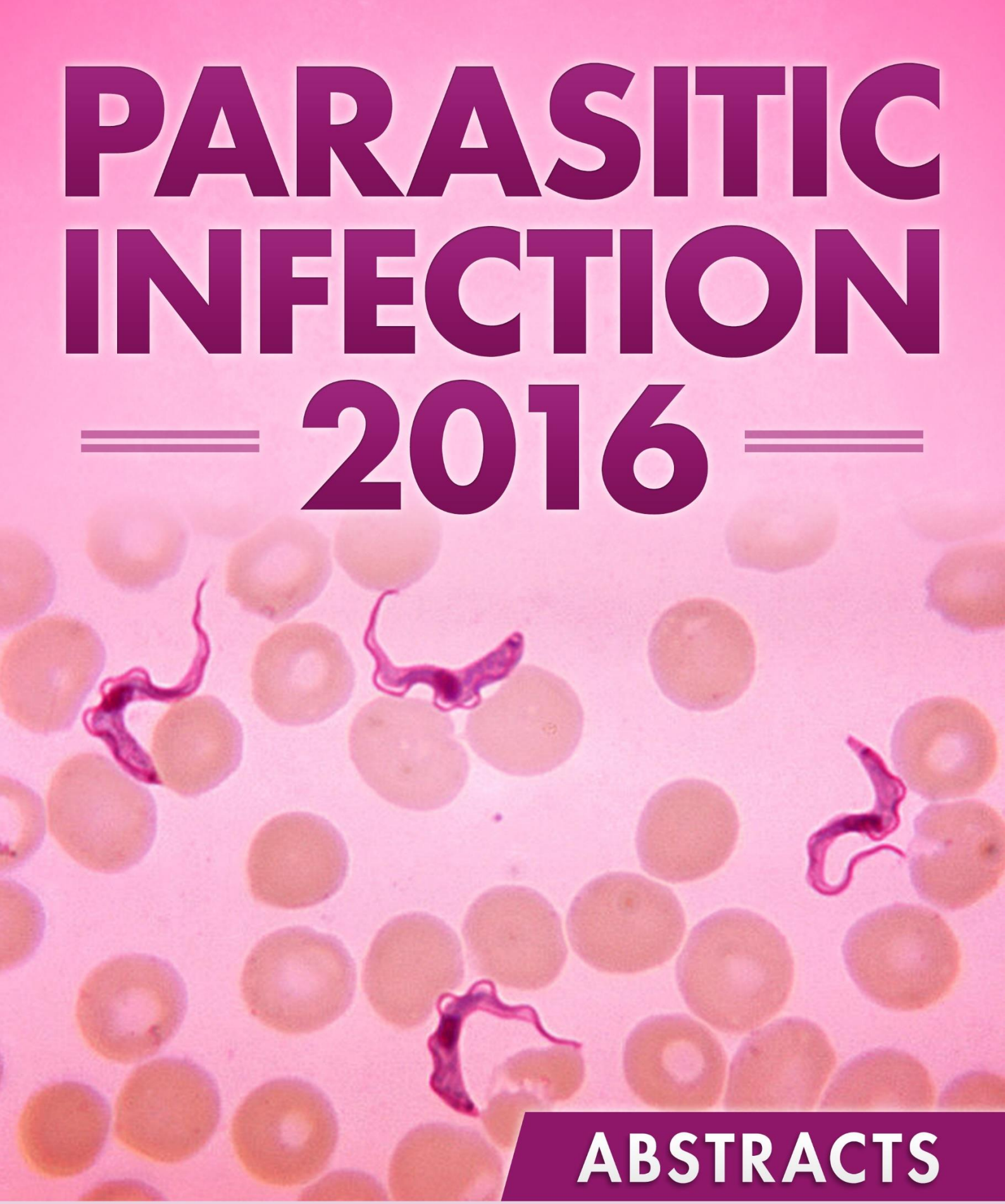
PARASITIC INFECTION 2016



ABSTRACTS

28th - 30th June 2016
London, UK

EuroSciCon

In an academic setting, this event will focus on the current research into parasitic infection and disease.

Over three days, this international summit will cover the cutting edge discoveries relating to diagnosis, treatment and drug design. Parasitic infections including malaria and neglected diseases, such as trypanosomiasis, will be discussed in detail, as well as discussion about methods of eradication.

This event has CPD accreditation

This abstract book will be finalised two weeks before the event
www.lifescienceevents.com/Parasitic2016

#Parasitic2016

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Invited Speakers Abstracts

Glimpse of index of infectious parasites incidence in Nigeria: Enugu study

Mr Emmanuel Chike Amadi, Department of Medical Microbiology, College of Medicine, Enugu State University of Science and Technology, GRA, Enugu, Enugu State, Nigeria

Phenomenon whereby certain creatures adopts, as a way of life, to partially or absolutely depend on another creature is enough a matter for serious concern, and where in addition it constitutes an irritating nuisance or even kills its host, it becomes a tragedy. The whole world, including Nigeria, has its share of such creatures, generally called PARASITES. Knowledge of them, their statistics and ways of life helps a great deal in their treatment, prevention and controls. Medical records of patients in two hospitals in Enugu (Eastern Nigeria) were critically analyzed between January – December of 2005 to 2009 and 2010 to 2014. Ages, sexes, occupation, locations, and monthly plus yearly incidences of diagnosed cases of infectious parasites were analyzed. 29660 records were analyzed in the first hospital and 27626 in the second hospital. The first hospital result revealed a 41% (12154/27626) of diagnosed cases of infectious parasites (Plasmodium spp, Ascaris lumbricoides, Entamoeba histolytica, hookworm, Giardia lamblia, Trichuria trichiura, Strongyloides stercoralis, Enterobius vermicularis, Trichomonas vaginalis/Taenia saginatta, Schistosoma haematobium and Balantidium coli, in descending order of prevalence). Malaria parasites alone was 91.48% of the lot, while all the other parasites put together constituted only 8.52%. Higher percentage (80% = 22093/27626) of similar types, though slightly in different prevalent order, of parasites was diagnosed in the second hospital, and malaria parasites again majorly (96.95%) constituted the lot. Also, in the first hospital, 40% (1035/2560) parasites were positive, but lower 19.6% (675/3446) in the second hospital. Parasitic infections were most prevalent during the rainy season (May - October). Likewise, females (56.75%/57.04%) and >35years of age (56.25%/42.3%) have the most prevalent rate, while 0 – 14years (8.75%/7.69%) have the least incidences, figures respectively of both hospitals. Farmers (30%/30.97%) were mostly infected, while students (11.25%/housewives (8.85%) were least infected, respectively in both hospitals.

Chemical genetics approach to study the role of essential protein kinases in malaria parasite.

Dr Mahmood Alam, Investigator Scientist, MRC, Toxicology Unit, Leicester, United Kingdom

Like higher eukaryotes, protein kinases play key regulatory role in all the cellular processes of malaria parasite and 36 protein kinases are known to be essential for survival of Plasmodium falciparum in host erythrocytes. In the absence of technologies like siRNA and limitation of conditional knockout system, it is very challenging to study the role of essential genes in malaria parasite. I will discuss the approach of chemical genetics to study the downstream signalling pathways associated with essential protein kinases with focus on PfPKG (cGMP dependent protein kinase) and PfCLK3 (cyclin dependent like kinase-3). We are applying this approach to inform our drug discovery.

