variants, CSPr, and four ookinete genes. The *P. vivax* that produced higher infection in *An. Albimanus* were haplotype Sal I type; 18S SSU rRNA, SOAP, Pvs25, CSPr, CTRP and Chitinase, and other different haplotypes were more infective to *An. pseudopunctipennis*. So far, all *P. vivax* examined from Nicaragua were Sal I type (18S SSU rRNA, Pvs25 and CSPr). However, parasites from other transmission foci of Mexico presented more complex haplotypes.

These results suggest that in some geographical sites molecular markers can be of help in vector compatibility. Based on this, *An. albimanus* is likely the main vector in the affected regions of Nicaragua. The haplotypes detected in different malaria foci of Mexico were not conclusive to determine vector compatibility; this complex situation would be discussed in terms of diversity, parasite transmission and surveillance.

This work was supported by CONACyT- CB-2009-01 -0131247

2007 Identification of minimal binding domain of *Plasmodium vivax* reticulocyte binding proteins (RBPs)

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Plasmodium vivax preferentially invades reticulocytes which comprise ~1 % of red cells in normal human blood. This specificity was demonstrated to be mediated by two apical merozoite proteins namely RBP1 and RBP2 (reticulocyte binding proteins 1&2), which specifically bind reticulocytes. We have mapped the reticulocyte binding domain (RBD) of RBP1 & RBP2 near the N-terminal region of these proteins. The binding regions of PvRBP1 and PvRBP2 were chosen on the basis of sequence homology with erythrocyte binding regions of *P. falciparum* reticulocyte binding protein homologues (RH proteins) and *P. knowlesi* normocyte binding proteins (NBPs) respectively. These regions expressed on the surface of COS7 cells showed specific binding to reticulocytes. Binding of transfected COS7 cells with reticulocytes was assessed by rosette formation in the binding assay. Further, these regions were produced as recombinant protein in *E.coli*. The recombinant RBP1-RBD (~30kDa) and RBP2-RBD (~40kDa) were found to bind reticulocytes with specificity. Antibodies against rRBP1-RBD were shown to inhibit binding of transfected COS cells expressing RBP1-RBD to reticulocytes. The functional region of RBPs may serve as a promising vaccine candidate for *P.vivax* malaria.

Funded by CSIR (Council of Scientific and Industrial Research, India)

2008 *MBL2* variations and malaria susceptibility in Indian populations

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Background: The pathogenesis of malaria is and its severity depends on complex interplay of host genetic make-up, the parasite virulence, parasite transmission dynamics and the host immune responses. The innate immune system mainly relies on a diverse set of germ line encoded receptors, soluble chemokines, cytokines and ligands. MBL2 is a soluble pattern recognition receptor of the innate immunity, which, recognize and react to specific repertoire of carbohydrates on the surface of invading organisms and plays an important role in the course of infectious diseases. In this study, we aim to investigate the association of *MBL2* variants with *P. falciparum* malaria infection in Indian populations.

Methods: We re-sequenced the 8.7kb of the entire *MBL2* gene in 434 clinically classified malaria individuals from malaria endemic regions of India. The study cohort includes 176 patients with severe malaria, 101 with mild malaria and 157 ethnically matched asymptomatic individuals. Additionally, 830 individuals from 32 socially, linguistically and geographically diverse endogamous populations of India were investigated for the distribution of functional *MBL2* variants.

Results: The *MBL2-221C* (*X*) allelic variant is associated with increased risk of malaria (mild malaria OR: 1.9, P^{Corr}=0.0036; severe malaria OR: 1.6, P^{Corr}=0.02). The exon1 variants *MBL2*B* (severe malaria OR: 2.1, P^{Corr}=0.036; mild vs. severe malaria OR: 2.5, P^{Corr}=0.039) and *MBL2*C* (mild vs. severe malaria OR: 5.4, P^{Corr}=0.045) increase the odds of malaria. The exon1 *MBL2*D/*B/*C* variant increases the risk towards severe malaria (OR:3.4, P^{Corr}=0.000045). The frequencies of low MBL haplotypes were significantly higher in severe malaria (14.2%) compared to mild malaria (7.9%) and asymptomatic (3.8%). The *MBL2*LYPA* haplotypes confers protection whereas *MBL2*LXPA* increases the malaria risk.

Conclusions: Our study suggests that the functional *MBL2* variants are significantly associated with malaria pathogenesis in Indian populations. Further, the high and low serum MBL haplotypes are not restricted to a particular geographic region. In same geographic region, populations show varied prevalence of *MBL2* haplotypes and hence, may show different level of susceptibility to malaria. Increased understanding on the genetic basis of disease susceptibility will help to identify the high-risk individuals, their treatment and effective disease management strategies.

2009 Development of an *in vitro* assay to improve preclinical assessment of vaccine efficacy against growth of *Plasmodium falciparum* blood stage parasitaemia

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The malaria vaccine technology roadmap called on the community to collaborate towards the development of a vaccine that provides 80% efficacy against clinical disease and protection against malaria for 4 years.
The RTS,S vaccine, while showing promising efficacy, particularly against severe malaria in children, will not achieve the roadmap protection goals, and hence second generation vaccine development remains a priority for future research and development. The efficacy of RTS,S may be partly attributable to a reduction in the numbers of merozoites released from the liver, and thus the blood stage should remain a potential candidate for vaccine development. Blood stage vaccine development to date has been hampered partly by the high degree of genetic diversity in target antigens such as AMA-1. Furthermore, AMA-1-based vaccines have not been protective against homologous challenge, leading us to question the relevance of the current clinical correlate *in vitro* assay, the GIA.
We are investigating whether vaccines targeting multiple antigens can overcome the plasticity of *P. falciparum* invasion, inhibiting a wider spectrum of parasite invasion pathways. We focus on conserved antigens, with key roles in erythrocyte invasion, and introduce a new *in vitro* GIA assay, with improved prognostic value for vaccines targeting *P. falciparum* blood stages.

2010 The way forward for malaria vaccine BK-SE36

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Success in smallpox eradication was due in part to the response, adaptation and shifting to a number of strategies as new evidence becomes available. Efforts to control malaria have yet failed in this aspect. Blood-stage vaccines would not only prevent disease caused by "incomplete" pre-erythrocytic immunity, but would also protect against epidemics in newly vulnerable populations. The serine repeat antigen 5 (SERA5) is a major, soluble late-trophozoite and schizont-stage protein of *Plasmodium falciparum*. Processing of SERA5 is believed to mediate parasite egress from the infected red blood cell. In epidemiological studies, antibody titers against the N-terminal domain (SE36 recombinant protein) correlate strongly with malaria protection. In 2005, a randomized, single-blind, placebo-controlled phase 1a clinical trial of BK-SE36 (SE36 with aluminum hydroxyl gel) was conducted in healthy Japanese adults. In 2010-2011, phase 1b trial was done in the malaria endemic area of Lira, Uganda in the following age cohorts: 21-40y; 16-20y; 11-15y; 6-10y. BK-SE36 was safe and well tolerated. Unlike the 100% seroconversion in Phase 1a; seroconversion was age dependent with young children responding remarkably to BK-SE36 (73% responders in 6-10y). Nevertheless, in a one-year follow-up research of the 66 vaccinees together with age-matched control volunteers, BK-SE36 showed 72% protective efficacy against malaria episodes with >5000 parasites/μL blood + fever and 70% reduction for multiple malaria episodes in volunteers that were classified as responders. SERA5 is neither variant-specific nor conformation-dependent. Results lend support that BK-SE36 could be an important contributor in malaria control and eradication.

2011 Mass Screening of G6PD Deficiency Using WST8/1-Methoxy-PMS Enzymatic Assay in China

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Background: Glucose-6-phosphaste dehydrogenase (G6PD) is an important enzyme in cellular metabolism, the deficiency of which poses impediment to primaquine therapy for malaria elimination due to haemolytic anemia that occurs in G6PD-deficient patients. The prevalence of G6PD deficiency in Jiangsu and Hainan provinces of China is little known. In this study, population G6PD status in these two provinces was assessed for guiding the malaria elimination program.

Methods: Samples collected from Jiangsu and Hainan were tested for G6PD activity by WST8/1-methoxy-PMS assay. Chi-square and odds ratio were used to test differences in prevalence of G6PD deficiency between genders, ethnic groups and regions.

Results: 960 individuals of Li nationality (527 males/433 females) were collected from Hainan. 9.5% of them (n=91) showed G6PD deficiency, and of these 4.3% (n=41) had severe deficiency. While there was a significantly higher prevalence of overall deficiency in males, with deficiency of 14.4% (n=62) and 5.5% (n=29) respectively for males and females ($p<0.0001$, OR=2.87, 95% CI 1.81-4.55), there was a higher preponderance of intermediate deficiency among females compared to males, 30.9% (n=163) and 20.8% (n=90) respectively. 1912 individuals of Han nationality from Jiangsu (855 males/1057 females) were analyzed and no G6PD deficiency was found.

Conclusions: WST8/1-methoxy-PMS assay was highly robust for population screening. The prevalence level of G6PD deficiency differed significantly in Jiangsu and Hainan with different ethnic groups. This study highlighted the critical need to consider G6PD deficiency for malaria elimination strategies in Hainan Province.

2012 Variability in Malaria Burden among Islands in Lake Victoria, Kenya: Challenges for Elimination?

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A decline in the burden of malaria in Kenya has been observed in recent years, however high levels of transmission remain in areas around Lake Victoria in Western Kenya. We conducted malariometric surveys in January (dry season) and August (wet season) of 2012 among five sites (three settings) in Lake Victoria: coast, large island and three small islands.
In both seasons, parasite rates as determined by microscopy and RDT were highest in the coast, followed by large island, and lowest in small islands, with significant ($p< 0.01$) seasonal fluctuations observed in islands but not the coast. Significant ($p< 0.01$) differences in parasite rates among settings were observed only in children and young adolescents. Parasite rates were significantly ($p< 0.05$) correlated with prevalence of fever in both seasons, however parasite rates were significantly ($p< 0.01$) correlated with enlarged spleen in the dry season only. Paradoxically, parasite rates were either not correlated (wet) or negatively correlated (dry) with rates of anaemia. Prevalence of *P. falciparum*, *P. malariae* and *P. ovale* by PCR in dry season was 29.3%, 8.5% and 2.1%, respectively; with no *P. vivax* was detected. Among positive cases, mixed infections were detected in 109/1307. G6PD deficiency was higher in males in all three settings, and its prevalence was highest in the coast.

Our preliminary analyses suggest that on islands of Lake Victoria, malaria disease burden is seasonally variable, and sustainable malaria elimination might be feasible with existing tools.

2013 Polyamine synthesis in a natural host/parasite system, *Anopheles gambiae* and *Plasmodium falciparum*

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Polyamines are multivalent organic cations that display a variety of functions essential to proliferating cells, including interacting with DNA, RNA, and proteins. α-difluoromethylornithine (DFMO), an inhibitor of polyamine synthesis, interrupts the sporogonous cycle of *Plasmodium berghei* in *Anopheles stephensi* mosquitoes, but does not cure infections in mice. We characterized expression of enzymes crucial to polyamine synthesis, ornithine decarboxylase (ODC) and arginase, in the natural host/parasite system of *An. gambiae* and *P. falciparum*. Both mosquito and parasite transcripts encoding ODC were detected in the midgut of infected females. However, only *P. falciparum* arginase transcript was detected in the midgut, whereas that of *An. gambiae* was found in the carcass. Infection with *P. falciparum* did not alter mosquito gene expression levels. The regulation and function of six *An. gambiae* ODCs were further explored through performing RNAi-mediated knockdown of ODC1. This ODC gene is predicted to produce a functional enzyme, whereas the five other ODCs are hypothesized to have regulatory functions. We evaluated the impact of ODC1 knockdown on the expression of polyamine synthesis enzymes, and found that ODC3 was induced in the midgut. Furthermore, we examined the impact of ODC1 knockdown upon expression of nitric oxide synthase (NOS). NOS converts L-arginine into nitric oxide, a component of the mosquito immune response. An induction of NOS expression was detected in both midgut and carcass upon silencing of ODC1. These findings support the hypothesis that within the midgut, crosstalk exists between the nitric oxide synthesis and polyamine synthesis pathways, both of which involve the amino acid L-arginine. Targeting this interaction by both depleting the pool of polyamines available to the parasite and increasing the mosquito immune response could alter the vector competence of *An. gambiae* and impact disease transmission.

Funding: Pasteur-Cantarini fellowship to AI

2014 Bioethics of Malaria Elimination

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Though malaria elimination efforts are underway in approximately 100 countries worldwide, ethical issues associated with this endeavour have received relatively little attention in bioethics discourse. While malaria shares certain ethical issues with other infectious diseases, its ethical implications have been neglected more than those of other diseases of comparable importance. As a vector-borne infectious disease, malaria raises some relatively unique ethical issues. Malaria elimination efforts arise in ethically significant contexts (involving historical colonial injustice, impoverished and marginalised populations, climate change) and raise particular ethical issues regarding (i) co-operation between public and private enterprise, (ii) drug patents and counterfeit drugs, (iii) resistance, (iv) coercive public health measures (directly observed therapy, isolation and quarantine), (v) risks of primaquine in *vivax* elimination, (vi) risks of insecticide use, and (vii) 'rebound' malaria. Specific ethical issues also arise in the context of malaria *research* involving (i) controlled infection studies, (ii) human landing catches, (iii) transmission-blocking vaccines, and (iv) genetically-modified mosquitoes, all of which are potentially relevant to malaria elimination. This paper maps the terrain of ethical issues associated with malaria elimination and demonstrates how ethical analysis offers practical guidance regarding malaria elimination and research agendas, whose ultimate goals are improvements in health in malaria endemic populations.

2015 Maintaining specimen integrity for G6PD Screening. Storage and Distribution of Cryopreserved Red Blood Cells for G6PD test evaluation

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Critical to the radical cure of *Plasmodium vivax* infections is the diagnosis of glucose-6-phosphate dehydrogenase (G6PD) activity. Individuals with G6PD deficiency are at risk of undergoing acute hemolysis when exposed to 8-aminoquinoline-based drugs such as primaquine, which is the only drug available for radical cure and eventual elimination of *P. vivax*. A point-of-care test for G6PD deficiency will best meet this diagnostic need. Due to the cost and time required to obtain G6PD-deficient blood specimens, the development and evaluation of new point-of-care G6PD tests would be significantly accelerated with the availability of pre-screened specimens with a range of G6PD activity. An essential component for the development of a repository of specimens for this purpose is ensuring specimen integrity. The results of this study inform methodologies for the robust cryopreservation of specimens required for a specimen repository in support of G6PD test development. Blood collected in different anti-coagulants was used to validate the integrity of G6PD activity. The specimens were characterized for stability and integrity by a number of G6PD phenotypic assays both at the time of collection and post-cryopreservation. Using this cryopreservation process, a G6PD specimen repository is currently under development at PATH and will be made available to the community.

2016 Next generation of genetically attenuated *Plasmodium falciparum* parasites (*Pf*GAP) for the development of a safe and protective live-attenuated malaria vaccine

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Immunization with live-attenuated *Plasmodium* sporozoites confers complete long-lasting protection against malaria infection in animal models and experimental human clinical studies, thus currently constituting the only proven vaccination tool that might critically contribute to malaria eradication. Advances in genetic manipulation of *Plasmodium* have enabled new methodologies to attenuate the parasite by gene deletion, which allows for the design of a live-attenuated parasite vaccine with optimal safety and potency as well as complete homogeneity of a potential vaccine product. Over the past years we, and others, have demonstrated using animal malaria models that such genetically attenuated parasites (GAP) constitute superior immunogens and confer greater-lasting complete protection when compared to parasites attenuated by more traditional methods. To investigate the potential of the GAP approach in humans we conducted an initial clinical study with the first generation *P. falciparum* GAP (*Pf*GAP) generated by deletion of two pre-erythrocytic stage-expressed genes in the NF54 strain. This *Pf*GAP showed severe attenuation and favorable immune responses in human volunteers but was not yet completely attenuated when administered at high doses. As a next step we pursued the creation of a multilocus-attenuated parasite. We will present data describing the creation and preclinical testing of a next generation of *Pf*GAP based on multiple gene deletions and focused on achieving the ultimate goal of creating a completely attenuated malaria parasite that can be used for vaccination with the goal of eradicating malaria.

2017 Lead Optimization of Broad-spectrum Antimalarial Acridones

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We have previously reported the discovery of a novel antimalarial acridone chemotype that displays efficacy against sporozoite-induced *Plasmodium* infection in addition to efficacy against blood stage parasites. An aggressive optimization process not only expanded our chemical library but more importantly produced a new lead candidate with significantly improved efficacy, both *in vitro* and *in vivo*. The new lead candidate also exhibits potent activity against atovaquone-resistant parasites. Details of the design, chemistry, structure-activity relationships (SAR), safety, metabolic studies, and mechanism of action will be presented.

2018 Host candidate gene polymorphisms and clearance of drug-resistant *P. falciparum* parasites in Kenya

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Background: Resistance to antimalarial drugs is a widespread problem for malaria control programmes. Malaria treatment outcome is determined by parasite, pharmacological and host factors. These parameters can be assessed using molecular methods (molecular markers in the parasite related to drug resistance; genetic markers in the host related to resistance to infection and parasite clearance); in vitro assays and in vivo clinical trials in patients to assess response to treatment. The correlation between these methods is imperfect. This study aimed to identify molecular markers in the human genome that correlate with the clearance of malaria parasites after drug treatment, despite the drug resistance profile of the protozoan as determined by molecular approaches.

Methods: 1374 samples from different malaria transmission zones in Kenya which were known to contain genotypically drug resistant and some sensitive parasites were analysed. These parasites were collected from patients who subsequently failed to clear their infection following drug treatment, as expected, but also from patients who successfully cleared their infections with drug-resistant parasites. 67 human polymorphisms (SNPs) on 17 chromosomes were analysed using Sequenom's mass spectrometry iPLEX gold platform, to identify regions of the human genome which contribute to enhanced clearance of drug resistant parasites.

Results: Preliminary analysis of the data from the different study sites revealed significant associations between the phenotype of ability to clear drug-resistant P. falciparum infection and human immune response loci common to all populations. Overall, three SNPs showed a significant association with clearance of drug-resistant parasites after adjustment for possible confounding factors. The first two SNPs (rs2706384 and rs1805015) are within loci involved in pro-inflammatory (interferon-gamma) and anti-inflammatory (IL-4) cytokine responses. The third locus encodes a protein involved in the degradation of mis-folded proteins within the endoplasmic reticulum, and its role, if any, in the clearance phenotype is unclear.

Conclusions: The study showed significant association of three loci in the human genome with the ability of parasite to clear drug-resistant P. falciparum in samples taken from different zones distributed across the country. The loci are involved in the Th1/Th2 balance, and the association of SNPs within these genes suggests a key role for antibody in the clearance of drug-resistant parasites. It is possible that patients able to clear drug-resistant infections have an enhanced ability to control parasite growth.

2019 Next-Generation Malaria Diagnostics: Improving Infection Detection for Elimination

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Malaria has been eliminated from many regions of the world using microscopy as the primary diagnostic tool. However, many of these same regions historically experienced rapid reintroduction of malaria once surveillance efforts and diagnostic testing resources waned. The long-term costs of achieving and maintaining malaria elimination in highly receptive tropical areas, such as sub-Saharan Africa or Southeast Asia, may be prohibitively high using conventional diagnostics such as microscopy and currently available rapid diagnostic tests. New and improved tools and tactics for infection detection can be employed to more efficiently identify and manage the very low density parasitemias observed following rapid decline in malaria incidence.

To catalyze and accelerate development of improved infection detection technologies, the DIAMETER project (Diagnostics for Malaria Elimination Toward Eradication) is taking a multidisciplinary approach: We are assessing user needs and market requirements for next-generation tools; evaluating the potential for new biomarkers and testing approaches, investigating pipeline technologies, and facilitating development of refined target product profiles with the highest potential to bring cost and temporal efficiencies to malaria elimination campaigns. Here we present the preliminary findings of this first phase of the DIAMETER project.

2020 Development of new modeling tools to improve determination of G6PD status

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The 8-aminoquinolone drugs are critical to malaria elimination campaigns due their unique ability to kill the dormant liver stage form of *Plasmodium vivax*. Safe administration of these drugs requires assessing a person's glucose-6-phosphate dehydrogenase (G6PD) activity due to the potential for hemolytic reactions in G6PD deficient patients. Gross phenotypic tests that assess overall G6PD activity within a blood sample are generally able to distinguish between normal and deficient patients but are unreliable in classifying patients with intermediate G6PD activity as well as heterozygous females. Cytochemical staining allows screening of G6PD activity within individual red blood cells (RBC). This method enables the discrimination of distinct cell populations based on G6PD activity thus facilitating the identification of heterozygous females. However, a limitation of this method is the cut-off for defining G6PD deficient cells must be arbitrarily determined. In the present study, we sought to develop a model to allow for a more quantitative interpretation of cytochemical staining through flow cytometry (FC) for G6PD classification. The model was developed by correlating gross assay results (G-6-PDH Kit, Trinity Biotech) and complete blood cell count (CBC) data with the distinct G6PD activity per RBC measured by FC. The sample set consisted of 214 specimens equal parts male and female. Additionally, genotypic information revealing polymorphisms associated with G6PD deficiency was acquired for a subset of 110 of the samples. These three measures where used to create a gold standard for the model's development. The model's supervised development was guided through an iterative cross validation of the data set. As an additional level of validation, the model will undergo blind testing with several hundred subsequent samples collected from multiple international sites. The future goal is to develop a publicly-available tool to aid clinical and research studies.

2021 The antiplasmodial activity of DHEA is mediated through increasing oxidative stress

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P. falciparum is highly dependent of the redox state for its survival; therefore, the antioxidant system in this parasite is a therapeutic target. In fact, the mechanism of action of many antimalarial drugs is the induction of death through oxidative stress by direct or indirect production of free radicals. Dehydroepiandrosterone (DHEA) is a pre-hormone synthesized from cholesterol in the adrenal cortex cells. This hormone has shown antiplasmodial activity against *P. falciparum in vitro*. In this work, we tested the hypothesis that the antiplasmodial activity of DHEA is mediated though the induction of oxidative stress.
Female and male mice were subcutaneously treated with DHEA, one day after the last injection mice were infected with *P. berghei* ANKA. Parasitaemia was measured in Giemsa stained blood smears and oxidative stress was evaluated by measuring the activity of superoxide dismutase (SOD), catalase and malonildialdehyde (MDA) levels.
Male and female mice treated with DHEA decreased significantly the level of parasitaemia compared to control mice treated with vehicle.
SOD activity in blood, spleen, liver and brain significantly increased in male mice treated with DHEA, but not changes were detected in female mice treated with the prehormone compared to control group.
Catalase activity increased in male, but significantly decreased in spleen of female mice both groups treated with DHEA.
Lipoperoxidation measured as MDA levels was significantly increased in blood, spleen and brain of female mice treated with DHEA compared to control mice. In contrast, male only showed a significant increment in brain compared to control group.
Conclusion. DHEA induces strong oxidative stress which is higher in female compared to male mice infected with *P. berghei* ANKA. Our results suggest that at least in part the antiplasmodial activity of DHEA is mediated by the induction of oxidative stress.
This work was funded by PAPIIT IN217412, DGAPA, UNAM.

2022 Mutations in *Spnb1* cause enhanced clearance of parasitized red blood cells and lead to increased malaria resistance in mice

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There is strong evidence that genetic polymorphisms which alter the red blood cell (RBC), such as sickle cell trait, can convey malaria resistance. Impaired ability of the parasite to invade altered RBCs has been widely suggested as an explanation for resistance in these cases. Here, we propose an alternate mechanism in which perturbations to the RBC cytoskeleton and membrane render parasitized RBCs (pRBCs) more susceptible to immune clearance.
We investigated two mutant mouse lines with dominant, heterozygous mutations located in *Spnb1*, which encodes the RBC cytoskeletal protein beta spectrin, produced through an ENU mutagenesis screen. The first mutant line, $Spnb1^{MRI26194}$, contained an IVS6+2T>A splicing mutation resulting in a premature stop codon, while the second, $Spnb1^{MRI53426}$, contained a V116E missense mutation. When infected with *P.chabaudi adami DS* both lines displayed a dramatic increase in survival (80-100% vs. 17%, $p<0.01$). iTRAQ LC/MS proteomics on RBCs revealed that $Spnb1^{MRI26194/+}$ mice had normal levels of beta spectrin but a nearly threefold increase in Band 3 compared to wild type, while $Spnb1^{MRI53426/+}$ had a twofold decrease in alpha and beta spectrin and normal levels of Band 3. Despite these differences *in vivo* labelling of RBCs indicated that parasites were able to invade and grow normally in both mutant RBCs. In contrast, clearance of pRBCs less than 30mins after invasion was enhanced by 15-27% compared to wild type ($p<0.001$). This clearance was only seen 4 days after infection began and an identical phenotype was observed in splenectomised mice.
This study presents the first evidence that mutations in *Spnb1* can lead to malaria resistance in mice. Surprisingly, these mutations had no effect on parasite invasion or growth but instead led to increased clearance of pRBCs, thus providing a new perspective on the host/parasite interaction.

This work was supported by the NHMRC

2023

WITHDRAWN

2024 Geographical variation of factors affecting effectiveness of Long-Lasting Insecticidal Nets in Tanzania

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The success of long-lasting insecticidal nets (LLINs) for malaria control is evident, as they provide a physical and chemical barrier from mosquitoes. Yet, quick deterioration of nets, insecticide resistance in mosquitoes, and reluctant net use pose serious threats to this intervention. Hence it is crucial that factors associated with net loss are identified. To optimize the LLIN strategy, this study will use Geographic Information Systems (GIS) and spatial analyses to investigate environmental and cultural factors and other risk factors that may affect net durability.

Across eight districts in Tanzania, two surveys will measure LLIN durability through attrition (presence or absence of nets), bio-efficacy (ability of nets to kill mosquitoes), chemical content (active ingredient in net fibers) and physical degradation (fabric integrity). In September 2013, a retrospective survey will be done on Olyset® nets distributed to households by the National Malaria Control Program in 2009-2010. Thereafter, a prospective survey will evaluate nets of three brands over three years in those same households. National health survey data in corresponding districts will be evaluated to relate net attrition to malaria incidence. Environmental factors will be assessed with satellite imagery.

A GIS database including net and household characteristics will be created and merged with environmental, socio-economic and health data for spatio-temporal analyses.

Our study hypothesizes geographic variation in net durability and LLIN effectiveness due to environmental, socio-economic and cultural diversity in Tanzania. By identifying these factors, decision makers may use results from this study to optimize procurement and product choice to achieve universal coverage of LLINs for malaria vector control.

Grant funding: Research Council of Norway, grant number 220757.

2025 Children Resistant to *P. falciparum* Infection in a Holoendemic Region of Tanzania Maintain Distinct Immunoreactivity Profiles

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In a longitudinal birth cohort study (2002-2005) in Muheza, Tanzania, we observed that a subset of children (<10%) never developed patent parasitemia on bloodsmears collected every 2-4 weeks. In ELISA studies, these "resistant" children developed no or only low levels of antibody to *P. falciparum* AMA-1 and MSP-1 compared to the susceptible children, who as a group developed substantial responses to these antigens. Conversely, the resistant children acquired equal or higher levels of seroreactivity to novel preerythrocytic antigens under investigation in our laboratory as potential vaccine candidates. From these results, we surmised that some children in the cohort may have controlled preerythrocytic malaria through unknown mechanisms. We re-enrolled a subset of these children for follow-up during 2011-2012 to assess their humoral and cellular immune profiles. The resistant children (n=41) were located, and then matched with susceptible children (n=162) on the basis of several baseline parameters. As observed during early childhood, the resistant children continued to have significantly lower reactivity to AMA-1 and MSP-1 during late childhood. Cellular immune responses to novel preerythrocytic antigens were similar between the two groups. Based on these data, we suggest that a subset of children living in holoendemic areas may develop a high degree of resistance to malaria that prevents patent parasitemia, and these children maintain a distinct immunoreactivity profile throughout childhood.

Funded by: NIAID/NIH (AI52059), Grand Challenges in Global Health/FNIH grant, Fogarty International Center/NIH (D43-TW005509) and Intramural Research Program, NIAID/NIH.

2026 Malaria infection and mosquito characteristics in fever hotspots and coldspots in a high transmission region

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Background: Understanding factors that contribute persistence of transmission and local heterogeneity may allow implementation of targeted in Eldoret, Kenya, terventions.
Methods: The Webuye Health and Demographic Surveillance Site in western Kenya has high, persistent malaria transmission. We identified local clusters with higher than average fever incidence ('hotspots') or lower than average fever incidence ('coldspots'). Sentinel villages – 4 in hotspots, 2 in coldspots – were selected for surveillance. One household in each site was randomly selected for window exit traps and two neighboring households were selected for pyrethrum spray catches (PSC). Mosquitoes are collected daily for 1 week/month from the exit traps and once/month by PSC. Female anopheles are identified to the species and analyzed for infectivity. Parasitological surveys of all the household members and their immediate neighbors are conducted quarterly.
Results: A total of 370 subjects were tested for malaria; 21.6% were positive. Children ages 5-10 years had the highest prevalence (41%). To date, a total of 331 mosquitoes were caught; 49.8% anopheles. There was heterogeneity between villages in both mosquito density (1.6-0.1 mosq/house/day) and infection prevalence (13% to 33%). One hotspot accounted for 78% of anopheles collected. The total anopheles mosquitoes peaked in May immediately after the major rains. The high percentage of gravid females captured by exit trap showed obligate endophily among these malaria vectors. There was a clear linear relationship between anopheles mosquito density and prevalence of malaria in humans. Malaria-infected individuals in fever hotspots were significantly more likely to have symptoms. Data will also be presented on mosquito species, sporozoite rates, and the relationship to incidence of new infections.
Conclusion: We show a clear correlation between malaria infection and mosquito density. However, there are variations in malaria transmission between villages which are not yet explained.

2027 Long-Lasting Insecticidal Treated Bed Net for Malaria Control in Tanzania: Barriers to Physical and Chemical Protection

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Scaling up of Long-Lasting Insecticidal Nets (LLIN) remains the main approach for malaria vector control. In Tanzania, by 2011, over 26.4 million free LLINs had been distributed throughout the country via the under-five and universal net coverage campaigns. Successes of this program in the country include, a reduction in all cause under-five mortality by 45% from 146/1000 live births in 1999 to the current level of 81/1000 live births in 2010. However, this success is dependent on continued LLIN efficacy and high coverage of LLINs. Through time LLIN efficacy decreases through net loss, loss of insecticide and physical damage. This has important implications because the political and donor support for these campaigns might reduce if interventions begin to fail.

There is therefore an urgent need to understand both physical and chemical factors that threaten the sustainability of high and effective net coverage. The information will help the government and public health policy makers in determining which is the most durable and cost effective LLIN (rather than the cheapest that might not last very long) to procure, and how often to replace them in order to save the available limited resources. In addition, the collected information can help to tailor behaviour change communication campaigns to support better utilization and care of LLINs and hence maximize its performance and fabric integrity.

The study will use both retrospective and prospective approaches. The retrospective approach will involve evaluating the causes for attrition of LLINs collected from the recent net campaigns. The prospective approach will involve follow up of three LLINs (Olyset®, PermaNet® 2.0 and Netprotect®) brands distributed in sampled communities for three years to compare their performance. Data from the retrospective study will be presented.

Research Council Norway. RCN project no. 220757

2028 Attracting and killing outdoor biting mosquitoes: small scale field evaluation of a prototype device that mimics humans

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Mosquitoes that bite people outdoors continue to contribute significantly to transmission of diseases such as malaria, filariasis and viral infections. This suggest for the new tools that can be used outdoors to complement existing indoor interventions, such as long lasting insecticide-treated bed nets (LLINs) and indoor residual insecticide spraying (IRS). We developed a prototype mosquito control device, named here, *the mosquito landing box (MLB)*, which is baited with odors that mimic real humans and can be treated with different mosquito killing agents, and then evaluated against the mosquitoes seeking to bite outdoors. Field experiments were conducted in rural Tanzania to assess: *a)* whether wild host-seeking mosquitoes could visit the MLBs, *b)* whether the mosquitoes stayed long or left shortly after arrival, *c)* whether the mosquitoes were active at times when humans are usually outdoors, and *d)* whether the visiting mosquitoes could be contaminated and killed. There were significantly more mosquito vectors, *Anopheles arabiensis*, *Anopheles funestus*, and *Culicines* species visiting baited MLB than unbaited controls (df=1, $P \leq 0.028$). Increasing sampling frequency from 2-hourly to either 1-hourly or half-hourly led to an increase in mosquito catches (df=2, $P<0.002$), indicating that many mosquitoes indeed visited the device but left shortly afterwards. Outdoor host-seeking activity was highest from 1930hrs to 2230hrs and from 0430hrs to 0600hrs, matching the times when people are usually outdoors. We observed significantly higher mortalities among mosquitoes visiting MLBs that were sprayed or painted with formulations of a candidate mosquito killing agent (i.e. pirimiphos-methyl) compared to untreated MLBs ($P < 0.05$).These findings indicate that the MLB might be useful for controlling outdoor-biting mosquitoes while complementing the existing interventions; by attracting, contaminating and ultimately killing the mosquitoes, hence potentially reducing disease transmission.

2029 Fall and rise of malaria among Mozambican pregnant women between 2003 and 2012 and its relationship with antimalarial immunity

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Malaria resurgence after elimination of the parasite is a major concern, as changes in the epidemiology and waning of host immunity can potentially increase the adverse impact of malaria rebounds. Here we report delivery-based malaria trends over a period of 10 years (2003-2005 and 2010-2012) in 1815 pregnant women from Manhiça (Mozambique) and relate them to anti-malarial immune responses and malaria trends in the community. *P. falciparum* prevalence (by qPCR) decreased from 24% in 2003 to 2% in 2010, with a subsequent increase to 5% in 2012. Parasite densities were significantly higher in 2010-2012 than in 2003-2005, with prevalence of submicroscopic infections following an opposite trend. Antibodies against the pregnancy specific antigen VAR2CSA declined between 2003 and 2010, whereas an increase was observed between 2010 and 2012. Our results show large changes in malaria trends over the last 10 years and suggest that only 5 years of malaria decline can lead to a significant reduction of antimalarial antibodies and an increase in the density of parasite infections. Antibodies against VAR2CSA mirror the pattern of infection among pregnant women, which is comparable to trends of malaria in the community, suggesting that measurement of these antibodies may be useful to estimate changes in the intensity of malaria transmission during elimination activities.