Long-term artemisinin pressure in falciparum Malaria induces multidrug tolerance

Dr Françoise Benoit-Vical, INSERM (National Institute of Health and Medical Research), Toulouse, France

Recent malaria progresses are threatened by emergence of resistance to artemisinins, the core components of first-line therapies. Artemisinin resistance, especially widespread across Southeast Asia, exposes a larger number of parasites to the antimalarials in patients, but the consequences on parasite evolution are unknown. Laboratory testing of malaria parasites indicates that after long-term of solely artemisinin pressure, artemisinin-resistant parasites present a novel multi-drug tolerance profile which allows parasites to survive high doses of not only artemisinin and other endoperoxides but also quinolines and antifolate including partner drugs in the currently recommended Artemisinin-based Combination Therapies (ACT).

Discovery of secondary metabolites for treatment of malaria disease on different stage of Plasmodium life cycle.

Dr. Giuseppina Chianese, University of Naples "Federico II", Napoli, Italy

Malaria continues to be one of the greatest health problems faced by sub-Saharan African countries. WHO recommends protection from the vectors with insecticide treated bed-nets, while artemisinin-based combination therapies (ACTs) constitute the treatment of choice for malaria. Natural products chemistry, through structure elucidation combined with biological evaluation of secondary metabolites from terrestrial plants and marine organisms allows to identify new antimalarial compounds. The aim of research is the exploration of natural compounds seeking not only activity on parasite stages developing in the vertebrate host but also transmission blocking effects against the sporogonic stages developing in the mosquito vector.

Plasmodium knowlesi malaria

Dr. Janet Cox-Singh, University of St Andrews, Scotland, United Kingdom

Plasmodium knowlesi causes uncomplicated, severe and fatal malaria in Southeast Asia. Severe P. knowlesi malaria fulfils the World Health Organization criteria for severe falciparum malaria with the exception of coma. Malarial coma is attributed to sequestration of P. falciparum infected erythrocytes in brain microvasculature. The absence of coma in severe P. knowlesi malaria is surprising because post mortem brain histology findings were indistinguishable from P. falciparum. P. knowlesi malaria will be compared and contrasted with P. falciparum and P. vivax malaria. A case will be presented to use P. knowlesi as a translational model for severe malaria.

DNA repair in Trypanosoma cruzi: A mechanism of survival and persistence in its hosts

Professor Norbel Galanti, Institute for Biomedical Sciences, Faculty of Medicine, University of Chile, Santiago, Chile

Trypanosoma cruzi is the agent of Chagas' disease. Transmission is produced by infected triatomine insects that upon feeding on mammalian blood, deposits feces with infective parasites (trypomastigotes) which invade macrophages taking a replicative form (amastigote). Amastigotes transform back to trypomastigotes that invade heart, ganglia and other tissues. T. cruzi is exposed to oxidative agents that induce DNA damage which may be repaired by the parasite. We have identified three T. cruzi main DNA repair enzymes (a DNA glycosylase, two TcAP endonucleases and a Flap enzyme). These enzymes play different roles in parasite DNA repair leading to its maintenance in mammalian hosts.

When peptide chemistry meets antimalarial drug development

Dr. Paula Gomes, University of Porto, Faculty of Sciences, Dept. Chemistry and Biochemistry, Porto, Portugal The talk will focus on the work that has been developed in the speakers research group over the past decade, where peptide chemistry approaches have been applied to the synthesis of rather promising antimalarial leads.

Acanthamoeba corneal infection

Professor John Dart, University College, London, London, United Kingdom

This presentation provides an overview of Acanthamoeba corneal infection (keratitis) that, although rare, is one of the most recalcitrant, painful and chronic causes of keratitis with a substantial morbidity, in that 25% of cases require corneal transplant surgery. Our current knowledge of the epidemiology, pathogenesis and management of the disease will be summarised. The status of current research that is probing our understanding of the complex interactions of host and organism, the reasons for the current outbreak of disease in the UK and elsewhere, and the search for better therapies, is outlined. Interaction with experts in protozoal diseases is anticipated.

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Natural Products in Drug Development and Environmental Control of Malaria

Dr Joseph M. Agbedahunsi, Drug Research and Production Unit, Faclty of Pharmacy, Obafemi Awolowo University, Ile- Ife, Nigeria

Malaria is a mosquito- borne human disease caused by a parasitic protozoan belonging to the genus Plasmodium. It continues to be a leading cause of morbidity and mortality in sub-Saharan Africa especially among children under 5 years of age. Right from the inception of malaria management chemotherapy, and environmental control of malaria vector had been prominent. Medicinal plants have been a great source of molecules used in the chemotherapy starting from Cinchona (quinine) to Artemisia annua (artemisinin). A number of other antimalarial drugs have also been developed from Medicinal plants. Some African countries are land-locked with water especially in the Delta regions of Nigeria and riverine areas of the tropical regions of the world, environmental control of mosquitoes could be the only viable way controlling the scourge of the disease. There are some plants that could be grown along the course of the river whose metabolites could selectively kill the larvae and eggs of the insect vectors such as Anopheles or Aedes without affecting the aquatic fauna. In this presentation drug development from some African medicinal plants such as Khaya , Tithonia, Dracaenia Crypsopteris species etc. will be discussed and the use of plants from the Asteraceae family in the environmental control of malaria vectors will be discussed.

Recent Progress in Structure-Guided Drug Discovery for Parasitic Diseases

Dr Raymond Hui, Structural Genomics Consortium, University of Toronto, Toronto General Research Institute (TGRI), Toronto, Ontario, Canada

Structural biology is now a standard component of workflow in drug discovery in pharmaceutical companies. Increasingly, this trend is being adopted in anti-parasitic drug discovery, even though a majority of the projects are carried out in academic labs. In this talk, a review of the progress made in structural biology of parasite proteins and the obstacles that remain. Relevant case studies showing how structural biology played key roles in development of anti-parasitic drug leads will be shown.

The parasitic worm immunomodulator ES-62 resets the effector: regulatory B cell balance in inflammatory disease

Professor Margaret Harnett, Professor of Immune Signalling, Institute of Infection, Immunity and Inflammation College of Medical, Veterinary and Life Sciences, Glasgow Biomedical Research Centre, University of Glasgow, Glasgow, United Kingdom

There is an inverse correlation between the incidence of allergy and autoimmunity and parasitic helminth infection, reflecting the secretion of anti-inflammatory products that promote worm survival. One such immunomodulator, ES-62 prevents development of pathology in mouse models of asthma, arthritis and systemic lupus erythematosus and this correlates with induction of a hypo-responsive phenotype of effector B cells and restoration of the levels of IL-10-producing "regulatory B cells". Importantly, the protection afforded against SLE-like kidney damage could be mimicked by the adoptive transfer of B cells from ES-62-treated mice, suggesting that ES-62 acts by resetting the effector:regulatory B cell balance.

Can the parasitic worm product ES-62 be used to develop drugs for treating allergic and autoimmune diseases?