Funding: Malaria Eradication Scientific Alliance, BBVA, EDCTP, Malaria in Pregnancy consortium, Spanish ministry of Health, AECID

2030 A rodent *Plasmodium*-based strategy for vaccination against human malaria

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Whole organism pre-erythrocytic (WOPE) vaccines against malaria are among the most promising immunization strategies against this disease. We developed a bold new approach to WOPE vaccination, based on the use of rodent *P. berghei* parasites as the immunizing agent. We demonstrated that this strategy meets the basic requirements for safety and for effective antigen presentation to liver hepatocytes. We are investigating the degree of cross-species protection conferred by *P. berghei* against *P. falciparum*, as well as the added protection afforded by the genetic engineering of *P. falciparum* immunogens onto the *P. berghei* platform. Data will be presented regarding cellular and humoral responses resulting from immunization with the rodent parasite-based vaccine, as well as their ability to specifically recognize and inhibit infection by *P. falciparum*. Finally, the pros and cons of the use of *P. berghei* as a vaccination platform against human malaria will be discussed in the context of currently available alternatives.

2031 Immunization with a CS Epitope-based VLP Elicits Sterile Immunity to Blood Stage Malaria

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To design P. falciparum pre-erythrocytic vaccine candidates a library of circumsporozoite (CS) epitopes (both B and T cell) displayed on VLP platforms (WHcAg) was produced. To test the protective efficacy of the CS-WHcAg VLPs, hybrid CS P.falciparum/P.berghei sporozoites fully infectious in mice were produced. VLPs carrying 1 or 2 CS-repeat B cell epitopes and 4 VLPs carrying different CS-nonrepeat B cell epitopes all elicited high levels of anti-insert antibodies (Abs) that recognized hybrid sporozoites. Whereas, VLPs carrying CS-repeat B cell epitopes conferred 98% protection of the liver against a 10,000 sporozoite challenge, the CS-nonrepeat B cell epitopes were minimally to non-protective. Although anti-CS repeat and nonrepeat Abs bound dry sporozoites, only anti-CS-repeat Abs recognized viable sporozoites. CS-specific CD4/CD8 T cell sites were also inserted onto VLPs. A construct containing 3 well characterized CS-specific T cell domains primed murine CS-specific as well as WHcAg-specific T cells, however, the CS T cell domain-carrying VLP failed to protect against a sporozoite challenge, indicating a requirement for anti-CS repeat Abs. Nevertheless, a VLP carrying 2 CS-repeat B cell epitopes and 3 T cell sites (i.e., VLP-162) elicited superior protective efficacy against liver stage infection when compared to VLPs carrying only the B cell epitopes.

Immunization with 2 doses of VLP-162 in alum adjuvant elicited high titer (>1x10^6) anti-CS Abs and provided 100% protection against blood stage malaria in mice challenged with hybrid-sporozoite infected mosquitoes. These results indicate that immunization with an epitope-based VLP containing selected B and T cell epitopes from the P.falciparum CS protein can elicit sterile immunity against blood stage malaria if sufficient anti-CS protective Abs are produced. It would be useful to compare candidate vaccines, including RTS.S, in this standardized challenge model.

2032 Experimental infection of *Anopheles aquasalis* by *Plasmodium vivax:* understanding knowledge gaps to eliminate malaria in Brazil

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Malaria parasites are transmitted by anophelines and infection of mosquitoes begins with uptake of viable mature gametocytes. A better understanding of this process should assist in the development of tools that act directly on the transmission cycle. This study aims at determining the susceptibility of *Anopheles aquasalis* to infection by *Plasmodium vivax (Pv)*. Blood samples were collected by finger puncture to confirm *Pv* infection. Samples from patients were investigated by microscopy. For samples of asymptomatic individuals living in the outskirts of Manaus, *Pv* infection was demonstrated by qPCR. For infection of *An. aquasalis* venous blood samples were collected from 39 patients. A hundred female mosquitoes, aged 3-5 days, were used per experiment. One group was fed with whole blood and a second group with whole blood of which serum had been heat-inactivated. Seven days after infection females were dissected to check for presence of oocysts. Out of 5,700 anopheline females, 3,979 (69.8%) fed and of these, 460 had at least one oocyst (8.1%). Infection rates and infection intensities were similar for whole blood and inactivated serum samples ($p>0.050$). The median of oocysts in whole blood samples varied from 1 to 49 oocysts per experiment and for inactivated serum samples from 0 to 25.5. Infection rate in whole blood ranged from 2.5 to 81.8% and for inactivated serum from 0 to 95.6%. No correlation between microscopical gametocytemia and infection rates ($p=0.425$) or median of oocysts ($p=0.492$) was observed. qRT-PCR gametocytemia is currently being carried out, which might result in a different outcome. Four from nine (44.4%) samples of asymptomatic patients were able to infect mosquitoes. Concluding, no correlation was found between *Pv* gametocytemia and infection rates or intensity for *An. aquasalis.* Submicroscopic infections may contribute significantly to the spread of malaria in Amazonian low endemic areas. The *An. aquasalis* model can give many useful answers for understanding knowledge gaps to eliminate malaria in Brazil.

Funding: Bill and Melinda Gates Foundation (Transepi Project).

2033 Namibia's path toward malaria elimination: A case study of malaria strategies and costs along the northern border

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Low malaria transmission in Namibia suggests that elimination is possible, but the risk of imported malaria from Angola remains a challenge. This case study reviews the transition from malaria control to elimination in three northern regions that comprise the Trans-Kunene Malaria Initiative (TKMI)—Kunene, Omusati, and Ohangwena.

Thirty four key informant interviews were conducted and epidemiological and intervention data were assembled for 1995 to 2013. Malaria expenditure records were collected for each region for 2009, 2010, and 2011, representing the start of the transition from control to elimination. Interviews and expenditure data were analyzed across activity and expenditure type.

Incidence has declined in all regions since 2004; cases are concentrated in the border zone. Expenditures in three regions have declined, from an average of $6.10 per person at risk per year in 2009 to an average of $3.61 in 2011. The proportion used for diagnosis and treatment declined and vector control increased. Indoor residual spraying is the main intervention, but coverage varies, related to acceptability, mobility, accessibility, stockouts and staff shortages. Bed nets were scaled up beginning in 2005, assisted by partners in later years, but coverage was highly variable. Distribution of rapid diagnostic tests in 2005 resulted in more accurate diagnosis and drove a decline in cases beginning in 2006, however operational challenges include training and supervision.

To achieve malaria elimination, operational challenges related to community engagement, adequate staffing and training, and building capacity for robust surveillance, management and M&E require strategic deployment of program resources, including TKMI. The program has developed a strategy to address these challenges, particularly with regards to case management.

2034 Purification and comparative inhibition studies on recombinant plasmodial and human glutamate dehydrogenases expressed in *Escherichia coli*

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Previous studies have reported that the cytosolic enzyme glutamate dehydrogenase (GDHa) in the most deadly species of the human malaria parasites, *Plasmodium falciparum,* is an attractive target for the development of new drugs due to an essential role in the production of reducing equivalents required for the parasite antioxidant defences. However, a more recent study has cast doubt on this. Two more GDHs (GDHb & GDHc) were identified upon the sequencing of the parasite genome. An initial proof of evidence suggests that GDHb is essential for the parasite. Thus inhibition of this enzyme might, in the long term, offer a new approach for treatment of malaria. An important question is whether it is possible to inhibit the parasite GDH without affecting the counterparts in humans, specially the house-keeping GDH1.

In this work, efforts were undertaken to express and purify GDHb from *Eschericia coli*. The enzyme was successfully expressed in autoinduction media with the aid of molecular chaperones. Successful purification was achieved with two chromatographic steps. The housekeeping human GDH, also expressed in *E. coli* was successfully purified to homogeneity using dye affinity chromatography and ion exchange chromatography.

Results from the inhibition study have demonstrated that selective inhibition could be achieved even before deploying comparative structural information which could aid in future efforts to design potent, selective inhibitors, if indeed it turned out to be useful to inhibit this enzyme.

2035 Validation of *Plasmodium falciparum* ClpQ protease as drug target and development of new anti-malarials

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The ATP dependent ClpQY system is a prokaryotic proteasome like multi-subunit machinery localized in the mitochondrion of malaria parasite. The ClpQY machinery consists of ClpQ threonine protease and ClpY ATPase. In the present study, we have carried out detailed functional characterization of PfClpQ protease machinery to validate its candidature as drug target against malaria. We show that PfClpQ is an essential protease in the parasite as it was not possible to disrupt the gene locus by double cross-over homologous recombination; in addition, transient interference in the protease activity by a conditional dominant negative approach resulted in parasite cell death. Further, development and functioning of the mitochondria in these parasites were found to be deregulated. These results demonstrate the functional importance of the PfClpQ protease for parasite survival, hence, validating it as a promising drug target for development of anti-malarial therapy. Further, we also identified specific lead compound targeting PfClpQ by screening the 'Malaria Box' compound library which consists of chemical entities with known antimalarial activity. This provides future directions for developing new anti-malarial that can be used in combination therapies for combating malaria.

3001 *De novo* Heme-biosynthetic Pathway of Malaria Parasite - Intriguing Aspects and Future Prospects

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Heme is required for the biogenesis of cytochromes - the essential components of parasite electron transport chain. Despite its ability to acquire heme from host hemoglobin, the parasite is also capable of synthesizing heme *de novo*. Our earlier studies had revealed the unique biochemical features of parasite enzymes and the existence of an unusual hybrid pathway. To address the role of dual sources of heme in parasite growth and development, knockouts (KOs) were generated in *Plasmodium berghei* (*Pb*) - for the first enzyme, δ-aminolevulinate synthase (ALAS), and the last enzyme, ferrochelatase (FC). The intraerythrocytic stages of *Pb*KOs grow and multiply normally in mice. *In vitro* radiolabeling studies carried out with *Pb*KOs and *P. falciparum* wild type parasites have revealed that the parasite can incorporate both hemoglobin-heme and *de novo* heme into mitochondrial cytochromes and hemozoin. The identical fates of the two sources of heme indicate that they serve as back up mechanisms in the intraerythrocytic stages. Future studies would address the context in which the *de novo* heme predominates in the intraerythrocytic stages.

Nevertheless, the *de novo* heme becomes indispensable in sexual and liver stages. *Pb*KO parasites show a drastic decrease in the formation of oocysts and no sporozoites could be detected in the salivary glands of mosquitoes. The basis for this absolute requirement of heme needs to be investigated. In *Pb*ALASKO parasites, this could be restored by supplementing the mosquitoes with ALA. Further, ALA supplementation to the animal is required for these sporozoites to undergo liver stage development in mice. Thus, the *de novo* heme-biosynthetic pathway in the malaria parasite offers new options for therapeutic interventions in the mosquito and liver stages. *Pb*ALASKO sporozoites obtained after ALA supplementation in the mosquitoes have the potential to be tested as genetically attenuated sporozoite vaccine.

3002 The use of Haemozoin as a diagnostic biomarker at different stages in the lifecycle of Plasmodium falciparum

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Several groups worldwide including ours are exploring the use of haemozoin as a biomarker for malaria as it offers the advantage of being detectable by reagent free techniques not dependent on cold chain availability. Under laboratory conditions our magneto-optic technique is sensitive to the presence of mature crystals (1000nm x 200nm) of haemozoin or its artificial analogue β-haematin at concentrations ≈ 1ng/ml. However during clinical evaluation in Thailand when the blood samples of all patients presenting were found by gold standard microscopy to display only early ring stage parasites the performance of our rugged, miniaturised magneto-optic device was significantly suppressed in comparison with earlier trials in Kenya. Theory indicates that both the response of crystals to a magnetic field and their interaction with polarised optical radiation decrease with crystal size. To properly understand the impact of this on instrument sensitivity in early stage infection and the prospect of hemozoin as a diagnostic biomarker we have studied the development of haemozoin crystals throughout the lifecycle of *P.falciparum*. Synchronized *in vitro* cultures of *P. falciparum* were grown and sampled at 2-3hrs intervals over a 48hrs period initiated when most parasites presented early ring stage characteristics. Intra-erythrocytic hemozoin was isolated at each time point and the purified crystals were examined via electron microscopy, enabling an accurate account of crystal shape and size distributions throughout the life cycle of the parasite with approximately 20,000 crystals analysed. Like all other optical techniques reliant on haemozoin assay, the detection sensitivity possible via magneto-optics is shown to be highly dependent on parasite development. Direct hemozoin detection may however prove insightful in evaluating drug sensitivity.
Global Health Grant Number OPP1204428

3003 Functional characterization of novel *Plasmodium falciparum* transmission-blocking vaccine targets

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Plasmodium falciparum malaria continues to evade control efforts in part through the complexity of its life cycle, with highly specialized sexual-stages that transmit infection by uptake from the peripheral blood of a human host into a mosquito vector. In a vaccination model, antibodies to sexual-stage antigens, ingested in the mosquito blood meal, can inhibit parasite growth in the insect mid-gut as judged by functional *ex vivo* experiments such as the standard membrane feeding assay (SMFA). To date, only a fraction of sexual-stage antigens have been screened by this methodology. Despite the rapid rise in recent transcriptomic and proteomic datasets for the sexual-stage, the list of proteins that elicit the robust inhibitory responses required of a transmission-blocking vaccine (TBV) has changed little over the past 30 years. This study aims to characterize 25 sexual-stage proteins as possible TBV targets; we present preliminary data for five antigens. In brief, genes of interest were cloned into a customized plasmid for protein expression in transiently transfected HEK293 cells followed by affinity-tag purification. We immunized BALB/c mice with recombinant protein in Addavax adjuvant to generate anti-sera for determining antibody immunogenicity by ELISA and recognition of native protein by indirect fluorescence assay (IFA). We then determined the functional inhibitory activity of the purified IgG by SMFA alongside the leading TBV candidate antigen Pfs25. We report one antigen that induces inhibition by SMFA and is also recognized by the serum of a cohort of individuals from an endemic area in Burkina Faso. The preliminary data serve as a proof-of-principle that it is valuable to apply this methodology to a broader range of targets.

3004 Malaria Prevention among Mothers of Under-five Children in Bépanda- Douala, Cameroon

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Background: Malaria is a major public health problem among children less than 5years in urban settings of Sub Saharan Africa including Cameroon.
Objective: This study was carried out to determine the knowledge, attitudes and practices (KAP) of mothers of under-five children on malaria prevention in a resource-limited urban setting in the city of Douala.
Methods: A pre-tested structured questionnaire was used to collect data in a KAP cross section study on malaria prevention among caregivers of under- five. A cluster sampling method was used and data was analyzed on SPSS.
Results: 92 mothers or caregivers of children below 5years were surveyed in Bepanda quarter of Douala. Majority of the respondents [45(48.91%)] were young women in the 25-29 age bracket. 90(97.85%) women knew that malaria is caused by mosquito bites. Predisposition factors to malaria among children included poor home hygiene [34 (36.96%)], presence of stagnate water near dwellings [28(30.43%)] and open windows and doors [11(11.96%)]. Majority (93.48%) of the women knew at least a correct sign of malaria. Knowledge of malaria prevention was variable among the women but many cited the use of long lasting insecticide treated nets [31(33.69%] and environmental sanitation. The disposal of household waste was a major problem which enhanced breeding grounds for mosquitoes. Only 46.73% of the women take their children to health facilities when they suspect malaria whereas auto-medication [17(18.47%)] and use of roadside drugs [21(22.82%)] were common.
Conclusion: Behavior change communication is needed to enhance malaria prevention among mothers of under-five in the city of Douala.

3005 Diversity of Panamanian *Plasmodium falciparum* isolates

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Elimination of malaria from Meso-America urges for the characterization of circulating field strains of *Plasmodium* parasites from the region. In this study we examined 39 DNA samples obtained from *Plasmodium falciparum* field isolates collected from eastern Panama during an epidemic that occurred in 2003-2008; with the aims: 1) to characterize their genetic diversity and relatedness using a SNP-Based Molecular Barcode assay and 2) to characterize their antimalarial drug resistance profile using High Resolution Melting Analysis (HRM) genotyping.

Principal Component Analysis of the genotyping data let us to characterize, map and group the isolates into three distinct clonal sub-populations ($p < 0.0001$), two from the pacific watershed of the isthmus identified as Madugandi and Darien that clustered together as one clonal group, while the other one belonged to the Guna Yala group and clustered into two distinct clonal sub-populations. The identical barcodes observed in three subpopulations of *P. falciparum* field isolates indicates that these subpopulations are highly related and could be the result of clonal propagation, epidemic expansion, or both.

HRM analysis detected chloroquine (CQ) resistance associated mutations *Pfcrt* N75E, K76T, H97Q and A220S in 100% of the isolates. While, *Pfmdr1* mutations N86Y, Y184F, N1042D and D1246Y associated with aminoquinoline resistance were present in 26.0%, 100%, 26% and 95% of the isolates, respectively. Likewise, *Pfdhps* mutations associated with sulfadoxine resistance A437G were found in 66% and *Pfdhfr* C59R and S108N associated with pyrimethamine and proguanil resistance in 100% of the isolates examined. In contrast, no mutations were found in the *Pfcytb* associated with atovaquone resistance and *PfATPase6* genes proposed to be associated with reduced susceptibility to artemisinin. These findings support the hypothesis that highly related parasite populations are evident in low transmission settings, such as those observed in Panama, and confirms the presence of CQ, pyrimethamine and sulfadoxine resistant mutations in *P. falciparum* isolates from Eastern Panama.

We anticipate that use of genomic tools such as the molecular barcode and drug resistance genotyping will detect changes in malaria parasite population structure that occur as malaria-reducing strategies are implemented regionally to lower transmission. Such tools allow tracking of specific parasite types and will help in the implementation of malaria elimination programs tailored for the southern region of Meso-America.

3006 Evaluation of impacts of control interventions on malaria transmission in an area of southwest Nigeria

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Malaria reduction in areas with high *Plasmodium falciparum* transmission is currently being combated with interventions such as treatment of infection with artemisinin based combinations (ACTs), use of insecticide treated nets (ITNs), environmental and vector control. The study evaluates the impact of control interventions on transmission and factors that contribute to high transmission in endemic communities of south-west Nigeria over a 5year period.

Overall, 5955 children aged <16years and 375 adults were evaluated; parasitaemia was detectable in 46% children and 24% adults. Malaria prevalence remained unchanged during this period (χ^2 for trend=3.07, P=0.079). The prevalence however declined significantly in children <5years (χ^2 for trend=10.44, P=0.0012) who become symptomatic within 3 days (Odds ratio [OR] 1.12, 95% Confidence interval [CI] 1.02-1.23, P=0.015) and are treated early with ACTs. However malaria prevalence remained unchanged in children >5years (χ^2 for trend=1.65, P=0.19) and in adults. Factors associated with higher risk of malaria were: age >5years (OR 1.44, 95% CI 1.29-1.63, P<0.001), delayed visit to clinic (OR 1.41, 95% CI 1.24 -1.61, P<0.0001), anaemia (OR 1.28, 95% CI 1.08 -1.52, P=0.004) and in adults, absence of symptom. Environmental conditions such as close proximity to river, valley areas and distance from health facility accounted for a higher number of patients from such areas; however, the relative prevalence of malaria was similar to that in other areas.

There is a significant reduction in malaria burden in younger children with the current preventive and control measures. However, transmission in endemic areas can be further reduced through periodic screening of older children and adults to detect and treat asymptomatic infections.

3007 Malaria In Africa and the Historical Perspective: Nigerian Concept

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This is a review on the definition of malaria in Nigeria, historical concept and the journey so far. Malaria is an infection of humans and other animals caused by eukaryotic organisms of the genus plasmodium. The protist first infect the liver, then act as parasites within system in the red blood cells, causing symptoms that typically include fever and headache, in severe cases progressing to coma or death. The disease is widespread in tropical and subtropical regions in a broad band around the equator, including much of sub-Sahara Africa,Asia and the united States of America. Five species of *Plasmodium* can infect and be transmitted by humans. Severe disease is largely caused by P.falciparum while the disease caused by P. vivax, P.ovale and P. malariae is generally a milder form that is rarely fatal. Malaria is prevalent in tropical regions because the significant amounts of rainfall, consistently high temperatures and high humidity, along with stagnant waters in which mosquito larvae readily mature, provide them with the environment they need for continuous breeding. Disease transmission can be reduced by preventing mosquito bites by distribution of mosquito nets and insect repellents, or with mosquito-control measures such as spraying insecticides and draining standing water. The World Health Organisation is working hard to reduce the burden of malaria in Nigeria and Africa as a whole.

3008 Evaluation of the CSIR synthetic library for activity against *Plasmodium falciparum*

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Malaria is one of the most important infectious diseases in the world, with malaria due to *P. falciparum* the most deadly form and predominating in Africa. A major contributor to malarial morbidity and mortality is the increasing resistance of the malaria parasite to the available drugs, with this resistance primarily seen in *P. falciparum*. Our research aim is to screen the CSIR synthetic library for activity against *P. falciparum,* in order to identify unique chemical classes that would be further developed through drug discovery channels.

The CSIR synthetic library consists of a large range of novel, structurally diverse compounds, from which we have identified various clusters of compounds based on an *N*- or *O*-heterocyclic core skeleton, with the potential for activity against malaria parasites. The CSIR synthetic library is currently being assayed for activity in intra-erythrocytic *P. falciparum*, against: (i) asexual stages of chloroquine-susceptible parasites (strain 3D7), (ii) asexual stages of chloroquine tolerant and/or -resistant strains of the parasite (strains W2 and/or FCR3), (iii) against the sexual stage gametocyte assay (strain NF54).

The *in vitro* antimalarial activity is measured by assessing parasite survival after drug exposure, using a parasite lactate dehydrogenase (pLDH) colorimetric enzyme assay. From the first cluster of compounds, twenty derivatives are classified as highly active, as they have exhibited IC_{50} values of less than 0.1 µM in the pLDH assay (*P. falciparum* strain 3D7). The active compounds are currently undergoing further screening against the chloroquine-tolerant/resistant and gametocyte strains of *P. falciparum*. "Hit" compounds will be further assayed against mammalian cell lines to determine cytotoxicity. In this way, we may be able to rapidly identify "lead compounds" for further drug development as novel chemotherapeutic agents against malaria.

Project Funding: CSIR YREF, NRF-PDP Programme

3009 Identification of active *Plasmodium falciparum* calpain to establish screening system for *Pf*-calpain-based drug and development of *Pf*-calpain-based therapeutic agents

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Malaria presents a substantial public health and the most common of the parasitic diseases in tropical and subtropical regions. Calpain inhibitor, *N*-Acetyl-L-leucyl-L-leucyl-L-norleucinal (ALLN), is proposed to inhibit parasite proliferation by suppressing haemoglobin degradation. Thus, calpain, a member of cysteine protease family, which is a central mediator for essential parasitic activities, is a potential drug target for malaria parasite.
In this study, recombinant *Pf*-calpain including catalytic subdomain IIa (r*Pf*cal-IIa) was heterologously expressed and purified. Enzymatic activity was determined by both fluorogenic substrate assay and gelatin zymography. Molecular homology modeling was carried out to address the activation mode of *Pf*-calpain in the aspect of structural moiety. Novel derivatives of ALLN based on a variety of dipeptidyl α,β-unsaturated amides containing lysine as a part also were synthesized and evaluated for anti-malarial efficacy against *Plasmodium falciparum* in vitro and *P. berghei* in vivo.
Based on the measurement of enzymatic activity and protease inhibitor assay, it was found that the active form of *Pf*-calpain only contains the catalytic subdomain IIa, suggesting that *Pf*-calpain may function as a monomeric form. The sequence prediction indicates that the catalytic subdomain IIa contains all amino acid residues necessary for catalytic triad (Cys-His-Asn) formation. Molecular modeling suggests that the *Pf*-calpain subdomain IIa makes an active site, holding the catalytic triad residues in their appropriate orientation for catalysis. The mutation analysis further supports that those amino acid residues are functional and have enzymatic activity. Previously, the identified active form of *Pf*-calpain was used to screen *Pf*-calpain inhibitors. Thus their inhibitory effects on *Pf*-calpain were determined using active recombinant *Pf*-calpain. ALLN, a non-specific calpain inhibitor, was used as a positive control. Our results showed that both ZRC032a and ZRC032d displayed comparable or stronger inhibitory activity against *Pf*-calpain protein.
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2013-035128).

3010 Comparison of the Efficacy snd Safety of Two Acts Plus Primaquine for Uncomplicated *Plasmodium Vivax* Malaria in North Sumatera, Indonesia: 1 Year Follow-Up

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Because of high prevalence of chloroquine resistant *P. vivax* in Sumatera, first-line treatment has shifted to artemisinin-based combination therapies (ACTs), combined with primaquine for radical cure. However, which combination is most effective and safe, against a background of significant prevalence of G6PD-deficiency needs to be established.

We conducted a prospective open-label randomized comparison of artesunate/amodiaquine with primaquine (AAQ+PQ) versus dihydroartemisinin-piperaquine with primaquine (DHP+PQ) for the treatment of uncomplicated *P. vivax* in Sumatera, Indonesia. Febrile patients with microscopically confirmed *P. vivax* mono infection were randomised to either standard 3 days AAQ (n = 167) or 3 days DHP (n=164), both combined with 14 days primaquine (0.25 mg/kg) without prior testing for G6PD-status. Follow-up for safety and efficacy was 1 year.

Between December 2010 and April 2012, 331 patients were included. Recurrent infection occurred in 0/167 within 42 days and in 15/130 (11.5%, C.I. 6.6% to 18.3%) within a year in patients treated with AAQ+PQ and in 1/164 (0.6%, C.I 0.01% to 3.4%) within day 42 and 13/143 (9.1%, C.I. 4.9% to 15.0%) within a year with DHP+PQ treatment . Intravascular hemolysis occurred in 5 patients, of which 3 males were hemyzygous for G6PD-Mahidol. Minor adverse events were more frequent with AAQ+PQ.

In North Sumatera, Indonesia, both AAQ and DHP, both combined with 0.25 mg/kg primaquine for 14 days, are safe and efficacious treatments for uncomplicated *P.vivax* without prior testing for G6PD deficiency, but DHP+PQ was better tolerated.

Clinical Trials Registration. NCT01288820.

3011 The role of the perforin-like protein PPLP2 during egress of malaria gametocytes from the red blood cell

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Malaria parasites are transmitted from the human host to the mosquito vector by the uptake of intraerythrocytic gametocytes during a blood meal, which in the mosquito midgut become activated and subsequently undergo gametogenesis. In order to form fertile gametes, the gametocytes have to egress from the erythrocytes within which they developed. Gametocyte egress starts with the destruction of the parasitophorous vacuole membrane, followed by the single-site rupture of the erythrocyte membrane approximately 10 min later. Five pore-forming perforin-like proteins are encoded in *Plasmodium*, termed PPLP1-5, which were assigned to breaching host cell membranes during tissue traversal and host cell egress. We now show that PPLP2 plays a crucial role for the egress of *Plasmodium falciparum* gametocytes from the red blood cell. PPLP2 is expressed in both blood stage schizonts and mature gametocytes and can be detected associated with the gametocyte surface during activation. While the PPLP2(-) parasites show normal egress dynamics during the blood stage replication cycle, the activated gametocytes were trapped in the erythrocyte during egress. Male gametocytes were thus unable to form functional microgametes, and thick axoneme bundles were regularly observed. Ultrastructural analyses of the trapped PPLP2(-) gametocytes revealed that the parasitophorous vacuole membrane has ruptured, while the enveloping erythrocyte remained intact. In consequence the PPLP2(-) parasites were not able to develop in the *Anopheles* mosquito vector, as shown by ex vivo assays. We hypothesize that PPLP2 is important for the perforation of the erythrocyte membrane during gametocyte egress, an essential step preceding the rupture of the red blood cell.

3012 Spatio-temporal analysis of malaria fevers in a large open cohort in western Kenya; implications for targeting 'hotspots'

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Geographic variation in malaria burden or risk of infection between villages and households within a village has been documented. As malaria transmission declines, these variations become more pronounced, giving rise to 'hotspots'. A hotspot of malaria transmission is defined as ' a geographical area within an endemic focus of malaria transmission where transmission intensity exceeds the average level'. Controlling hotspots may be strategic in moving towards malaria elimination if hotspots 'fuel' continual transmission within a larger area. Targeting control measures towards these hotspots is predicted to be more effective than spreading equivalent resources over larger areas or populations.

Most of the information available about hotspots comes from data collected over small geographic areas and/or short time intervals. What is unclear from previous analyses is whether hotspots are stable across multiple years and between wet and dry seasons. Here we present a spatio-temporal analysis of 3 years of morbidity data collected from a population of 75,000 people. Every 6 months, morbidity events are recorded in a 'round' of data collection. We explore the stability in space and time of foci of self-reported malaria fevers. On average, residents reported 1050 malaria morbidity events in each 6-month period, 35% in children under-5 years. There were significant differences in incidence between rounds. Six-monthly rounds had between 2 and 11 significant clusters. Clusters in children under 5 did not coincide geographically with those in the 6 + years group. Clusters moved consistently from south to north in subsequent rounds, with the trend most apparent in young children. Cluster locations are not consistent across time; only 13% of the population falls into a cluster in more than one round. We will present further analyses on the relationship of locally moving clusters to potentially dynamic environmental and population data such as local rainfall, surface temperature, humidity and migration.

Malaria fever hotspots that move in space over time present challenges to targeting control measures.

3013 Prevalence of Severe Vivax Malaria: A Systematic Review and Meta-Analysis Since 1900

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Background: *Plasmodium vivax* (*P. vivax*) was long considered a benign disease. However, several large studies have recently reported severe and complicated vivax malaria cases, especially during the last decade.
Methods: The primary objective of this systematic review and meta-analysis was to describe the prevalence and characteristics of severe vivax malaria from English-language articles published since 1900. To our knowledge, this is the first systematic review and meta-analysis of its kind. For inclusion as part of our study, WHO criteria (2010) for the diagnosis of severe falciparum malaria were applied, with some modifications.
Results: A total of 59 studies (totaling 23,005 vivax-malaria patients) were included in this systematic review. Most studies were reported from India (25 studies), followed by the USA (8 studies) and Indonesia (5 studies). A diagnosis of vivax mono-infection was confirmed by PCR in 11 studies; co-morbidities were ruled out in 19 studies; 9 studies used both PCR confirmation and ruled out co-morbidities. Among general vivax malaria patients, severe thrombocytopenia was the most prevalent (20.3%), while death was least (1%). Among the severe vivax malaria patients, severe thrombocytopenia was the most prevalent (39.6%) while hypoglycemia was the least (2.8%). This pooled prevalence of severe manifestations is only among studies with reported vivax malaria patients.
Conclusion: This systematic review shows that *P. vivax* malaria mono-infection can be severe, complicated, and even fatal. The true incidence of severe vivax malaria will have to come from detailed epidemiological studies including quantification of background parasitemia, uncomplicated vivax and severe vivax prevalence/incidence rates. More studies of severe vivax malaria with careful exclusion of comorbidities and mixed infections are needed, especially in *P. vivax*-endemic countries.

3014 The effect of Violacein on *P. falciparum* and *P. vivax* isolates and against multidrug resistant *P. chabaudi*

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Malaria is responsible for about 300 million infections and one million deaths per year. In Brazil, in 2009, about 300 million cases were reported, and 85% of these were for malaria vivax. Today, treatment failure is frequently reported with conventional antimalarials against infections by *P. falciparum* and *P. vivax*. Thus, combination of artemisinin and its derivatives (ACTs) are currently recommended in malaria treatment. In a previously work, we have shown that violacein extracted from *Chromobacterium violaceum* (vCv) was able to inhibit *in vitro* growth of laboratory strains of *P. falciparum* and almost abrogate the parasitemia caused by *P. chabaudi in vivo*. This work aims to investigate the antimalarial activity of violacein in recent Amazonian isolates harvested from of *P. falciparum* or *P. vivax* infected-patients. Violacein (vCv) tested *in vitro* against seven field isolates of *P. falciparum* showing similar IC_{50} than against *P. falciparum* 3D7, respectively IC_{50} Mean: 419.8 nM and 390± 62 nM. Moreover, vCv was able to inhibit parasite maturation in four isolates of *P. vivax* tested. In addition, when tested *in vivo* with against *P. chabaudi* multidrug resistant parasites (30CQ-resistant to chloroquine and ATNMF1 resistant to chloroquine, mefloquine and artesunate), vCv plus ATN in ATNMF1 parasites, reduce significantly (P<0,05) the peak of parasitemia when compared with untreated animals. Finally, vCv is as efficient on Amazonian isolates as on 3D7 parasites and displays an *in vivo* effect against multidrug resistant murine parasites.

3015 Contribution of *P. vivax* hypnozoites to the burden of malaria infection and disease in children from Papua New Guinea

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In Papua New Guinea (PNG), *Plasmodium falciparum* and *P. vivax* are co-endemic, with a higher prevalence of *P. vivax* in young children. To investigate the contribution of relapses from *P. vivax* hypnozoites to the burden of infection and disease, a treatment to re-infection study was conducted in children aged 5-10 years.
Briefly, 524 children were randomised to receive chloroquine(3d)/artemether-lumefantrine(3d) and primaquine(20d;0.5mg/kg); or chloroquine(3d)/artemether-lumefantrine(3d) and placebo(20d) and actively monitored for re-infection every fortnight for 8 months. The primary aim was to compare the effect of combined liver/blood-stage treatment with blood-stage treatment only on subsequent rates of *P. vivax* infection and illness, as well as on the molecular force of *P. vivax* infection.
Preliminary analysis revealed 244 children (48.1%) became re-infected with *P. vivax* during follow-up. Of these, 66 occurred in the 249 children that received primaquine (26.5% with recurrent parasitamia) compared to 178 in those 258 that did not (69.0%, $p < 0.0001$). The majority of these recurrent infections (82%) occurred within 12 weeks of treatment suggesting rapid activation of hypnozoites. Both the overall rate and the efficacy of the primaquine treatment in preventing recurrent infections were only marginally different in children with and without PCR-confirmed *P. vivax* infections prior to treatment. Failure to adequately treat *P. vivax* infections with effective anti-hypnozoite drugs will severely impede attempts to control *P. vivax* in PNG. The data also suggests that mass drug administration would be a more effective strategy than mass screening and treatment for *P. vivax* elimination.