Professor William Harnett, University of Strathclyde, Glasgow, United Kingdom

ES-62 is an anti-inflammatory protein secreted by the filarial nematode Acanthocheilonema viteae, which we have previously shown to suppress development of disease in mouse models of allergy and autoimmunity. ES-62's anti-inflammatory activity relies on post-translational attachment of phosphorylcholine (PC) and thus a library of novel drug-like PC-based small molecule analogues was produced. Like ES-62, two library compounds were found to suppress development of pathology in models of asthma, rheumatoid arthritis and systemic lupus erythematosus. We thus provide proof-of-principle that drug-like compounds can be produced from parasitic worm products for treatment of autoimmune and allergic conditions.

Fake Medicines: How can we know

Dr Harparkash Kaur, London School of Hygiene and Tropical Medicine, London, UK

Pharmaceutical counterfeiting is a global threat that can kill patients, contribute to the rise of drug resistance, and increase the citizens' mistrust of health systems. To monitor drug quality governments and health programs must invest in the regulations, technologies, and infrastructure needed, including specialised analytical facilities run by experienced staff, and portable technologies for screening medicines in the field.

This presentation will focus on the high performance liquid chromatography methods used to analyse over 10,000 packets of the first line antimalarial medicines purchased in six countries, using representative sampoling and showed that falsified antimalarials were only found (<8%) in two countries

New biomarkers and interventions for severe and cerebral Malaria

Dr. Kevin C. Kain, Toronto General Hospital - University Health Network, Toronto, Canada

Compelling evidence suggests a critical role for endothelial dysfunction in the pathogenesis of life-threatening infections including severe malaria. However there are currently no agents available to prevent or treat endothelial dysfunction. This talk will explore a mechanistic understanding of malaria-induced endothelial dysfunction to identify biomarkers enabling early recognition and risk stratification of severe malaria. Moreover, since outcomes are poor despite antimalarial therapy, we prioritize pathways that are causally involved and therefore represent a direct measure of disease severity and constitute novel targets for intervention.

Detection of Opisthorchis viverrini Infection in the Rural Community of thailand by Using Korat-Ov Verbal Screening Test and Mini Parasep SF Concentration Technique

Dr. Natthawut Kaewpitoon, Parasitic Disease Research Unit, Suranaree University of Technology, Nakhon Ratchasima, Thailand

Opisthorchis viverrini infection is associated with Cholangiocarcinoma particularly in the cases of chronic or re-infection. These are a serious health problem in northeast and north of Thailand. A community base approach is required for surveillance. Therefore, a pilot project, re-examination of O. viverrini infection was conducted in the 3 districts of Nakhon Ratchasima province, Thailand, during June and October 2015. A total of 355 participants from 194,152 populations, was selected through Korat Ov verbal screening tesst. O. viverrini infection was determined using mini parasep SF concentration technique. Participants were 229 males and 126 females, and age ≥ 30 years old. Prevalence of O. viverrini infection was 2.25% (8/355 participants). O. viverrini infection was slightly in female (3.17%), and age group between 41-50 years old (4.49%). Mueang Yang district had a highest of O. viverrini infection (2.82%), and followed by Bua Yai (2.48%), and Chum Phuang (1.84%), respectively. O. viverrini infection rate was increased from year 2012 to 2015 particularly in Bua Yai and Mueang Yang. These re-examine results indicate that opisthorchiasis is still problem in community of Nakhon Ratchasima province, therefore, the provincial-wide scale is need required, furthermore health education is need intervened in the infected group, and screening of cholangiocarcinoma is urgently concerned.

Differential local immune response of the human placanta against the protozoan parasites Trypanosoma cruzi and Toxoplasma gondii

Professor Ulrike Kemmerling, Institute for Biomedical Sciences, Faculty of Medicine, Universidad de Chile, Santiago, Chile

Congenital Chagas Disease, caused by the protozoa Trypanosoma cruzi (T. cruzi) is a major health problem in Latin America. Toxoplasmosis is a zoonotic disease caused by the protozoan Toxoplasma gondii (T. gondii), one of the most successful parasites on earth. During vertical transmission both parasites must cross the placental barrier, where the trophoblast is the first tissue in contact with maternal blood circulating pathogens. The trophoblast expresses all of the mammalian Toll like

receptors (TLRs) identified in human. TLRs are Pathogen Pattern Recognition Receptors, which recognize and bind to highly conserved sequences, known as pathogen-associated molecular patterns (PAMPs). T. cruzi and T. gondii is recognized by TLR-2, TLR-4, TLR-7 and TLR-9. Activation of TLRs leads to expression and secretion of immune-modulating cytokines and chemokines. The parasites induces a differential profile of TLRs and associated cytokines which might partially explain the high (T. gondii) and low (T. cruzi) transmissiona rates

Point-of-care device for malaria diagnosis and drug resistance status

Professor Sanjeev Krishna, St. George's, University of London, London, United Kingdom

Prompt diagnosis of malaria allows appropriate treatment and reduces both morbidity and mortality. Present diagnostics at point-of-care do not provide information regarding the resistance status of the plasmodial parasite underlying the infection. The NANOMAL consortium has developed innovative technologies to confirm malaria diagnosis and detect drug resistance in malaria parasites by analysis of resistance-associated mutations using nanowire technology. This will result in the development of a simple, rapid (sample to result time of < 15 min) and affordable point-of-care handheld diagnostic device. We present recent advances and where these could be used to assist the elimination agenda for malaria.

A chemical drug delivery approach to improve antimalarial activity

Dr. Francisca Lopes, Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, Lisboa, Portugal

Artemisinin-based combination therapies (ACTs) are the first-line treatment for uncomplicated Plasmodium falciparum malaria. However, recently decrease of sensitivity to artemisinin has reinforced the urgent need to discover novel chemotherapeutic strategies to treat and control malaria. Herein, we report the development of tetraoxane-based hybrid compounds as a strategy to deliver falcipain inhibitors upon activation by ferrous iron in the parasite. Falcipains are cysteine proteases that localize in the parasitic food vacuole and play a key role in the hydrolysis of host hemoglobin into amino acids that are essential to parasite growth. The results presented indicate that the intrinsic activity of the tetraoxane partner compound can be masked, suggesting that a tetraoxane-based delivery system offers the potential to attenuate the off-target effects of known drugs.

Modelling Importations and Exportations of Infectious Diseases via Travelers

Professor Eduardo Massad, School of Medicine, University of Sao Paulom, Brazil

Abstract This paper is an attempt to estimate, through a mathematical model, the risk of infection importation and exportation by travelers. Two countries are considered: one disease-free country and one visited or source country with a running endemic or epidemic infectious disease. Two models are considered. In the first model (disease importation) susceptible individuals travel from their disease-free home country to the endemic country and come back after some weeks. In the second model (disease exportation) it is calculated the probability that an individual from the endemic (or epidemic) country travels to a disease-free country in the condition of latent infection (asymptomatic). The models are exemplified with two distinct real situations: the risk of dengue importation from Thailand to Europe and the risk of Ebola exportation from Liberia to the USA.