3016 Effect of training on knowledge of antimalarial treatment policy and treatment practices of patent medicine vendors operating in rural areas of Lagos State Nigeria

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Patent medicine vendors (PMVs) play an important role in community-based management of malaria in Nigeria. Nigeria adopted artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria in 2004. This study aimed to determine the effect of training on the knowledge of the new antimalarial treatment policy and treatment practices of PMVs operating in rural local government areas (LGAs) of Lagos State Nigeria.
A group - randomized controlled trial was conducted. Two out of the four rural LGAs in the state were randomly selected into the intervention and control LGAs. Baseline data were collected using a questionnaire, observational checklist, and mystery client form. In each LGA, 90 PMVs were interviewed, their shops were observed, and mystery clients visited 20 of the shops. A training programme was conducted for the intervention LGA and post-intervention data were collected using the same instruments. The main outcome measures were "good" knowledge of the new policy, stock of recommended ACTs and sale of recommended ACTs.
The training increased "good" knowledge of the policy by 35.5% ($p<0.0001$) in the intervention LGA compared to 6.6% in the control LGA ($p=0.189$). Shops having a stock of recommended ACTs increased by 25.6% ($p<0.001$) in the intervention LGA compared to 4.5% ($p=0.597$) in the control LGA. Post-intervention, 20% more PMVs ($p=0.273$) offered mystery clients ACTs as first antimalarial drug compared to 15% ($p=0.501$) in the control LGA.
Training of PMVs improved their knowledge of the current antimalarial treatment policy and their treatment practices but other determinants of malaria treatment in the rural areas need to be addressed. Nation-wide training of PMVs operating in the rural areas is recommended.

3017 Ivermectin to malaria elimination: evaluation of a novel tool against an American vector

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Ivermectin is an endectocide widely used in the treatment of parasites such as helminths and arthropods. It is a safe and has a low toxicity to vertebrates. It has a good effect on a stratum of vector population of mosquitoes with outdoor behavior, on which the current instruments have little effect. In addition, the drug can be combined with other drugs used to treat malaria, adding another field of action to an existing tool. The goal of this work is to verify the effect of ivermectin on the survival of *Anopheles aquasalis*.
The blood samples were collected from volunteers before drug administration and subsequently, ivermectin was administered as recommended (200mcg/Kg body weight, VO). After different times (4h and 14 days post-ingestion - DPI) we proceeded to the respective blood collections. Blood samples were used to artificially feed groups of female *An. aquasalis*, using artificial feeder with Parafilm® membrane. The mosquitoes were kept for 8 days followed by checking the mortality every 12 hours. The cumulative mosquito mortality was 59,2%, 94,5% and 76,2% to control, 4h and 14 DPI, respectively ($p<0.01$). A Kaplan-Meier survival analysis has shown significant differences, indicating that ivermectin decreased survival time of females of the experimental groups ($p <0.01$).
This result points to a great perspective for the use of the drug as a novel tool in malaria eradication local programs at Latin America. Considering the safety profile of the drug, it is possible to glimpse its use in some situations like in mass drug administration in areas where mosquitoes are exophilic.
Acknowledgement: CNPq, FMT-HVD

3018 Direct on blood PCR-NALFIA system: a simple but sensitive molecular diagnostic platform for malaria elimination

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Molecular tools allow for specific/sensitive malaria diagnosis, but current formats, like PCR with gel-electrophoresis, are difficult to implement in resource poor settings. Therefore, a simple, fast, sensitive/specific molecular diagnostic platform, direct on blood PCR combined with nucleic acid lateral flow immunoassay (NALFIA) to detect amplified PCR products of Pan-*Plasmodium* and human GAPDH (internal control) was developed and evaluated under laboratory conditions, a multi country ring trial and in two malaria endemic countries.

Analytical sensitivity/specificity of PCR-NALFIA in a single laboratory evaluation was >95% and able to detect 1 parasite/µl blood. All laboratories in the ring trial reported ease of use of the system and could successfully perform the protocol. Overall laboratory inter variability was low and the agreement of reported results was high. Overall k-value was 0.89 (95% CI: 0.83 – 0.94; $p<0.001$). Overall test sensitivity and specificity was >95% with very small confidence intervals. Field evaluations in disease endemic countries, Thailand and Burkina Faso, were performed. In Burkina Faso the relative sensitivity was 94,8% and relative specificity 82,4% compared to microscopy and 93,3% and 91.4% compared to RDT. In Thailand the relative sensitivity and relative specificity was 93,4% and 90,9 respectively compared to microscopy and 95,6% and 87.1 % compared to RDT. These numbers are under estimation of test performance as the results are not PCR corrected. The simplicity of the system combined with its high sensitivity make the PCR-NALFIA a suitable system to be employed in malaria elimination programmes.

Funding: EU FP7 grant 201889 Multi drug resistance in malaria under combination therapy: assessment of specific markers and development of innovative rapid and simple diagnostics (MALACTRES), to be further developed in DIAGMAL EU FP7 grant: 601714.

3019 The science of biodegradable nanoparticles and magnets for the development of DNA blood-stage malaria vaccines

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Biodegradable nanoparticles can be engineered to be affective antigen carriers as well as immune adjuvants for DNA vaccines against blood-stage malaria. In the case of DNA vaccines, we further investigated the use of nanomagnets to enhance the efficiency of transfection by vaccine plasmids in dendritic cells (DC). Such DNA vaccines also benefit from activating DC, increasing their capacity to stimulate T cells. We used magnetic nanovectors comprising polyethyleneimine (PEI)-coated superparamagnetic iron oxide nanoparticles (SPIONs), formulated with/without further hyaluronic acid (HA) polymers of different molecular weights. The later was used to further reduce cytotoxicity, and facilitate endocytosis of particles via specific surface receptors, as well as to activate DC maturation., A number of SPION/HI/PEI/DNA nanoplexes encoding *Plasmodium yoelii* merozoite surface protein MSP1-19 and yellow fluorescent gene (YFG), efficiently transfected and matured DC *in vitro*. Vectors with the highest molecular weight HA yielded superior transfection efficiency and the application of magnetic fields further significantly enhanced DC transfection and maturation. The above formulations were further tested *in vivo* as malaria nanovaccines via different routes of administration (intraperitoneal, intramuscular and subcutaneous), further with/without the influence of a magnetic field at the site of injection, to promote an antigen depot effect. The results confirmed *in vitro* findings, with up-regulation of CD86 and increased DC transfection *in vivo* after immunization, and the induction of high levels of antibodies, which were further increased by using a magnetic field during immunization. Different polymer ratios and the magnetic field influenced preferential induction of Th1 or Th17 cells and cytophilic antibodies to MSP-19.

3020 Identification of a gene that is essential for commitment to gametocytogenesis in malaria parasites

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Progressive decrease in *Plasmodium* gametocytogenesis, a critical & major population bottleneck, has been observed during prolonged maintenance of bloodstream forms. This loss of gametocytogenesis is not associated with gross genetic variations but smaller mutations remain undetected. Multiple genetic loci that become mutated & positively selected during repeated asexual multiplication may control gametocytogenesis.
We explored the hypothesis that the loss of gametocytogenesis is reflected in the parasite at genome sequence and/or epigenetic level. Ten parallel infections of mice with *P. berghei* ANKA clone 820 (produces RFP in female & GFP in male gametocytes) were set up. The parasites were asexually maintained in mice for about 52 weeks by weekly mechanical passages to naïve mice. Each week, gametocytemia was monitored with FACS. Three out of potential ten lines became Gametocyte Non-Producers (GNPs) during the passage period. The GNPs & the parental producer lines were sequenced using the Illumina platform & comparatively analyzed for SNPs/indels. Data analyses reveal one & the same single gene, an ApiAP2 protein, which is uniquely mutated in each of the 3 GNP lines. Evidence from pre-existing GNP lines also supports the gene involvement. Knockout of the identified gene using multiple approaches produced the GNP phenotype. Complementation of the natural mutants restored the wild type phenotype. Electromobility shift assays show that the tagged DNA binding domain from the gene recognizes & binds to its identified cognate motif in a sequence-specific manner.
The data clearly show that the ApiAP2 protein is essential (& is the likely molecular switch) for commitment to gametocytogenesis. The study opens new avenues for exploiting the gene as a transmission-blocking target.

3021 Large-scale evaluation of mosquito repellent as an additional control measure in tackling malaria in pre-elimination areas

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In southeast Asia a substantial decrease of malaria has been achieved during the last decade. Cambodia alone reported a 75% decrease in microscopically confirmed malaria cases and elimination is now becoming a realistic goal. However outdoor and/or early biting vectors expose humans to a transmission window which is not covered by a wide distribution of insecticide treated nets (ITNs). This may compromise elimination efforts. Massive use of repellents may close the gap. Hence we set up a study to evaluate the public health value of mass use of a topical repellent in addition to ITNs. In the province of Ratanakiri, Cambodia a community based randomized study was conducted covering a population of 40,000 inhabitants. Following a pre-trial survey, 98 clusters were randomly divided in two arms: one intervention arm (ITN and repellent) and one control arm (only ITNs). The principal indicator of effectiveness is the prevalence of parasite carriers measured by PCR techniques using a mobile molecular lab in the field. This will allow us to evaluate the treatment effect in both symptomatic and asymptomatic individuals. Secondary indicators include the measurement of multiple malaria antibodies and passive case detection based on an extensive network of local health centres and Village Malaria Workers. The effectiveness of the intervention will depend on the efficacy of the repellents against vector bites and the effective use of the repellent in the population, which are evaluated by entomological and socio-anthropological field studies. The study is registered as NCT01663831. Preliminary results will be presented.

3022

WITHDRAWN

3023 Q_o vs. Q_i Inhibition of Cytochrome bc_1 Produces Distinct Biological Responses in *Plasmodium*

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The treatment and eradication of malaria depends on the ability of antimalarial drugs to safely and effectively eliminate *Plasmodium* parasites. Mitochondrial inhibitors, including inhibitors of the cytochrome bc_1 complex, are especially valuable therapeutics due to their sustained activity throughout the *Plasmodium* life cycle. Although the cytochrome bc_1 complex contains two inhibitable quinoid binding sites: a reductive (Q_i) site and an oxidative (Q_o) site, the vast majority of *Plasmodium* bc_1 inhibitors act exclusively at the Q_o site, and the benefits of Q_i vs. Q_o inhibition in *Plasmodium* have never been fully characterized.

Here, we introduce a subset of endochin-like quinolones (ELQs) that demonstrate Q_i site inhibition, and characterize the biological effects of these compounds in comparison with the canonical Q_o inhibitor, atovaquone. We verify Q_o vs. Q_i site inhibition using affinity assays, cytochrome *b* reduction, and EPR, and subsequently assess growth, resistance propensity and compensative responses in *Plasmodium* following drug treatment. Strikingly, we find that although Q_o inhibitors have more rapid antiplasmodial activity, Q_i site inhibitors are both more resistant to mutation and more likely to retain potency against clinically relevant, drug resistant *Plasmodium* strains. We hypothesize that these effects result from mitochondrial bypass reactions that increase oxidative stress conditions in response to Q_i site inhibition, which ultimately results in a two-pronged, insurmountable stress against the parasite. The vastly different outcomes observed with Q_i vs. Q_o site inhibition in *Plasmodium* suggest that clinical formulations combining Q_i and Q_o site inhibitors could have significant impact as fast-acting, dual-action therapies that limit the propensity for drug resistance.

NIH-AI-079182, NIH-AI-100569

3024 Tackling imported malaria: the elimination endgame

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As countries move towards malaria elimination, imported infections become increasingly important as they often make up the majority of cases, can sustain transmission and cause resurgences. A variety of different methods are used to tackle importation but these vary by country and are often not evidence based. Furthermore, criteria used to classify imported cases vary between countries. This presentation reviews and critiques current methods used in malaria settings, including improving healthcare accessibility, border screening, improving personal protection, reducing local receptivity, introducing Public Private Partnerships to target migrant workers and at-source testing and treatment. In addition, we look at potentially useful methods applied in other settings such as mobile alerts, screening incentives and network sampling approaches. Moving forward will require standardized methods to classify infections as imported, which may include, or be validated by, information from genotyping. In addition, a better understanding of the characteristics and sources of imported infections is required alongside an assessment of diagnostic performance in screening campaigns and an exploration of methods to improve uptake of personal protection. Furthermore, effort should be made to minimize local receptivity and reduce the transmission potential of imported infections once they have entered an eliminating region. Cross border and regional initiatives should also be encouraged as these have been effective tools to reduce rates of importation in the past. A better understanding of human movement patterns in relation to malaria transmission would help to identify which countries should work together and where interventions should be targeted. Determining the optimal combinations of approaches will ultimately require an evaluation of their impact, cost-effectiveness and operational feasibility.

3025 Transdermal Hemozoin-Generated Vapor Nanobubbles for Noninvasive Reagent- and Needle-Free Detection of Malaria

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Successful diagnosis, screening and elimination of malaria critically depend upon the ability to detect any type of malaria parasite with high sensitivity and speed, preferably *in vivo* and without sophisticated reagents.

Here we show that the high optical absorbance and nanosize of intracellular heme crystals called hemozoin, a unique component of all blood-stage malaria parasites, generate a transient vapor nanobubble around hemozoin in erythrocyte stages of the malaria parasite in response to a short picosecond laser pulse. The optical scattering and acoustic signals of these nanobubbles, generated with a miniature laser probe, detect hemozoin and malaria parasites in a wide range of parasitemias and with the high sensitivity: 5 per microL in whole blood *in vitro* and 15 per microL transdermally in malaria-infected mice *in vivo*. This first transdermal non-invasive detection of a malaria infection on a mouse took 20 seconds without using any reagents or a needle to obtain blood due to the high sensitivity, speed, safety and simplicity of hemozoin-generated vapor nanobubbles.

This nanobubble transdermal detection adds a new dimension to malaria diagnostics separate from previous diagnostic approaches, which all rely upon using a needle to obtain blood, reagents to detect the infection and are time- and labor-consuming.

Grant acknowledgement-NIH R01GM094816 (DOL) and S10RR026399-01

3026 Prospective Analysis of Peripheral Blood Parasitemia in *Plasmodium Vivax* Patients Revealed an Unexpected Low Percentage of Circulating Schizonts

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Plasmodium vivax malaria research has received a renewed interest in view of the new elimination/eradication proposal. *P. vivax* is known to be predominant in the Brazilian Amazon reaching 91.72% of the total cases in 2012. To help clarify the field for a *P.vivax* research speed up strategy onwards eradication, from August 2012 until May 2013 we collected samples from 188 patients to revise some of the basic concepts generally given by fact. We first determined the mean peripheral parasitemia throughout the year which was of 0.32%. Next, we determined the percentage of asexual blood stages as it is amply accepted that all stages circulate in peripheral blood of *P. vivax* patients. Strikingly, only 21.87% of our patients presented peripheral blood schizonts at the moment of collection and of them, 83.3% had less than 20% schizonts, representing only 3.81% in peripheral blood during the period studied while rings and trophozoites represented, respectively, 33.92% and 33.14%. Schizontizemia and parasitemia were not related to each other Gametocytes were present in 81.7% of our patients with a mean of 28.66%. Of further interest, 46.80% of the patients presented synchrony and 12 out of 40 (30%) ring-synchronized patients studied presented multi-parasitization. In summary, schizonts were mostly not observed in peripheral blood reinforcing the recent *in vitro* data indicating that *P.vivax* parasites cytoadhere in internal organs and obligating us to take this latest into account when planning interventions towards *P.vivax* eradication.

3027 Artesunate Mode-of-Action may Involve Decreased Translation Accuracy

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The design of novel antimalarial entities could be accelerated by better understanding of the modes-of-action of current drugs. The yeast model provides a powerful tool for mode of action discovery. Here, yeast was used to gain new insights to the action of artesunate, a current drug of choice for treating severe malaria.
A genome-wide collection of yeast deletion mutants was screened for sensitivity to artesunate. Genes associated with transcription elongation and ribosome-related function were over-represented among the annotations of mutants which exhibited artesunate sensitivity. This led us to hypothesize that artesunate may perturb protein synthesis. In both yeast and *Plasmodium berghei* we observed synergy in the actions of artesunate and the aminoglycoside paromomycin, an agent known to cause translation errors during protein synthesis. Further investigation using a luciferase reporter assay showed that artesunate perturbs normal protein (re)folding, through an oxidative stress-independent mechanism, again indicating protein synthesis errors. Errors in translation appeared to be amino acid specific as artesunate sensitivity could be rescued by serine addition but was exacerbated by threonine. This affect is been further investigated using a novel yeast reporter strain.
The work presented here points to a new mechanism of artesunate action, involving perturbation of translation fidelity. The results suggest the possibility of novel drug combinations for malaria treatment and the potential for targeting the translation machinery in future drug development.

Funded by the BBSRC (UK): Biotechnology and Biological Sciences Research Council

3028 Very high rates of asymptomatic, submicroscopic *P. vivax* infections in an area of low transmission in the Solomon Islands

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Solomon Islands is intensifying its efforts towards malaria elimination. At low transmission, many infections are asymptomatic and of low density and access to sensitive molecular diagnosis of parasites is required. A cross-sectional survey of 3501 participants of all ages (>6 months) was conducted in Ngella to assess carriage of microscopic and submicroscopic *Plasmodium falciparum* (*Pf*) and *Plasmodium vivax (Pv),* including gametocytes. Light microscopy (LM) was accompanied by genus-specific and species-specific *18S* rRNA gene qPCR for diagnosis of *Pf* and *Pv* infections. *Pfs25* and *pvs25* RT-qPCR assays were used for the detection of sexual stages.

The overall LM prevalence by any *Plasmodium spp.* was 3.9% (125 *Pv, 5 Pf* & 7 mixed *Pf/Pv*). Analysis by qPCR revealed a 3 times higher prevalence of *Plasmodium spp.* infections of 13.1% (455 *Pv* and 5 mixed *Pf/Pv*). Overall, submicroscopic infections accounted for 77.2% of all infections. There was significant variation in the prevalence of *Pv* infections between villages (3.0% to 30.7%, $p < 0.001$) and among age groups (5.6% to 22.5%, $p < 0.001$). The prevalence of microscopic (8.5%) and submicroscopic *Pv* infections (14.3%) peaked in children aged 10-15yrs. The proportion of submicroscopic infections was highest in participants ≥15 year (81.6%). Children under the age of 5 revealed the lowest prevalence of *Pv* infections of any density. Of 132 individuals with microscopic *Pv* infections, 16.7% were febrile as compared to 14.3% of participants with submicroscopic *Pv* infections. qPCR confirmed 5 *Pf* infections, all from the same village. Four were positive by LM and, interestingly, in 3 of these only gametocytes were detected.

In conclusion, Ngella remains endemic for *P. vivax* malaria, with the vast majority of detected infections being asymptomatic (85%) and below the detection limit of light microscopy used by the Solomon Islands malaria program. *P. falciparum* malaria on the other hand was found in only one location and it remains unclear whether these infections represent a focus of local transmission or imported infections.

Funding acknowledgement: NIH/NIAID UN19AI089686 and NHMRC (GNT1021544; APP1056511)

3029 Effective program management: a cornerstone of malaria elimination

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To eliminate and eventually eradicate malaria effective program management is essential. Program management in a malaria elimination setting differs from program management in a malaria control setting in a number of ways, and there is currently a lack of research and understanding of these distinctions. In addition to elimination specific program management, several core features of successful health program management are critical to achieve elimination. These include: strong leadership and supervision at all levels, sustained political and financial commitment, reliable supply and control of physical resources, effective management of data and information, appropriate incentives and consistent accountability. However, confronting malaria is a unique challenge that requires additional program management considerations. Adding to the complexity, the requirements of an elimination program may conflict with those of a control regime. Thus, an additional challenge is successfully managing the transition from control to elimination. This paper identifies potential solutions by exploring managerial approaches that are relevant and sustainable in various cultural contexts and where local health systems are themselves under constant change. These approaches must be flexible, successfully contributing to malaria elimination despite operational variation in the field.
Understanding how program management has contributed to the success or failure of malaria elimination programs is essential to identify efficacious managerial approaches. There is evidence that malaria elimination often fails, even in countries where malaria control programs have been successful. Some countries overcame these challenges by following elimination program failures with successful corrective action, not only to the interventions but also to management approaches. Success of a malaria elimination program is determined not just by the public health interventions *per se*, but by the ability to manage the implementation of those interventions, including a sustained surveillance and readiness to respond. Failures result from a combination of complex factors, and include the operational constraints of malfunctioning health systems in target regions and the difficulties of developing and sustaining financial and political commitment. This paper offers an analysis of these factors and provides guidance to address them.

3030 A high throughput approach to creating monoclonal antibodies recognizing *Plasmodium falciparum* gametocytes

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One important goal necessary for eradicating malaria is eliminating transmission from the human host to the mosquito. However, the process of gametocytogenesis in *Plasmodium falciparum* is not well understood, limiting the use of rational design approaches for drugs and vaccines. In order to identify new proteins associated with gametocyte development, improve high throughput compound screens and identify transmission blocking targets we are creating a large panel of novel gametocyte-specific antibodies. We are using an unbiased, high-throughput approach to maximize the number and type of different monoclonal antibodies created. Briefly, three Balb/C mice were immunized with protein lysate derived from parasites harvested at all five stages of *P. falciparum* gametocyte development. Afterwards, we performed an electrofusion of the mouse splenic B-cells with myeloma cells and were able to generate 24194 hybridoma clones. In a large scale ELISA, we screened these hybridomas for reactivity against gametocytes using mixed-stage gametocyte lysate. This resulted in 919 gametocyte reactive clones, which were counter-screened against erythrocytes and asexual stage parasites. After elimination of the hybridomas with crossreactive signal, we were able to identify 196 gametocyte-specific monoclonal antibodies. Using immunofluorescence we show that ~55% of these recognize a variety of intracellular and even extracellular structures found only in mixed *P. falciparum* gametocytes but not in asexual parasites.
Those antibodies are currently being tested *in vitro* for possible stage and sex specificity by immunoflourescence. In addition to serving as reagents that can be used to characterize the action of small molecules against gametocytes, these antibodies may reveal targets that are critical to gametocyte development and this could lead to new vaccines and drugs with transmission blocking activity.

3031 Development of Fluorescent Qualitative and Quantitative assay with high sensitivity for diagnosis of Malaria

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ELISA, PCR, and RDT have been developed to diagnose malaria but due to time-consuming for diagnosis and inefficiency of mass screening, those approaches have practical limitations.
In this study, the novel fluorescence immune diagnostic assay was developed with the monoclonal antibody against *Plasmodium* Lactate Dehydrogenase (LDH) and fluorescence dye optimized at Light Emitting Diode (LED).
The monoclonal antibody against *Plasmodium* LDH was able to diagnose human *P. vivax* and *P. falciparum* as well as rodent *P. berghei*.
Fluorescence-linked immunosorbent assay (FLISA) and fluorescent immunochromatographic test (FICT) using fluorophore and monoclonal antibody determined parasitemia up to 0.2% and at least 0.1 ng of LDH antigen.
FLISA and FICT with malaria specimens showed 100% of the sensitivity and cross-reactivity was not found in other patient's specimens (i.e., HCV and HIV).
Moreover, using standard specimens of *P. falciparum* infected patient in Burma, the intensity of fluorescence were found to be increased upon infection rate (R^2=0.9879).
Standard samples of *P. berghei* infected mouse showed the same diagnostic performance of quantitative analysis (R^2=0.9922).
Therefore, new fluorescent immunochromatographic assay are applicable for both qualitative and quantitative diagnosis of malaria.

This research was supported by a Research fund(2013E5400800) of the Korea Centers for Disease Control and Prevention, and by the Public Welfare & Safety Research Program through the National Research foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2010-0020803).

3032 High Population Genetic Diversity of *Plasmodium vivax* in Jiangsu and Anhui Provinces in Central China

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Background: *Plasmodium vivax* (*P. vivax*) is the world's most widely distributed parasite causing malaria. Jiangsu and Anhui are geographically adjacent provinces in central China with low prevalence of *P. vivax*. Genetic diversity data of *P. vivax* in this region is limited. In this study, we used microsatellite genotyping to investigate genetic diversity and population structure of *P. vivax* in this region.

Methods: A total of 150 *P. vivax* isolates (Jiangsu: 43/Anhui: 103) collected from 2007 to 2010 were genotyped by molecular markers including Pv3.27, MS16, MS1, MS5, MS8, MS10 and msp1F3. Population genetic statistics was conducted by Menzies-APMEN *P. vivax* genotyping database.

Results: 133 *P. vivax* isolates (Jiangsu: 34/Anhui: 99) were successfully genotyped. *He* values of Pv3.27, MS16, MS1, MS5, MS8, MS10 and msp1F3 were 0.88, 0.94, 0.79, 0.78, 0.76, 0.46 and 0.82, respectively. Population level diversity (*He*) was high and average *He* of Jiangsu and Anhui was 0.77±0.06 and 0.80±0.04. Multi-locus linkage disequilibrium (LD) was significant in Anhui (I^S_A=0.2128, p<0.01), Jiangsu (I^S_A=0.2915, p<0.01) and central China as a whole. Four identical haplotypes were shared by Jiangsu and Anhui. The pair-wise Fst value (0.027±0.014) did not identify genetic differentiation between Jiangsu and Anhui population.

Conclusions: Although Jiangsu and Anhui are low malaria transmission areas, microsatellite genotyping showed high population genetic diversity of *P. vivax* in this region. *P. vivax* genetic diversity data from this study can be used to compare with data from other countries.

3033 Genome wide association via Loss of Heterozygosity Identifies *Toll* genes related to *Plasmodium falciparum* susceptibility in *Anopheles gambiae*

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Despite the successful application of genome-wide association studies (GWAS) techniques to both parasite and human hosts of malaria, the insect vector remains intractable. Due to a combination of extremely high genetic diversity and a complex population structure, individual-based studies are frequently unsuccessful; an unfeasibly large number of samples are needed in order to make significant associations.
We present here a two-stage experimental design in which a single infection of ~100 individuals is pooled on the basis of phenotype and deep sequenced. Loss-of-heterozygosity is subsequently used to identify regions that have been 'swept' in the phenotype pools, before SNP typing (Sequenom) is used to confirm the association in individuals.
This method was applied to wild populations of *Anopheles gambiae* mosquitoes from Mali and Burkina Faso that were infected via bloodmeal with *Plasmodium falciparum*. Pooled sequencing identified large (3-8mb) loci, that were further confirmed and refined with sequenom typing. This lead to robust statistical associations for a single (0.5mb) locus containing two *Toll* genes. RNAi KD of genes within this locus shows a phenotypic effect on infection prevalence. Work is currently underway to further investigate mutations within this locus for direct association with vector competence.

3034 Genetic diversity in parasite populations and the clinical outcome of *Plasmodium falciparum* infection in children from north-central Nigeria

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Background
Malaria is the world's most important tropical parasitic disease. *Plasmodium falciparum*, the most virulent human malaria parasite, responsible for most of the malaria-related deaths, exhibit substantial genetic variability especially in merozoite surface antigens, which are considered potential targets for malaria vaccine. This study investigated the genetic diversity of *P. falciparum* infections and its possible association with disease outcome by genotyping the nucleotide sequence encoding the merozoite surface protein-2 (*MSP-2*) in children in Lafia, north-central Nigeria.

Methods
A total of 437 children were enrolled into this study and grouped based on clinical presentation into three categories: severe malaria, uncomplicated malaria, or asymptomatic infection. DNA was extracted using the QIAmp® DNA Mini Kit. Genetic diversity was analyzed by PCR genotyping of *MSP-2*. Purified PCR products of samples showing single band were sequenced on ABI PRISM® 3100 Genetic Analyzer.

Results
Multiplicity of infection was 2.1 (95% CI=1.9-2.3) in the non-symptomatic group, 2.0 (95% CI=1.8-2.4) in the uncomplicated malaria and 1.3 (95% CI=1.2-1.6) in the severe malaria group. Polyclonality was significantly higher in non-symptomatic (61%) and uncomplicated malaria (60%) groups compared to the severe malaria (34%) group ($P<0.001$). A total of 32, 35 and 28 distinct *MSP-2* alleles were found in the non-symptomatic, uncomplicated and severe malaria groups respectively. Frequency of the 3D7 allele type was significantly higher in the severe malaria group (54%) and the uncomplicated malaria group (51%) compared to the non-symptomatic group (38%; $P=0.008$ and $P=0.014$ respectively). Sequence analysis showed that the FC27-type sequence was characterised by two distinct subtypes and a hybrid sharing amino acid sequences from the two subtypes. The 3D7-type sequence was characterised by three subtypes of repetitive domains: the GSA-rich repeat unit, a TPA repeat motif (present in 1 to 7 copies) and a poly-Threonine stretch (present in 8 to 14 copies). However, variations in the sequence of the repeats were not significantly different between the groups.

Conclusions
Isolates in this region are genetically heterogeneous. Carriage of the 3D7 allele was associated with clinical disease. Furthermore, the study provided sequence haplotypes that are dominant in this region. Data from this study will also serve as baseline for assessing future interventions.

3035 Identification of Potent Combinations of Key *Plasmodium falciparum* Merozoite Antigens That Elicit Strain-Transcending Parasite-Neutralizing Antibodies

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Blood-stage malaria vaccines that target single *Plasmodium falciparum* invasins have not induced optimal protection in field trials. Blood-stage malaria vaccine development has faced two major hurdles, antigenic polymorphisms and molecular redundancy, which have led to an inability to demonstrate potent, strain-transcending, invasion-inhibitory antibodies. Vaccines targeting multiple invasion-related parasite proteins may inhibit erythrocyte invasion more efficiently. Our approach is to develop a blood-stage vaccine against *P. falciparum* that targets the erythrocyte binding domains of multiple parasite adhesins. However, with numerous invasion ligands, the challenge is to identify combinations that elicit potent strain-transcending invasion inhibition. We evaluated the invasion inhibitory activities of 30 different triple combinations of antibodies mixed *in vitro* against a diverse set of seven key *P. falciparum* merozoite ligands, namely PfAARP, EBA-175 (PfF2), PfRH1, PfRH2, PfRH4, PfRH5 and PTRAMP, which are localized in different apical organelles and are translocated to the merozoite surface at different time points during invasion. They bind erythrocytes with different specificities and are thus involved in distinct invasion pathways. PfRH5-based antibody combinations produced the most efficacious strain-transcending invasion inhibition. Two of these were further selected for co-immunization as mixtures that induced balanced antibody responses against each antigen and inhibited erythrocyte invasion efficiently. We have thus demonstrated a novel two-step screening approach to identify antigen combinations that elicit potent strain-transcending invasion inhibition. Our results strongly support the development of PfRH5 based combination blood-stage malaria vaccines.

3036 Modulation of privileged structures by prenylation: A new tool for antiparasitic drug discovery

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One of seven people in the world is affected by Neglected Tropical Diseases. Treatments of these diseases are insufficient and inefficient and require constant development of new drugs and strategies. Within the universe of small organic molecules, the isoprenoids are the most important and numerous families of metabolites. In this regard, it is useful to focus on the design, synthesis and studies of molecular probes that interfere with different biosynthetic routes, particularly the isoprene and sterol pathways. The implemented strategies used modern medicinal chemistry approaches like diversity-oriented synthesis, parallel solution library preparation, conventional multistep synthesis, midthroughput screening, bioinformatics and computational chemistry, allowed to generate more than 100 new compounds.
The generated libraries were tested against the parasites responsible of the malaria (*P. falciparum* chloroquine sensitive and resistant strains), visceral leishmaniasis (*L. donovani*), HAT (*T. brucei*) and Chagas´ disease (*T. cruzi*). As result of our effort we have found very promising new hits to develop drugs against malaria and other diseases.
Our strategy also included action mechanism studies of the lead compounds. To do that, fluorescent tagged isoprenes were synthesized to be incorporated on the lead structure to perform cellular localization by fluorescent microscopy.

Acknowledgments: This investigation received financial support from the WHO Special Programme for Research and Training in Tropical Diseases (TDR), National Scientific and Technical Research Council – Argentina, Josefina Prats Foundation and National Agency for Science and Technology – Argentina.

3037 Development of *Plasmodium falciparum* Reticulocyte binding-like Homologous Protein 2 (PfRH2) as a Blood-Stage Malaria Vaccine Candidate

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The *P. falciparum* reticulocyte binding-like homologous (PfRH) family of proteins are key determinants of different erythrocyte invasion pathways. Out of five functional PfRH proteins, we report that only native PfRH2 undergoes processing yielding fragments that exhibit differential erythrocyte binding specificities. Consistent with previous PfRH2 knockout studies, the RBC binding specificity of native PfRH2 was sialic acid-independent, trypsin resistant and chymotrypsin sensitive. However, a smaller processed fragment bound erythrocytes with a different phenotype. To further characterize the processing sequence and localization of the resulting fragments, we have raised specific antibodies against different regions of the PfRH2 ectodomain. We have mapped the erythrocyte binding domain of PfRH2 to a conserved 40kDa N-terminal region ($rPfRH2_{40}$).Recombinant $rPfRH2_{40}$ bound to erythrocytes in a sialic acid independent, trypsin resistant, chymotrypsin sensitive manner, consistent with the binding of the native protein. PfRH2 antibodies against only the 40 kDa receptor binding domain were able to efficiently block erythrocyte invasion and further produced synergistic inhibition of invasion in combination with antibodies against other parasite ligands such as EBA-175 and PfAARP. A recent study has demonstrated that PfRH2 is naturally immunogenic in humans residing in malaria endemic regions and that PfRH2 antibodies exhibited the highest association with protection against malaria among a pool of 91 recombinant blood-stage antigens. We have developed and optimized a process for the production of $rPfRH2_{40}$ with cGMP specifications for it's clinical development. Thus, $rPfRH2_{40}$ is a major candidate antigen under the ICGEB portfolio for the development of a new generation combination based blood-stage malaria vaccine.