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endemic (or epidemic) country travels to a disease-free country in the condition of latent infection (asymptomatic). The models are exemplified with two distinct real situations: the risk of dengue importation from Thailand to Europe and the risk of Ebola exportation from Liberia to the USA.

Establishment of chronic infection in malaria involves a novel method of immune evasion

Dr. Adam James Reid, Wellcome Trust Sanger Institute, Cambridge, United Kingdom

Chronic infection of the vertebrate host is crucial to ensure mosquito transmission of malaria parasites and completion of the life cycle. It is widely accepted that establishment of chronic infection involves evasion of adaptive immunity by antigenic variation. However, early events in this process have been difficult to study and genes involved in antigenic variation have been identified in only two species of Plasmodium. Here we demonstrate that chronic infection is established by a minority of parasites expressing one of several clusters of virulence-associated pir genes. This clonal selection is independent of adaptive immunity and therefore distinct from classical antigenic variation. As pir genes are common to all species of malaria parasite, this process may be a universal way of establishing chronic malaria infections.

An integrated approach to control intestinal helminth infections

Dr. Giovanna Raso, University of Basel, Basel, Switzerland

A study is beeing carried out to assess the effect of combining preventive chemotherapy with community-led total sanitation (CLTS) and health education on soil-transmitted helminth infections using a cluster randomized trial in 56 communities of south-central Côte d'Ivoire. Baseline epidemiological survey revealed a prevalence with STH of 17%. The ongoing community participatory interventions are still ongoing, but results from a first follow-up survey suggest that STH infections have decreased following mass drug administration. The results of this study will provide an evidence base for integrated control approaches in rural settings of Côte d'Ivoire and other similar socio-ecological settings.

Zoonotic Malaria – A 2016 Update

Professor Ranjan Ramasamy, Anglia Ruskin University, Cambridge, Cambridge, United Kingdom

The four parasites causing human malaria, P. falciparum, P. vivax, P. malaria and P. ovale, are transmitted between humans by Anopheles mosquito vectors. Plasmodium knowlesi, a malaria parasite of forest macaque monkeys, can be transmitted by anophelines to cause zoonotic malaria in humans in Southeast Asia. The likely origin of the four human malaria parasites in African apes are examples of ancient zoonoses that may still be continuing with P. vivax, P. ovale and P. malariae. P. cynomolgi in Southeast Asia and P. brasilianum and P. simium in South America are additional examples of zoonoses.

Control of schistosomiasis and soil-transmitted helminthiasis: A COUNTDOWN to WHO 2020 Roadmap targets for neglected tropical diseases

Professor Russell Stothard, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Schistosomiasis and soil-transmitted helminthiasis (STH) are grouped within those neglected tropical diseases (NTDs) amenable to preventive chemotherapy. The global burden of schistosomiasis and STH is vast and continues to blight the lives of millions in sub-Saharan Africa. In this talk I give an overview of contemporary aspects of disease diagnostics and issues related to access to treatment. I highlight the launch of ESPEN (expanded special programme for elimination of NTDs) and COUNTDOWN, a five-year research consortium funded by DFID, UK.

Epidemiological profile of cutaneous leishmaniasis in the province of Taza (Morocco)

El-houcine Sebbar, SMPM, the Military Hospital of Instruction Med V, Rabat, Morocco

Cutaneous leishmaniasis is a persistent public health problem in Morocco, our study was conducted in order to report the data of epidemiological surveillance of cutaneous leishmaniasis in the province of Taza and also enjoy the therapeutic and preventive strategy to fight against this parasitosis.

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Control of arthropod-borne infectious diseases – extrapolating from the known to the unknown

Professor Andrew Taylor-Robinson, CQ University, Queensland, Australia

Mosquito-transmitted infectious diseases impact significantly on human health. Experiences with malaria, dengue and yellow fever may inform strategies for diagnosis, treatment, control and prevention of (re)-emerging infectious diseases. This applies to notable aetiological agents such as Zika but also less well characterized arboviruses, of which there are over 70 identified in Australia alone, a putative cause of fevers of unknown origin. Given changes in climate, human movement and vector distribution, these neglected diseases should be researched further so that if conditions become conducive to an outbreak that poses a public health threat suitable emergency control measures may be efficiently enforced.

Exploration of natural compounds to treat drug resistant malaria

Dr Prakash Udhawdas Tahiliani, Clinical Researcher, Prime Ever Ayurvedic Research Laboratories, Navsari, Gujarat, India

History indicates development of resistance to anti-malarial drugs has been a usual & well anticipated phenomenon. Now malaria parasite is rapidly acquiring resistance towards latest Artemisinins & Artemisinin Combination Treatment. This is high time to discover natural compounds from medicinal herbs & other natural sources.

Discovery of new compounds can be done with the help of Traditional as well as Modern literature of natural compounds. Development of these compounds is then possible by 'Reverse Pharmacological Approach'. This approach is time saving & cost effective. WHO is encouraging discovery & development of new drugs from natural sources.

NANOHAT: developing a safer and more effective sleeping sickness drug

Dr. Sarah A. Thomas, King's College London, London, United States

Human African Trypanosomiasis causes death if left untreated. Treatment depends on the presence of the parasite in the brain. CNS drugs must cross the blood-brain barrier (BBB). Anti-HAT drugs that enter the brain are toxic compounds and cause side effects. Pentamidine is a less toxic blood stage drug, which has a limited ability to cross the BBB due to its removal by transporters. We will present our latest studies in this area this includes the use of nanotechnology to improve the brain delivery of pentamidine, whilst reducing its side effects. Funded by The Wellcome Trust and MRC.

Natural Products as Leads to New Antiprotozoal Drugs

Dr Colin Wright, Reader in Pharmacognosy, University of Bradford, Bradford School of Pharmacy, Bradford, West Yorkshire, United Kingdom

Natural products derived from traditional medicines are an important source of antiparasitic drugs. For example, the Chinese herbal drug Qing Hao Su (Artemisia annua), is the source of the antimalarial artemisinin. In this presentation, the potential of traditional medicines to yield new antiparasitic drugs against malaria and African sleeping sickness will be explored with reference to recent research on medicinal plants. For example, the roots of the West African shrub Cryptolepis sanguinolenta are used for the treatment of malaria and contain the alkaloid cryptolepine which has been shown to be a potential lead compound towards new antimalarial agents.

New tools for Malaria Intervention

Dr David W. Wright, Vanderbilt University, Nashville, TN, United States

Widely available malaria diagnostics are missing critical features necessary for elimination campaigns. While the current rapid diagnostic tests for malaria confirm diagnosis of heavily infected individuals, they leave asymptomatic carriers of the disease unidentified, sustaining a constant reservoir for re-infection. In addition, such one-off tests are not integrated into the healthcare infrastructure for effective reporting and surveillance. This proposal describes the development and

field evaluation of additions to the well-accepted rapid diagnostic test strategy. A major goal is to maintain the test's inherent simplicity of operation but reduce the reservoir for re-infection by enhancing the test's sensitivity and flexibility.