3038 Awareness of Artemisinin Combination Therapy in the treatment of malaria at some rural communities in Ekiti State, Southwest Nigeria

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Many of the West African countries have changed antimalarial treatment policy to Artemisinin-based Combination Therapy (ACT) as an effective approach to limit the wide spread of *Plasmodium falciparum* resistance. It is however still common for many people to use CQ or other conventional antimalarial drug for treatment of malaria in Ekiti State. This study therefore sought to assess the use of chloroquine (CQ) after change of policy in Nigeria and awareness of people to the use of ACT in the treatment of malaria.
A community-based cross-sectional study was conducted in Ekiti State, Southwest Nigeria. Questionnaire was administered to randomized selected communities in Ekiti. A total of 110 questionnaires were sent out and had 103 respondents. The questionnaire sought to know demography details, socioeconomic, educational status, drug use habit of individuals and their awareness of the antimalaria treatment policy.
Their age ranged from 17- 83 years (mean 37.5±17.1yrs). Out of the 87 respondents who have been using CQ, 12.6% used CQ less than a year ago, while 29.9% used CQ to treat malaria over a year ago, and 57.5% of the respondent cannot recall when they last took CQ. 17.3% prefer to use CQ for malaria treatment. Similarly, 65.0% of the respondents are not aware of the change in policy to ACT. Most respondents that are not aware of ACT were 59.7% of females, 44.7% unemployed and 8.9% were uneducated individuals. Among those that were aware, 45.5% of them have never used ACT before based on the report that the drug was not readily available and even expensive to buy.
People in the rural communities of Southwest Nigeria are not aware of the policy change in the treatment of malaria. Therefore, there is need for health education of the populace on the appropriate treatment of malaria. This will contribute to a reduction in the level of antimalaria drug resistance in our community

3039 Low use of Insecticide Treated Nets and other antimalarial practices during pregnancy in urban in Sub-Ghana

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Introduction: Insecticide Treated Nets (ITNs) are effective tools in the reduction of morbidity and mortality from *Plasmodium falciparum* infection among children and pregnant women living in malaria endemic areas. The recommended coverage of bednets among pregnant women is 60%. As part of efforts to achieve the Millennium Development Goal No. 4 free ITN distribution was commenced for pregnant women at their initial visit for antenatal care (ANC) after prior information on its benefits and use. Although the bednets were distributed, there was no evaluation to assess their use by the pregnant women. The study was therefore carried out to assess knowledge, ownership and use of the ITNs and to collect information on other antimalarial practices among pregnant women in a Sub-urban town in coastal Ghana.
Methods: A cross-sectional survey was conducted to collect information on the use of ITNs during pregnancy. Two hundred and thirty-five women who were reporting for a first post-natal appointment at the Maternal and Child Health Unit of a sun-urban hospital were interviewed. A structured questionnaire was administered to randomly selected women the bi-weekly child welfare clinics over a period of 10 weeks. Other information was obtained from their antenatal records in their ANC attendance books.
Results: The pregnant women had a high knowledge (93.2%) of ITNs and previous experience in the use of bednets in general (58.7) with 39.6% possession of the ITNS. The usage of ITNs ranged from a scale of usage the previous night of the interview to never used as follows; Used the previous night was 20.9% and never used was 6.4 %. The rest ranged from sometime to occasional use 72.8%. The main reasons for non-use of ITNs were; fear that chemicals used to treat the nets will harm their baby (87%), no mosquito presence or nuisance (73%). Other anti-vector personal protection measures were not used. A health facility was the first point of call for most of the women.
Conclusions: The coverage of bednets is low in this community. The distribution system for ITNs needs to be reviewed in order to improve coverage. Some pregnant women still sleep under untreated nets, while others are not convinced that the chemicals used to treat the nets are safe for themselves and for their unborn children. In spite of poor ITN coverage other prevention methods against mosquito bites are not used due to perceived low mosquito populations and absence of mosquito.

Key words: Malaria, pregnancy, ITNs, Usage, insecticide

3040 Gut associated and systemic antibody response, age variation in antibody responses and histopathological changes in mice immunized with *Lactococcus lactis* expressing a malaria parasite protein

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Gram positive food grade bacteria like Lactococci have significant advantages over attenuated pathogens as vaccine delivery vehicles because of their inherent safety. Plasmodium falciparum merozoite surface antigen2 (PfMSA2) was expressed in recombinant Lactococcus lactis in a form that was partially covalentlyanchored to the peptidoglycan of the cell wall (MSA2cP). Recombinant L. lactis strain was delivered oro-nasally for mucosal immunization to Balb/c mice of ages 1wk (neonates), 6wk (young adults) and more than 25 wks (old adults). Non-recombinant L.lactis was used as control. The serum and faecal antibody response was investigated by ELISA using recombinant MSA2 as antigen and by immunofluorescence assay. Histopathological changes in gut associated lymphoid tissue were investigated.

Antibodies in the faecal pellets were detectable after oro-nasal immunizations by IFA. Serum IgG anti-MSA2 response was significantly higher in young adult Balb/c mice, after oronasal delivery, compared to old mice and neonates. Antibodies elicited in young mice reacted with native MSA2 in the surface of P. falciparum merozoites in an immunofluorescence assay. Enlargement of mesenteric lymph nodes and increased lymphatic infiltration of the lamina propria were noted in both recombinant and non recombinant L. lactis immunized mice. The gastro-intestinal tract was otherwise normal in oronasally immunized mice. The spleen showed periarteriolar lymphoid aggregations in immunized mice.

Recombinant L. lactis is a suitably safe vector for subunit vaccines. Oro-nasal immunizations give rise to detectable faecal antibodies. The foreign proteins expressed in L. lactis can be used in nasal or oral vaccination procedures to elicit protective secretory antibodies in the gut. The antibody responses to recombinant L. lactis were markedly weaker in extremes of age. The histological changes of spleens of older mice support weak antibody response seen. These findings are relevant for further developing L. lactis to deliver vaccines mucosally for use in humans of different ages.

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University of Pittsburgh
School of Medicine

Jerrold R. Turner
University of Chicago

Thomas Tuschl
HHMI/Rockefeller University

Stephanie Wengert Watts
Michigan State University

David R. Webb
The Scripps Research Institute

Thomas P. Zwaka
Icahn School of Medicine at Mount Sinai

Meeting Room Policy

No video equipment, cameras, audio equipment or any other type of recording device will be allowed in the meeting rooms or poster sessions. Occasionally, Keystone Symposia may use such devices for its own publicity purposes. While we do not prohibit laptop computers, cell phones and PDAs, they must not be used for recording and should be operated in "silent" mode out of consideration for speakers and other conference attendees.

Attendees will be required to wear name badges for access to meeting sessions. Due to problems we have encountered at some meetings, we will be performing random badge checks. Attendees without badges will be turned away from the session.

Please note that spouses traveling with registered conference attendees are not permitted inside the sessions unless they pay the registration fee. However, they are welcome to attend evening receptions. They may attend breakfasts upon payment of a nominal daily fee.

Harassment Policy

Keystone Symposia is committed to maintaining a positive and respectful environment at its meetings. To this end, we ask and expect attendees to assist in ensuring that the meetings are free of harassment, sexual or otherwise, including reporting any instances of improper conduct to us. Keystone Symposia expects attendees to conform their conduct at these meetings to the policies and procedures of their employing institution or company. If we learn of improper conduct by an attendee, we will take appropriate action, including reporting such conduct to the attendee's employing institution or company and barring the attendee from participation in our meetings.

Privacy Policy

Keystone Symposia is committed to protecting the privacy of its website visitors and meeting attendees. Keystone Symposia collects personal information when individuals register for our meetings and upon a visitor's request to subscribe to newsletters and meeting announcements (both print and online). Information that our visitors and attendees provide or that is derived from internal website tracking is not sold, rented or shared with any third-party individual or organization. Once on our mailing lists, individuals always have the option of unsubscribing so that they no longer receive all or certain types of our communications.

By participating in a Keystone Symposia meeting, attendees acknowledge that their name and photograph may be published in a limited fashion in materials produced by Keystone Symposia. For example, to make the meeting a more valuable experience for all involved, attendee names and institutions are listed on our website in a secure section accessible only by attendees of the same meeting. Attendee names and institutions are also pre-populated in the mobile app that is publicized only to meeting attendees, but attendees decide for themselves whether to enter further information in the app.

Attendee names and contact information are also listed in the meeting Abstract Book. Except in the Abstract Book in this fashion, we will not disclose attendee contact information, even to other attendees. Photographs of meeting interactions taken by Keystone Symposia may occasionally be used in our marketing literature.

For our full privacy policy, please visit **keystonesymposia.org/privacy**.

If you have any further questions or comments about our privacy policy, please send your feedback to **info@keystonesymposia.org**.

Media and Communications Policy

Keystone Symposia recognizes that presenters of scientific data may have reasons for not wanting early results reported to the general public prior to peer review. We also recognize, however, that raising society's level of science knowledge and awareness is essential for appropriate scientific input into public policy and decision-making by political leaders, which is in everyone's best interest. We therefore encourage and will try to facilitate interactions between the scientists attending our conferences and the media. We ask both to be understanding when considering each other's objectives and the overarching goal of raising science literacy worldwide.

If approached with sufficient advance notice, Keystone Symposia can provide assistance to journalists to contact our speakers and abstract authors directly. We can prearrange interviews with specific meeting organizers, speakers, authors or Keystone Symposia staff.

We ask that all writers attending a Keystone Symposia conference gain approval from a speaker or poster presenter prior to quoting or publishing that individual's scientific results. This policy applies whether you are a professional writer/journalist or a non-journalist blogging about the conference or otherwise sharing information among a group of individuals.

Audio, still photo and video recording by any device (e.g., cameras, laptops, PDAs, cell phones, watches) is strictly prohibited during the sessions, unless in certain circumstances when prior permission must be obtained from Keystone Symposia. Photographs taken by Keystone Symposia may be available on request.

Keystone Symposia welcomes members of the scientific and general media at our meetings. Due to the costs of providing meals and other facilities, payment of the regular registration fee is required. Keystone Symposia may be able to give some consideration to journalists from nonprofit organizations, as well as to journalists who wish to attend the meeting for just one day. Such inquiries and arrangements should be made in advance.

Keystone Symposia does not require our presenters to submit papers, nor do we record or transcribe our sessions. Speaker abstracts are available in the Abstract Book provided to each registrant. Abstract Books are available after the meeting to non-attendees for a nominal fee.

Keystone Symposia provides a venue for scientists to come together and share their ideas with each other in a relaxed setting. While we wish to accommodate members of the press, we ask that all members of the media respect our mission and the freedom we allow our scientists to discuss their work in a protected and informal environment.

If you have questions about this policy, contact Yvonne Psaila, Director of Marketing and Communications, **yvonnep@keystonesymposia.org**, **1.970.262.2676**.

Policy for Displaying Literature at Keystone Symposia Meetings

Keystone Symposia provides financial and in-kind donors with the ability to display a limited amount of literature or small promotional items on a table near the registration desk at Keystone Symposia meetings. Financial donors at certain levels can also insert literature into delegate bags at the specific meeting(s) they have chosen to support. Literature placed by organizations that are not current supporters will be removed until the meeting participant who placed it can be contacted.

Please contact the following Keystone Symposia staff if you are interested in displaying literature at our meetings and becoming a donor:

Financial support (e.g., corporations, foundations):	**Sarah Lavicka**, Assistant Director of Development **1.970.262.2690**; **sarahl@keystonesymposia.org**
In-kind support (e.g., publishers, societies/associations, conference organizers):	**Yvonne Psaila**, Director of Marketing and Communications **1.970.262.2676**; **yvonnep@keystonesymposia.org**

Nonprofit, academic and government institutions may post a flyer about grant and job opportunities or upcoming events of interest on the bulletin board in the registration area. Please see a Keystone Symposia on-site representative if you need help with this or have questions while at the conference.

2013–2014 Keystone Symposia Meeting Series

Advancing Vaccines in the Genomics Era (T1)
Organizers: Bali Pulendran, Chris Wilson and Rino Rappuoli
Oct 31–Nov 4, 2013 | Windsor Barra Hotel | Rio de Janeiro | Brazil

Sensing and Signaling of Hypoxia: Interfaces with Biology and Medicine (A1)
Organizers: Peter J. Ratcliffe, L. Eric Huang, Michael Ohh and Cynthia M. Beall
Jan 7–12, 2014 | Beaver Run Resort | Breckenridge, Colorado | USA

The Ubiquitin System: From Basic Science to Drug Discovery (A2)
Organizers: Ingrid E. Wertz and David Komander
Jan 7–12, 2014 | Big Sky Resort | Big Sky, Montana | USA

Nuclear Receptors: Biological Networks, Genome Dynamics and Disease (A3)
Organizers: Kevin P. White, Donald P. McDonnell and Gordon L. Hager
Jan 10–15, 2014 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

Tissue-Resident Memory T Cells (A4)
Organizers: Cornelia L. Trimble, Rachael A. Clark, Leo Lefrançois (in memoriam) and David Masopust
Jan 12–16, 2014 | Snowbird Resort | Snowbird, Utah | USA

Aging – Pushing the Limits of Cellular Quality Control (A5)
Organizers: Andrew G. Dillin, Daniel E. Gottschling and Thomas Nyström
Jan 12–17, 2014 | Sheraton Steamboat Resort | Steamboat Springs, Colorado | USA

Challenges and Opportunities in Diabetes Research and Treatment (J1)
Organizers: Domenico Accili, Masato Kasuga and Morris F. White
joint with
Obesity: A Multisystems Perspective (J2)
Organizers: Roger D. Cone, Barbara Cannon and Lee M. Kaplan
Jan 12–17, 2014 | Fairmont Hotel Vancouver | Vancouver, British Columbia | Canada

Emerging Cytokine Networks (J3)
Organizers: Daniel J. Cua, Hergen Spits and Federica Sallusto
joint with
Inflammatory Diseases: Recent Advances in Basic and Translational Research and Therapeutic Treatments (J4)
Organizers: Chen Dong, Tadamitsu Kishimoto and Richard A. Flavell
Jan 17–22, 2014 | Fairmont Hotel Vancouver | Vancouver, British Columbia | Canada

Pathogenesis of Respiratory Viruses (J5)
Organizers: Adolfo García-Sastre and Peter J.M. Openshaw
joint with
Innate Immunity to Viral Infections (J6)
Organizers: Caetano Reis e Sousa, Kate A. Fitzgerald and Charles M. Rice
Jan 19–24, 2014 | Keystone Resort | Keystone, Colorado | USA

New Frontiers in the Discovery and Treatment of Thrombosis (A6)
Organizers: Jane E. Freedman, Bruce Furie and Dietmar Seiffert
Jan 26–30, 2014 | Keystone Resort | Keystone, Colorado | USA

Mechanisms and Consequences of Invertebrate-Microbe Interactions (A7)
Organizers: Bruno Lemaitre, Nicole M. Gerardo and Jason Rasgon
Jan 26–30, 2014 | Granlibakken Resort | Tahoe City, California | USA

Growth and Wasting in Heart and Skeletal Muscle (A8)
Organizers: Elizabeth M. McNally, Nadia A. Rosenthal and Leslie A. Leinwand
Jan 26–31, 2014 | Eldorado Hotel & Spa | Santa Fe, New Mexico | USA

RNA Silencing (A9)
Organizers: V. Narry Kim, David P. Bartel and Julius Brennecke
Jan 31–Feb 5, 2014 | Sheraton Seattle Hotel | Seattle, Washington | USA

The Science of Malaria Eradication (F1)
Organizers: Pedro L. Alonso, Chetan E. Chitnis and Lee Hall
Feb 2–7, 2014 | Fiesta Americana | Merida, Yucatan | Mexico

Developmental Pathways and Cancer: Wnt, Notch and Hedgehog (J7)
Organizers: Frederic J. de Sauvage, Mariann Bienz and Jon C. Aster
joint with
Stem Cells and Cancer (J8)
Organizers: Tannishtha Reya, Craig T. Jordan and Philip A. Beachy
Feb 2–7, 2014 | Fairmont Banff Springs | Banff, Alberta | Canada

Cancer Epigenetics (Q1)
Organizers: Sharon Y.R. Dent, Jean-Pierre Issa and Peter A. Jones
joint with
Transcriptional Regulation (Q2)
Organizers: Richard A. Young, Robert G. Roeder and Joanna Wysocka
Feb 4–9, 2014 | Santa Fe Community Convention Center | Santa Fe, New Mexico | USA

Plant Signaling: Dynamic Properties (B1)
Organizers: Ottoline Leyser, Junko Kyozuka and Pamela C. Ronald
Feb 5–10, 2014 | Beaver Run Resort | Breckenridge, Colorado | USA

Molecular Cell Biology of Macrophages in Human Diseases (B2)
Organizers: Frederic Geissmann, Judith E. Allen and Christopher K. Glass
Feb 9–14, 2014 | Hilton Santa Fe Historic Plaza Hotel | Santa Fe, New Mexico | USA

Prophylactic and Therapeutic Antibodies (Q3)
Organizers: Margaret Karow and Neil Stahl
joint with
Biology of B Cell Responses (Q4)
Organizers: Hedda Wardemann, Michael G. McHeyzer-Williams and Michel C. Nussenzweig
Feb 9–14, 2014 | Keystone Resort | Keystone, Colorado | USA

Omics Meets Cell Biology: Applications to Human Health and Disease (B3)
Organizers: Anne-Claude Gingras, Igor Stagljar and A.J. Marian Walhout
Feb 18–23, 2014 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

Mitochondrial Dynamics and Physiology (Q5)
Organizers: Rodrigue Rossignol and Heidi M. McBride
joint with
The Chemistry and Biology of Cell Death (Q6)
Organizers: Guy S. Salvesen, Matthew S. Bogyo and Jennie R. Lill
Feb 18–23, 2014 | Santa Fe Community Convention Center | Santa Fe, New Mexico | USA

The NF-κB System in Health and Disease (B4)
Organizers: Alexander Hoffmann and Louis M. Staudt
Feb 23–28, 2014 | Keystone Resort | Keystone, Colorado | USA

Long Noncoding RNAs: Marching toward Mechanism (B5)
Organizers: Thomas Cech, Edith Heard and Ronald R. Breaker
Feb 27–Mar 4, 2014 | Eldorado Hotel & Spa | Santa Fe, New Mexico | USA

Cilia, Development and Human Disease (C1)
Organizers: Elizabeth Petri Henske, Jeremy F. Reiter and Joel Rosenbaum
Mar 2–7, 2014 | Granlibakken Resort | Tahoe City, California | USA

Parkinson's Disease: Genetics, Mechanisms and Therapeutics (Q7)
Organizers: Patrick A. Lewis, Thomas Gasser and Marcel P. van der Brug
joint with
Alzheimer's Disease – From Fundamental Insights to Light at the End of the Translational Tunnel (Q8)
Organizers: John Q. Trojanowski, Charles F. Albright and Hui Zheng
Mar 2–7, 2014 | Keystone Resort | Keystone, Colorado | USA

Mobile Genetic Elements and Genome Evolution (C2)
Organizers: Nancy L. Craig, Henry L. Levin and Cedric Feschotte
Mar 9–14, 2014 | Hilton Santa Fe Historic Plaza Hotel | Santa Fe, New Mexico | USA