New insights into the role of mast cells in malaria infection

Dr. Panop Wilainam, Mahidol University, Salaya, Thailand

Mast cells are immune cells which attract much interest for their involvement in a variety of physiological and pathological processes, however, few research findings have been reported for their involvement in malaria pathogenesis. Interestingly, recent research has firstly reported the response of mast cells in skin of patients with Plasmodium falciparum malaria. Mast cell activation and associated histopatholgy, including leukocyte infiltration, perivascular edema, and erythrocyte extravasation, were demonstrated and these changes were correlated with disease severity and parasitemia. Therefore, mast cells might contribute to the malaria pathogenesis through the effects mediators released from cytoplasmic granules of activated mast cells.

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Day 1:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

Day 2:

Oral Presentation Abstracts

A MULTI-STAGE PRECLINICAL CANDIDATE FOR THE POTENTIAL TREATMENT OF MALARIA

Authors: Neil R. Norcross, Beatriz Baragaña, Irene Hallyburton, Raffaella Grimaldi, Maria Osuna-Cabello, Suzanne
Norval, David W. Gray, Alan H. Fairlamb, Paul Willis, Kevin D. Read, Ian H. Gilbert; Drug Discovery Unit, Division of Biological Chemistry and Drug Discovery, College of Life Sciences, University of Dundee, Dundee DD1 5EH, UK

Abstract: Malaria is a devastating parasitic disease causing widespread mortality and morbidity across many parts of the developing world. Many medicines for the treatment of malaria are failing due to the increasing development of resistance and new therapies for both treatment and prevention of this deadly disease across all of its life cycle stages are urgently needed. In the search for new antimalarials, a collaborative project between the University of Dundee and Medicines For Malaria Venture (MMV) was initiated with the high throughput phenotypic screening (HTS) of an in-house library of protein kinase scaffolds. Initial screening identified multiple structurally diverse chemical series that blocked asexual blood stage parasite viability and served as a catalyst for a new drug discovery programme. Using a focussed medicinal chemistry approach involving drug design, chemical synthesis, biological testing and rigorous compound profiling, we identified a highly efficacious compound with potent activity against multiple life cycle stages. The biological target of our lead molecule has also been determined and represents a novel mode of action. This presentation will reveal a small molecule inhibitor of P.falciparum malaria with good pharmacokinetic properties and excellent possibilities for chemoprotection, single dose blood stage treatment and transmission blocking.

EVALUATION OF EFFICACY OF ARTEMETHER LUMEFANTRINE AND DIHYDRO-ARTEMISININ PIPERAQUINE IN CLEARANCE OF GAMETOCYTES IN UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA AND EFFECTIVENESS OF MICROSCOPY AND RT-PCR IN GAMETOCYTES DETECTION

1. Author: *E. Too*, Kenya Medical Research Institute.
2. S. Omar, Kenya Medical Research Institute.
3. F. Kimani, Kenya Medical Research Institute.
4. B. Ongondo, Kenya Medical Research Institute.

BACKGROUND
Over 80 countries worldwide have now implemented WHO recommendations to use artemisinin-based combination therapy (ACT) as first-line treatment for Plasmodium falciparum malaria. There is need to determine whether these antimalarial drugs have effects on gametocytes. The sexual parasites are responsible for the transmission of malaria parasites to infectious mosquitoes.
The aim of this study was therefore to determine the clearance rates of Artemether lumefantrine(Coartem) and Dihydro-artemisinin piperaquine (Dou-cotecxin) in uncomplicated P. falciparum, and to evaluate the effectiveness of microscopy and reverse transcriptase polymerase chain reaction (RT-PCR) in gametocytes detection

METHODS
The RT-PCR assay is based on pfs25 gene specific to gametocytes. Carried out in Tiwi Kwale County. Randomized controlled clinical trial, malaria positive patients, gametocytes densities were quantified by microscopy by counting against 500 leukocytes in the thick smear converted to numbers of parasites per microliter by assuming a standard count of 8000WBC/µl after staining with 10% giemsa stain and by RT-PCR using primers specific to pfs25 gene. Recorded in case record form and lab book Student's t-test and ANOVA were used to test for significance.

RESULTS
Results showed that there was no significant difference between the drugs in clearance of gametocytes ($p<0.14$). Day 0 gametocytes density were 112 treated with artemether lumefantrine and by day 28 it was zero, in day 0 gametocytes density were 96 treated with dihydro-artemisinin piperaquine and by day 28 it was zero. RT-PCR detected pfs 25 gene gametocyte specific with intense band of 500bp representing amplification. The most effective RT-PCR technique gave estimates of gametocyte prevalence 3.8- fold higher than microscopy 97.8% versus 26% respectively. There was significant difference between the two methods in detection of gametocytes ($p<0.01$).

CONCLUSIONS AND RECOMMENDATIONS
This study showed that Coartem and Dou-cotecxin have gametocytocidal effects on P. falciparum. The RT-PCR is more effective than microscopy in detection of low levels of gametocytes.

Day 3:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

CONTRIBUTORY ROLE OF SOCIOECONOMIC FACTORS TO THE DEVELOPMENT AND SPREAD OF ANTIMALARIAL DRUG RESISITANCE: A QUALITATIVE STUDY OF ANTIMALARIAL DRUG USE BEHAVIOURS

P. E. ANYANWU; J. FULTON; T. PAGET & E. EVANS
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ABSTRACT
Introduction
Malaria has been a major global health issue for centuries. Evidently, malaria is intrinsically linked with poverty. Despite the current global reduction in malaria mortality and morbidity, the burden of malaria is still very significant, especially considering the economic, social, political and public health effects to endemic countries. A major threat to sustaining the present reduction in malaria burden is the development and spread of resistance to antimalarial drugs by the Plasmodium parasites (mostly P. falciparum and P. vivax). Resistance to the recommended first line treatment for malaria (Artemisinin based combination therapy) has been confirmed in Southeast Asia. Drug use behaviour/practice is a very important factor in the development and spread of antimalarial drug resistance as it is attributed to human behaviours and activities, and can affect some of the other factors implicated in antimalarial drug resistance. This study conducted a qualitative inquiry to explore how different measures of socioeconomic factors can influence the adoption of antimalarial drug use behaviours that promote drug resistance.

Methods
We conducted 15 in-depth interviews with household heads (HHH), drug vendors and pharmacy attendants from two rural and two urban areas in Nigeria. The interviews with HHH explored their households' malaria treatment seeking and antimalarial drug use behaviours. While that of the drug vendors and pharmacy attendants focused on the quality of services they provide. We analysed the data using a thematic analysis. The interpretation of the data was done using an adapted Donabedian model.

Results
From the analysed interview data, the key socioeconomic factors that affect the decisions on malaria treatment were income level, type of settlement and educational level. Affordability was a very important factor that contribute to adoption of behaviours like presumptive treatment, sharing of antimalarial drugs, use of monotherapies, drug 'mixing' and decisions on where to seek for malaria treatment. These behaviours were reported mostly as coping strategies by low income participants and participants from rural areas. Participants' type of settlement influence decisions on where to seek for treatment and the type of antimalarial drug they use.

Discussions
Socioeconomic factors were identified as a key contributor to the misuse of antimalarial drugs. Behaviours like presumptive treatment, sharing of antimalarial drugs and use of monotherapies have been implicated in the development and spread of antimalarial drug resistance. These behaviours facilitate resistance through the exposure of the parasites to sub-therapeutic doses and drug over use. With the complexity of antimalarial drug resistance, there is need to adopt multiple approach in protecting the effectiveness of antimalarial drugs.

Poster Presentation Abstracts

Poster abstracts will be finalised weeks before the event

DIMINISHED PREVALENCE OF CHLOROQUINE-RESISTANT GENE MARKER PFCRT-76 13 YEARS AFTER CESSATION OF CHLOROQUINE USE IN KENYA

Investigators: F. Kimani, W. Chege, E. Too, S. Kaniaru and S. Omar, *M. Otinga*
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Abstract
BACKGROUND. Plasmodium falciparum resistance to chloroquine (CQ) Resistance has been proven to be due to point mutations on the parasite's pfcrt gene, particularly on codon 76. This study sought to determine the prevalence of pfcrt K76T mutation 13 years after CQ cessation in Kenya.

METHODS. Finger-prick whole blood was collected on 3MM Whatman ® filter paper from 99 falciparum malaria patients. DNA was extracted via Chelex method from blood spots and used as template in nested PCR amplification of pfcrt. Apo1 restriction enzyme was used to digest the amplified DNA to identify the samples as wild type or sensitive at codon 76. Prevalence figures of the mutant pfcrt 76T gene were calculated by dividing the number of samples bearing the mutant gene with the total number of samples multiplied by 100 %. Chi square tests were used to test the significance of the findings against previous prevalence figures.

RESULTS. Out of 99 clinical samples collected in 2013, prevalence of mutant pfcrt 76T gene stood at 41 %.

CONCLUSION. The results indicate a significant [χ 2 test, P ≤ 0.05 (2006 vs 2013)] reversal to sensitivity by the P. falciparum population in the study site compared to the situation reported in 2006 at the same site. This could be driven by diminished use of CQ in the study area in line with the policy. Prevalence of the pfcrt 76T gene could be expanded countrywide to establish the CQ sensitivity status and predict a date when CQ may be re-introduced as part of malaria chemotherapy.

OCULAR TOXOPLASOMOSIS ANIMAL MODEL BY SUBRETINAL INJECTION OF TOXOPLASMA GONDII

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Ocular toxoplasmosis, a vision-threatening ocular disease caused by Toxoplasma gondii is the most common cause of infectious uveitis. However, many critical aspects of disease including the therapeutic approach to ocular toxoplasmosis still remain be elucidated. Recently, we reported an easy, effective viral vector delivery technique of limbal approach-subretinal injection. Subretinal injection is the best approach to deliver viral vectors or cells directly to retinal pigment epithelial cells. Herein, we provide the easy and replicable technique for subretinal injection of toxoplasma gondii or toxoplasma gondii-infected monocyte to experimental mice and suggest the effective toxoplasma infection around of retina and retinal pigment epithelial cells, which would be modified to larger animals to investigate diagnostic and therapeutic trials of ocular toxoplasmosis.

TOXOPLASMA GONDII-INFECTED MONOCYTES IMPAIR OUTER BLOOD RETINAL BARRIER VIA IL-8 SIGNALING PATHWAY

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In patients with ocular toxoplasmosis, disruption of retinal pigment epithelium is frequently observed. The retinal pigment epithelial layer constitutes outer blood retinal barrier that lies between retina and leaky choroidal vasculature. The disruption can increase permeability and impair homeostatic function of retinal pigment epithelium leading to visual disturbance. In this study, we investigated the effect of Toxoplasma gondii on in vitro model of outer blood brain barrier using retinal pigment epithelial cell line, ARPE-19. After confluent monolayer was formed on transwell, tachyzoites of Toxoplasma gondii (PTG strain), monocytes infected with Toxoplasma gondii or their conditioned medium were treated. After the tachyzoites treatment at MOI 10 for six hours, cells were diffusely infected with Toxoplasma gondii. The evaluation of barrier function revealed decreased transepithelial electrical resistance (TEER) and disrupted tight junction protein between cells. After treatment of monocytes infected with Toxoplasma gondii or their conditioned medium for twenty four hours, TEER was decreased and tight junction protein was disrupted. Evaluation of IL-8 concentration by ELISA in conditioned medium from monocytes infected with Toxoplasma gondii revealed increased expression of IL-8 compared to the conditioned medium from monocytes infected with heat-inactivated Toxoplasma gondii. The decreased TEER and disrupted tight junction protein by conditioned medium was suppressed with treatment of neutralizing antibody against IL-8 and FAK

inhibitor (PF-573228). In conclusion, Toxoplasma gondii can impair outer blood brain barrier in various forms: direct influence of tachyzoites and infected monocytes and paracrine effects of infected monocytes. The paracrine effects are mediated by IL-8 signaling.

NANOLIPOSOMAL ARTEMISININ FOR THE TREATMENT OF MURINE VISCERAL LEISHMANIASIS

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Abstract
Visceral leishmaniasis (VL) is a fatal, vector borne disease caused by the intracellular protozoa of the genus Leishmania. Most of therapeutics for VL are either toxic and or expensive or are ineffective. Sesquiterpenes are a new class of drugs with proven antimicrobial and antiviral activities. Artemisinin, belongs to a class of sesquiterpenes with limited access to infected cells, being a highly lipophilic molecule with potential antileishmanial activity. Association of artemisinin with liposome is a desirable strategy to elude the problem of poor accessibility, thereby ameliorating its efficacy in a murine model of experimental VL. Nanoliposomal artemisinin (NLA) was prepared by thin film hydration method, optimized using Box-Behnkehn design with a mean particle diameter, polydispersity index, zeta potential and drug loading of 83 ± 16 nm, 0.2 ± 0.03, -27.4 ± 5.7 mV and 33.2 ± 2.1 percent, respectively. Morphological study of these nanoliposomes by microscopy depicted smooth and spherical surface. Mechanism of release of artemisinin from the liposomes followed Higuchi model in vitro. The NLA was free from concomitant signs of toxicity, both ex vivo on murine macrophages as well as in vivo in healthy BALB/c mice. NLA significantly denigrated the intracellular infection of L. donovani amastigotes as well as the number of infected macrophages ex-vivo with an IC50 of 6.0 ± 1.4 and 5.1 ± 0.9 µg/ml, respectively. Following treatment in murine model of VL, NLA demonstrated superior efficacy than artemisinin with percentage inhibition of 82.4 ± 3.8 % in the liver and 77.6 ± 3.7 % in spleen at the highest dose of 20 mg/kg bw with modulation of cell mediated immunity toward protective Th1 immunity. Ours is the first report on the use of liposomal drug delivery system for artemisinin as a promising alternative intervention against VL.

CASE REPORT AND LITERATURE REVIEW: SEVERE MALARIAL ANEMIA AND BLACKWATER FEVER IN A 3-YEAR-OLD BOY IN KEEROM, PAPUA, INDONESIA

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Abstract
Background
Malaria is still a major health problem in Indonesia, particularly in Papua as one of the most endemic area in the country. Children less than 5 years old are at risk of malarial infection, mostly severe malaria with relatively rapid development of illness into fatality. We report a case of 3-year-old boy with manifestations of severe malarial anemia as well as suspect blackwater fever and treated, thus survived and discharged with clinical improvement.