Inflammation, Infection and Cancer (X1)
Organizers: Johanna A. Joyce, Timothy C. Wang and Frances R. Balkwill
joint with
Immune Evolution in Cancer (X2)
Organizers: Suzanne Ostrand-Rosenberg, Olivera J. Finn and Lisa M. Coussens
Mar 9–14, 2014 | Fairmont Chateau Whistler | Whistler, British Columbia | Canada

HIV Vaccines: Adaptive Immunity and Beyond (X3)
Organizers: Nicole Frahm, Susan W. Barnett and Galit Alter
joint with
HIV Pathogenesis–Virus vs. Host (X4)
Organizers: J. Victor Garcia-Martinez, Daria J. Hazuda and Dan R. Littman
Mar 9–14, 2014 | Fairmont Banff Springs | Banff, Alberta | Canada

Metabolism and Angiogenesis (X5)
Organizers: Peter F. Carmeliet and Michael Simons
joint with
Tumor Metabolism (X6)
Organizers: William G. Kaelin, Jr., Benjamin F. Cravatt III and Peter K. Jackson
Mar 16–21, 2014 | Whistler Conference Centre | Whistler, British Columbia | Canada

Lipid Pathways in Biology and Disease (C3)
Organizers: Michael P. Czech, Tobias C. Walther and Morris J. Birnbaum
Mar 19–24, 2014 | Royal Dublin Society | Dublin | Ireland

Big Data in Biology (F2)
Organizers: Lincoln D. Stein, Doreen Ware and Michael Schatz
Mar 23–25, 2014 | Fairmont San Francisco | San Francisco, California | USA

Fibrosis: From Bench to Bedside (C4)
Organizers: Jeremy S. Duffield, Steven R. Ledbetter and John P. Iredale
Mar 23–28, 2014 | Keystone Resort | Keystone, Colorado | USA

Chromatin Mechanisms and Cell Physiology (C5)
Organizers: Thomas Jenuwein and Shelley L. Berger
Mar 23–28, 2014 | Oberstdorf Haus | Oberstdorf | Germany

Complications of Diabetes (X7)
Organizers: Michael A. Brownlee, Matthew D. Breyer and Susan Quaggin
joint with
Innate Immunity, Metabolism and Vascular Injury (X8)
Organizers: Ajay Chawla, Peter Tontonoz and Gwendalyn J. Randolph
Mar 23–28, 2014 | Whistler Conference Centre | Whistler, British Columbia | Canada

The Ins and Outs of Viral Infection: Entry, Assembly, Exit and Spread (C6)
Organizers: Karla Kirkegaard, Mavis Agbandje-McKenna and Eric O. Freed
Mar 30–Apr 4, 2014 | Beaver Run Resort | Breckenridge, Colorado | USA

Novel Therapeutic Approaches to Tuberculosis (C7)
Organizers: Christopher M. Sassetti and Thomas G. Evans
Mar 30–Apr 4, 2014 | Keystone Resort | Keystone, Colorado | USA

G Protein-Coupled Receptors: Structural Dynamics and Functional Implications (Z1)
Organizers: Christopher G. Tate and Fiona H. Marshall
joint with
Frontiers of Structural Biology (Z2)
Organizers: Andrew Ward and Wayne A. Hendrickson
Mar 30–Apr 4, 2014 | Snowbird Resort | Snowbird, Utah | USA

Exploiting and Understanding Chemical Biotransformations in the Human Microbiome (D1)
Organizers: Peter J. Turnbaugh, Curtis Huttenhower and Michael A. Fischbach
Apr 1–6, 2014 | Big Sky Resort | Big Sky, Montana | USA

Epigenetic Programming and Inheritance (D2)
Organizers: Joseph H. Nadeau, Marisa S. Bartolomei, Peter Gluckman and Wolf Reik
Apr 6–10, 2014 | Boston Park Plaza | Boston, Massachusetts | USA

Emerging Concepts and Targets in Islet Biology (D3)
Organizers: Rohit N. Kulkarni, Raghavendra G. Mirmira and Eckhard Lammert
Apr 6–11, 2014 | Keystone Resort | Keystone, Colorado | USA

Engineering Cell Fate and Function (Z3)
Organizers: Darrell J. Irvine, Sangeeta N. Bhatia and Christopher S. Chen
joint with
Stem Cells and Reprogramming (Z4)
Organizers: Deepak Srivastava and Shinya Yamanaka
Apr 6–11, 2014 | Resort at Squaw Creek | Olympic Valley, California | USA

Adult Neurogenesis (E1)
Organizers: Jonas Frisén and Fred H. Gage
May 12–17, 2014 | Clarion Hotel Sign | Stockholm | Sweden

Autophagy: Fundamentals to Disease (E2)
Organizers: Christina H. Eng, Daniel J. Klionsky, Guido Kroemer and Li Yu
May 23–28, 2014 | Hyatt Regency Austin | Austin, Texas | USA

The Brain: Adaptation and Maladaptation in Migraine and Chronic Pain (E3)
Organizers: Frank Porreca, David Borsook and David W. Dodick
Jun 15–20, 2014 | Keystone Resort | Keystone, Colorado | USA

2014–2015 Keystone Symposia Meeting Series

The following meetings are in development as part of Keystone Symposia's 2014–2015 meeting series. Details are subject to change. Visit us online at ***www.keystonesymposia.org*** *or join our various mailing lists and online networks for updates as we finalize details, including dates and locations, over the next few months.*

The Modes of Action of Vaccine Adjuvants (S1)
Organizers: Philippa C. Marrack, Steven Reed and Robert A. Seder
Oct 8–13, 2014 | Sheraton Seattle Hotel | Seattle, Washington | USA

Cell Death Signaling in Cancer and the Immune System (S2)
Organizers: Gustavo Amarante-Mendes, Douglas R. Green and Kim Newton
Oct 28–Nov 2, 2014 | Casa Grande Hotel | Guaruja, São Paulo | Brazil

Precision Genome Engineering and Synthetic Biology (A1)
Organizers: Philip D. Gregory, Jennifer A. Doudna and Ron Weiss
Jan 11–16, 2015 | Big Sky Resort | Big Sky, Montana | USA

Viral Immunity (A2)
Organizers: Jonathan W. Yewdell, Donna L. Farber, Nicole Baumgarth and Jack R. Bennink
Jan 11–16, 2015 | Beaver Run Resort | Breckenridge, Colorado | USA

The Biological Code of Signaling – A Tribute to Tony Pawson (F1)
Organizers: Tony Hunter and Rune Linding
Jan 11–16, 2015 | Sheraton Steamboat Resort | Steamboat Springs, Colorado | USA

Integrating Metabolism and Tumor Biology (J1)
Organizers: Ralph J. DeBerardinis, Robert T. Abraham and Eyal Gottlieb
joint with
PI 3-Kinase Signaling Pathways in Disease (J2)
Organizers: Lori Friedman, David A. Fruman and Phillip T. Hawkins
Jan 13–18, 2015 | Fairmont Hotel Vancouver | Vancouver, British Columbia | Canada

Immunity to Veterinary Pathogens: Informing Vaccine Development (A3)
Organizers: William T. Golde, Wendy C. Brown and Ivan Morrison
Jan 20–25, 2015 | Keystone Resort | Keystone, Colorado | USA

Host Response in Tuberculosis (J3)
Organizers: JoAnne L. Flynn and Willem A. Hanekom
joint with
Granulomas in Infectious and Non-Infectious Diseases (J4)
Organizers: Thomas A. Wynn, Paul Kaye and Vishva M. Dixit
Jan 22–27, 2015 | Santa Fe Community Convention Center | Santa Fe, New Mexico | USA

Epigenetics and Cancer (A4)
Organizers: Tony Kouzarides and Kristian Helin
Jan 25–30, 2015 | Keystone Resort | Keystone, Colorado | USA

Neuroinflammation in Diseases of the Central Nervous System (A5)
Organizers: Richard M. Ransohoff, Christopher K. Glass and V. Hugh Perry
Jan 25–30, 2015 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

Mitochondria, Metabolism, and Heart Failure (J5)
Organizers: Richard N. Kitsis, Gerald W. Dorn II and Rong Tian
joint with
Diabetes and Metabolic Dysfunction (J6)
Organizers: Jeffrey E. Pessin, Alan R. Saltiel and Deborah M. Muoio
Jan 27–Feb 1, 2015 | Santa Fe Community Convention Center | Santa Fe, New Mexico | USA

Autoimmunity and Tolerance (B1)
Organizers: Jane L. Grogan, Joanne L. Viney and Gerald T. Nepom
Feb 3–8, 2015 | Keystone Resort | Keystone, Colorado | USA

Endoderm Lineages in Development and Disease (B2)
Organizers: Lori Sussel, Hans-Willem E. Snoeck, James M. Wells and Aaron M. Zorn
Feb 8–13, 2015 | Keystone Resort | Keystone, Colorado | USA

Plant Receptor Kinases: From Molecules to Environment (B3)
Organizers: Cyril Zipfel and Steven C. Huber
Feb 8–13, 2015 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

Tumor Immunology:
Multidisciplinary Science Driving Combination Therapy (J7)
Organizers: Elizabeth M. Jaffee and Axel X. Hoos
joint with
Antibodies as Drugs: Immunological Scaffolds as Therapeutics (J8)
Organizers: Pablo Umaña, Mark X. Sliwkowski and Martin J. Glennie
Feb 8–13, 2015 | Fairmont Banff Springs | Banff, Alberta | Canada

Systems Biology of Lipid Metabolism (B4)
Organizers: Matej Oresic, Antonio J. Vidal-Puig and Ana Maria Cuervo
Feb 9–13, 2015 | Beaver Run Resort | Breckenridge, Colorado | USA

RNA Silencing in Plants (G1)
Organizers: Robert Martienssen and Craig S. Pikaard
Feb 17–22, 2015 | Keystone Resort | Keystone, Colorado | USA

Neuroepigenetics (B5)
Organizers: Hongjun Song and Li-Huei Tsai
Feb 22–26, 2015 | Eldorado Hotel & Spa | Santa Fe, New Mexico | USA

Hematopoiesis (B6)
Organizers: Timm Schroeder, Hanna K.A. Mikkola and Patricia Ernst
Feb 22–27, 2015 | Keystone Resort | Keystone, Colorado | USA

Gut Microbiota Modulation of Host Physiology:
The Search for Mechanism (C1)
Organizers: Fredrik Bäckhed, Ruth E. Ley and Yasmine Belkaid
Mar 1–6, 2015 | Keystone Resort | Keystone, Colorado | USA

Heart Disease and Regeneration: Insights from Development (X1)
Organizers: Vincent M. Christoffels, James F. Martin and Deborah L. Yelon
joint with
Cell Biology of the Heart: Beyond the Myocyte-Centric View (X2)
Organizers: Peter Kohl, Robert G. Gourdie and Stefanie Dimmeler
Mar 1–6, 2015 | Copper Mountain Resort | Copper Mountain, Colorado | USA

DNA Replication and Recombination (X3)
Organizers: Simon J. Boulton, Karlene A. Cimprich and Stephen D. Bell
joint with
Genomic Instability and DNA Repair (X4)
Organizers: Daniel Durocher, Jiri Lukas and Agata Smogorzewska
Mar 1–6, 2015 | Whistler Conference Centre | Whistler, British Columbia | Canada

Hybrid Methods in Structural Biology (C2)
Organizers: Jens Meiler, Patrick Cramer and Ron A. Milligan
Mar 4–8, 2015 | Granlibakken Resort | Tahoe City, California | USA

Biology of Sirtuins (C3)
Organizers: Raul Mostoslavsky, Shin-ichiro Imai, Marcia C. Haigis and Eric M. Verdin
Mar 8–12, 2015 | Hilton Santa Fe Historic Plaza Hotel | Santa Fe, New Mexico | USA

Dendritic Cells and Macrophages Reunited (C4)
Organizers: Jacques F. Banchereau and Siamon Gordon
Mar 8–13, 2015 | Fairmont The Queen Elizabeth | Montreal, Quebec | Canada

Optogenetics (C5)
Organizers: Edward S. Boyden, Klaus M. Hahn and Chandra Tucker
Mar 12–16, 2015 | Westin Downtown Denver | Denver, Colorado | USA

Co-Infection: A Global Challenge for Disease Control (C6)
Organizers: Rodrigo Corrêa-Oliveira, David Dunne and Andrea Graham
Mar 15–20, 2015 | Speke Resort & Conference Centre | Kampala | Uganda

Long Noncoding RNAs: From Evolution to Function (C7)
Organizers: Leonard Lipovich, Jeannie T. Lee, John L. Rinn and James (Ben) Brown
Mar 15–20, 2015 | Keystone Resort | Keystone, Colorado | USA

Pathways of Neurodevelopmental Disorders (C8)
Organizers: Randi J. Hagerman, Mustafa Sahin and Paul J. Hagerman
Mar 16–20, 2015 | Granlibakken Resort | Tahoe City, California | USA

HIV Vaccines (X5)
Organizers: Giuseppe Pantaleo, Rafick P. Sekaly and Leonidas Stamatatos
joint with
The Golden Anniversary of B Cells (X6)
Organizers: Patrick C. Wilson, Michael P. Cancro and Anne Durandy
Mar 22–27, 2015 | Fairmont Banff Springs | Banff, Alberta | Canada

Obesity and the Metabolic Syndrome: Mitochondria and Energy Expenditure (X7)
Organizers: Johan Auwerx, Eleftheria Maratos-Flier and Thomas Langer
joint with
Liver Metabolism and Nonalcoholic Fatty Liver Disease (NAFLD) (X8)
Organizers: Jay D. Horton, Douglas G. Mashek and Brian N. Finck
Mar 22–27, 2015 | Fairmont Chateau Whistler | Whistler, British Columbia | Canada

On Stem Cell States: Transcriptional and Epigenetic Influences (C9)
Organizers: Thomas P. Zwaka, Rudolf Jaenisch and Joanna Wysocka
Mar 23–28, 2015 | Sheraton Steamboat Resort | Steamboat Springs, Colorado | USA

Gram-Negative Resistance (D1)
Organizers: Robert E.W. Hancock and Eric D. Brown
Mar 29–Apr 2, 2015 | Granlibakken Resort | Tahoe City, California | USA

Viruses and Human Cancer (D2)
Organizers: Charles R.M. Bangham, Thomas F. Schulz and Paul M. Lieberman
Mar 29–Apr 3, 2015 | Big Sky Resort | Big Sky, Montana | USA

T Cells: Regulation and Effector Function (D3)
Organizers: Alexander Y. Rudensky, Dan R. Littman and Kristin A Hogquist
Mar 29–Apr 3, 2015 | Snowbird Resort | Snowbird, Utah | USA

DNA Methylation (Z1)
Organizers: Alexander Meissner and Dirk Schübeler
joint with
Epigenomics (Z2)
Organizers: Bing Ren and Daniel Zilberman
Mar 29–Apr 3, 2015 | Keystone Resort | Keystone, Colorado | USA

Neural Control of Metabolic Physiology and Diseases (D4)
Organizers: Dongsheng Cai and Martin G. Myers, Jr.
Apr 12–17, 2015 | Snowbird Resort | Snowbird, Utah | USA

Beige and Brown Fat: Basic Biology and Novel Therapeutics (D5)
Organizers: Bruce M. Spiegelman and Sven Enerbäck
Apr 17–22, 2015 | Snowbird Resort | Snowbird, Utah | USA

The Crossroads of Lipid Metabolism and Diabetes (D6)
Organizers: Russell A. DeBose-Boyd, Sudha Biddinger and Alan D. Attie
Apr 19–24, 2015 | Tivoli Hotel and Congress Center | Copenhagen | Denmark

Innate Immunity and Determinants of Microbial Pathogenesis (Z3)
Organizers: Robert L. Modlin, Jenny P.Y. Ting and Foo Y. Liew
joint with
Mechanisms of Pro-Inflammatory Diseases (Z4)
Organizers: Virginia Pascual, Mark S. Anderson and Daniel Kastner
Apr 19–24, 2015 | Resort at Squaw Creek | Olympic Valley, California | USA

The Human Proteome (D7)
Organizers: Matthias Mann, Mathias Uhlén, Catherine E. Costello and Albert J.R. Heck
Apr 24–29, 2015 | Clarion Hotel Sign | Stockholm | Sweden

Mechanisms of HIV Persistence: Implications for a Cure (E1)
Organizers: Olivier Lambotte, Steven G. Deeks and Guido Silvestri
Apr 26–May 1, 2015 | Boston Park Plaza | Boston, Massachusetts | USA

The Arthropod Vector: The Controller of Transmission (E2)
Organizers: Serap Aksoy, Stephen K. Wikel and David S. Schneider
May 12–17, 2015 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

Hypoxia: From Basic Mechanisms to Therapeutics (E3)
Organizers: Cormac T. Taylor, M. Celeste Simon, Sean P. Colgan and Roland H. Wenger
May 12–17, 2015 | Royal Dublin Society | Dublin | Ireland

Hippo Pathway: Signaling, Development and Disease (E4)
Organizers: Fernando D. Camargo, Kun-Liang Guan and Helen McNeill
May 17–21, 2015 | Sagebrush Inn and Conference Center | Taos, New Mexico | USA

MicroRNAs and Noncoding RNAs in Cancer (E5)
Organizers: Frank J. Slack, Manel Esteller and Lin He
Jun 7–12, 2015 | Keystone Resort | Keystone, Colorado | USA

Autophagy (E6)
Organizers: Eric H. Baehrecke and Jayanta Debnath
Jun 19–24, 2015 | Beaver Run Resort | Breckenridge, Colorado | USA