Case Description

A 3-year-old boy from low socioeconomic status and remote forest area presented to Kwaingga Keerom District Hospital with seizure and dark coffee-colored urine, as he referred from Arso primary health center. There was history of high fever, jaundice and severe abdominal pain. Urinalysis revealed hematuria. A thick blood smear revealed many Plasmodium falciparum ring forms (4+). Intravenous artesunate was administered; the jaundice and urine color was improved. However, the patient developed severe tachypnea and generalized pallor. Hemoglobin level dropped into 4.0 g/dL from 6.0 g/dL on admission. The patient was then referred to Marthen Indey Military Hospital and 3 bags of 150 cc Packed Red Cells were transfused. Hemoglobin level finally reached 10.0 g/dL. Clinical improvement was observed and patient was discharged from hospital with parasite clearance.

Conclusion

Severe malarial anemia was one of the most common presenting manifestations in pediatric population, while blackwater fever was less common. Understanding the nature of the disease development, prompt recognition of the symptoms and proper treatment is crucial in preventing fatality and reducing morbidity of the illness in the future.

SYNTHESIS OF SOME THIAZOLE BASED HETEROCYCLIC COMPOUNDS AS POSSIBLE ANTIMALARIAL, ANTHELMINTIC AND ANTIMICROBIAL AGENTS

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Abstract

Background: The present work describes synthesis of a series of 5-((1-(4-(4-chlorophenyl)thiazol-2-yl)-3-aryl-1H-pyrazol-5-yl)methylene)-2-(aryllimino)thiazolidin-4-one derivatives and their biological evaluation as possible antimalarial, anthelmintic and antimicrobial agents. Method: The synthesis of compounds has been accomplished by adopting suitable synthetic methods. Structures of newly synthesized compounds were characterized and authenticated by suitable spectral methods. Synthesized compounds were screened for their in vitro antimicrobial activity against selected bacterial strains and fungal (B. subtilis, S. aureus, E. coli, P. fluorescens, C. albicans, C. glabrata) and antimalarial studies against P. falciparum. Titled compounds were also tested against Pheretima postuma (earthworm) for their anthelmintic activity. Result: All the compounds exhibited moderate to significant antimicrobial activities. Antimalarial activity screening revealed that one compound 8e showed significant activity of IC500.59 µg/mL as compared to standard drugs chloroquine (IC50= 0.020 µg/ml) andquinine (IC50= 0.268 µg/ml). The most active compound exhibited the mean paralysis time of 19.2 ± 0.9 minutes and mean death time 31.7 ± 2.5 minutes. Conclusion: The results of the present investigation prove that the synthesized compounds have interesting antiinfective, antimalarial and anthelmintic activity and are suitable candidates for further scientific exploration.

Keywords: Thiazole, heterocycles, antiinfective activities, antimicrobial, anthelmintic, antimalarial.

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*Presenting author

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME 2-(4-HYDROXYPHENYL)-4,5-DIPHENYL-1 H- IMIDAZOLYL THIAZOLIDIN-4-ONE DERIVATIVES FOR ANTIMALARIAL AND ANTIBACTERIAL ACTIVITIES

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Abstract:
Five imidazole clubbed 4-thiazolidinone derivatives have been synthesized and evaluated for their biological potential in the present investigation. Synthesis of the title compounds have been accomplished employing benzil as a starting material which was refluxed with 4-hydroxybenzaldehyde, ammonium acetate and sulphanilic acid as catalyst in the presence of ethanol to yield 2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazole. In the next step, 2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazolyl ester was formed by refluxing the imidazole with ethylchloroacetate in basic medium composed of sodium hydroxide and ethanol. This ester was converted to 2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazolyl hydrazide using hydrazine hydrate in the presence of methanol. In the proceeding step 2-(4-hydroxyphenyl)-4,5-diphenyl 1-H-imidazolyl hydrazide was treated with different aromatic aldehydes in acidic media made by using small amount of glacial acetic acid. The different Schiff,s bases formed were then treated with thiomalic acid in N,N-dimethyl formamide containing a pinch of anhydrous ZnCl2 to yield 2-(4-hydroxyphenyl)-4,5-diphenyl-1H-imidazolyl thiazolidin-4-one derivatives. The chemical structures of all the synthesized compounds were confirmed by IR and 1H NMR spectral data. Synthesized compounds were evaluated for antimalarial and antimicrobial activity. Compounds have demonstrated interesting antimalarial and antimicrobial activity profile. Keeping in view the commendable antimicrobial and antimalarial activity of the synthesized compounds, further scientific endeavors may prove to be fruitful in harnessing the therapeutic potential of these compounds optimally.

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*Presenting author

DESIGN, SYNTHESIS, ANTIMALARIAL AND ANTILEISHMANIAL ACTIVITIES OF SOME NEW AMINOALCOHOL-PYRROLO[1,2-a]QUINOXALINE DERIVATIVES.

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A novel series of piperazinylalcohol pyrrolo[1,2-a]quinoxaline derivatives 1-2 were synthesized from 2-nitroaniline or 2-amino-3-nitrophenol and tested for in vitro activity upon the intraerythrocytic stage of W2 and 3D7 Plasmodium falciparum strains. Biological results showed good antimalarial activity with Inhibitory Concentrations 50 in the micromolar range. These molecules were also tested against the promastigote form of Leishmania donovani and the results revealed a selective antiplasmodial profile. In parallel, the in vitro cytotoxicity of these molecules was assessed on the human HepG2 cell line. Structure-activity relationships could be drawn for these new synthetic compounds. The most promising antimalarial results were observed for the three 9-substituted pyrrolo[1,2-a]quinoxalines 13a, 13b and 13c bearing a 3-(4-substituted-piperazin-1-yl)-2-hydroxypropoxy chain. Moreover, the calculation of selectivity indexes (SI) led to the identification of compound 13c as the most potent antimalarial candidate with SIs of 40.9 for the W2 strain and of 122.7 for the 3D7 strain, respectively.

MALARIAL BIFUNCTIONAL DHFR-TS ENZYME AS A TARGET FOR DRUG DISCOVERY AGAINST ASEXUAL STAGES OF P. FALCIPARUM

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Malaria is a deadly infectious disease which affects millions of people each year in tropical areas. The causative agent is a protozoan parasite that belongs to the genus Plasmodium. Resistance to current antimalarial treatments is alarming, being necessary to discover new drugs efficacious against the parasite displaying novel mechanisms of action able to bypass current resistances. With this aim, the Bill & Melinda Gates Foundation has granted several laboratories to identify new antimalarial targets using chemogenomic approaches. A progression cascade using diverse chemical libraries was established in GSK in order to select compounds with good potency and a presumable novel mode of action. Then, P. falciparum in vitro resistant mutants have been selected under drug exposure using standard methodologies.

In this work, an example of the successful chemogenomic approach is show using the compound MMV027634. After two weeks, a culture under continuous drug pressure at a dose of 10x IC50 rendered parasite growth. Selected mutants displayed a high level of resistance specific for this compound when compared to the wild type strain. Whole genome sequencing of resistant mutants to MMV027634 revealed mutations in the dihydrofolate reductase-thymidylate synthase (dhfr-ts) gene. Mutations mapped in aminoacids of the highly conserved TS domain.
The role of this enzyme in Plasmodium metabolism, mode of action studies including metabolic bypass, cross-resistance of analogs as well as combinations of MMV027634 with other antimalarials are discussed. Results of these studies highlight the importance of the DHFR-TS enzyme in parasite metabolism and open possibilities to explore thymidylate synthase as a target to discover promising novel drugs with therapeutic efficacy against asexual stages of P. falciparum.

ANTIMALARIAL INTERACTIONS OF LAWSONIA INERMIS, TITHONIA DIVERSIFOLIA AND CHROMOLAENA ODORATA

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Background: Medicinal plants are usually used in combination in folk medicine; and drug combination has been known as an effective means of managing parasite resistance and reducing risk of resistance development in many infectious diseases including malaria. Chromolaena odorata, Tithonia diversifolia and Lawsonia inermis are medicinal plants used both singly and in combination to treat malaria in traditional medicine system but there is no scientific evidence of their antiplasmodial activities in combination.

Methodology: Aqueous and dichloromethane:methanol(1:1) extracts of Chromolaena odorata, Tithonia diversifolia and Lawsonia inermis leaves were subjected to in vitro test against P. falciparum Chloroquine sensitive (D6) and Chloroquine resistant (W2) strains. The organic extracts were then combined at different ratios against D6 and W2 P. falciparum strains. The organic plant extracts were further tested singly and in combination in vivo against P. berghei ANKA. Cytotoxicity and acute toxicity tests were also carried out.

Result: Dichloromethane, methanol (1:1) extracts of all the plants had high activity against the two strains of P. falciparum with L. inermis having the lowest IC50 of 3.98±0.3 and 4.69±0.1 against D6 and W2 strains respectively. In vitro combination of L. inermis and T. diversifolia exhibited synergistic activities while the combinations of C. odorata with T. diversifolia and L. inermis were antagonistic. However, in vivo results of C. odorata with T. diversifolia and L. inermis showed some degrees of

synergy. The extracts were not toxic at the concentrations of 100µg/ml and 5000mg/kg in vitro and in vivo respectively.

Conclusion: These findings rationalized the use of these plants singly and in combination as antimalarials in traditional medicine. However, the combination of Chromolaena odorata with other medicinal plants should be used with caution because of its possible antagonistic effect.

Keywords: Lawsonia inermis, Tithonia diversifolia, Chromolaena odorata, Plasmodium species

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STRUCTURAL CHARACTERIZATION OF POTENTIAL ANTIMALARIAL MOLECULES BASED ON PICOLINAMIDE HYDRAZONE AND SULFADOXINE

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Between 2000 and 2015, the global malaria incidence rate has fallen by an estimated 37 per cent, and the global malaria mortality rate has decreased by 58 per cent. As a result, the global Millenium Development Goal malaria target has been achieved. As of 2015, 98 malaria-endemic countries have reversed the incidence of malaria nationally compared to 2000. Yet malaria continues to pose a major public health challenge, with an estimated 214 million cases and 472,000 deaths globally in 2015. The disease is still endemic in 97 countries and territories around the world—3.3 billion people are at risk of infection—and it accounts for a large proportion of health spending in low-income countries [1]. The situation is made even worse by the fact that the parasitic organism responsible for the disease viz. Plasmodium falciparum has acquired resistance against most of the antimalarial agents used clinically [2]. There is thus an urgent need to develop new effective and selective antimalarial drugs.

Heterocyclic thiosemicarbazones such as 2-acetylpyridine thiosemicarbazones have been shown to possess potent antimalarial activity [3]. The carboxamidrazones bear a close structural resemblance to these thiosemicarbazone compounds and have shown promising antitumor and antimalarial properties upon metal conjugation to copper(II) [4-6]. The first clinical trials to prove a substantial curative and suppressive effect of the long-acting sulfonamide sulfadoxine in human malaria were performed by Laing in Tanzania. The favourable results were confirmed by further studies in both naturally acquired and experimentally induced malaria [7]. We will present the structural characterization of carboxamidrazone and sulfadoxine organic molecules and the synthesis and characterization of carboxamidrazone complexes with iron(III), cobalt(II), and zinc(II) as potential antimalarial agents.

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PHYSICAL AND ENTOMOLOGICAL CHARACTERISTICS OF SOME CULICIDAE BREEDING SITES IN DOUALA, CAMEROON

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Vector-borne plant and animal diseases, including several newly recognized pathogens, reduce agricultural productivity and disrupt ecosystems throughout the world. These diseases profoundly restrict socioeconomic status and development in countries with the highest rates of infection, many of which are located in the tropics and subtropics. [1] Activities to control transmission in the habitats of immature and adult stages of the vector in the household and immediate vicinity, as well as other settings where human–vector contact occurs is key to their prevention or reduction. Physical characteristics of mosquito breeding sites and information on the biodiversity of species implicated and their ecology, all included in the Larval Source Management (LSM) is required for the development of an effective program for vector control. [2]

We present a longitudinal study from August to December 2014 to characterize the mosquito breeding sites in the neighborhoods of Nyalla and Kambo in Douala, Cameroon. Collections were done on 20 breeding sites, among temporary and semi-permanent water collections, according to their larval potential. These breeding sites are artificial because of their mode of formation, have variable dimensions and sun exposition, and are associated with vegetations at close proximity of living areas. Adult mosquitoes obtained were morphologically identified and distributed in three genera: the genus Culex (73.14 %), the genus Anopheles (22.69 %) and Aedes (4.15 %). In total, Eleven (11) Culicidae species were identified: Culex duttoni, Culex descens, Culex poicilipes, Culex univittatus, Culex trigripes, Culex antennatus, Culex simpsoni, Culex pipiens, Anopheles gambiae ss, Aedes aegypti and Aedes albopictus.

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SERUM CITOKINE CONCENTRATION OF BOVINE WITH HIDATIDOSIS AND CO-INFECTED WITH DISTOMATOSIS.

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INTRODUCTION.
Hydatidosis (HT) and distomatosis (DS) are recognized worldwide public health problem. They are known to produce local immune response but data regarding the host systemic immune response to both diseases are still lacking.

MATERIAL AND METHODS.
A cross-sectional study was conducted on 2781 animals to characterize the presence of HT and DS in slaughtered cattle. Postmortem examination comprised visual inspection, palpation and incision of lungs and liver for the presence and distribution of hydatid cysts and liver fluke. Serum samples were obtained from 36 bovines before slaughter and they were divided in: Healthy (H), distomatosis only (DS), distomatosis+hidatidosis with fertile cyst (DHfertile), distomatosis+hidatidosis with infertile cyst (DHinfertile), hidatidosis only (HT) according to their health status. Samples were analyzed in duplicated thought MULTIPLEX (EMD Millipore) to determine it concentration of IL-2, IL-4, IL-10 and IL-12.

RESULTS.
There was no significative diference in the concentration of IL-2 and IL-12 between all studied groups. While the concentration of IL-4 (78.3±29.9ng/mL) was slighy higher in DHfertile compared to the rest of the groups. The most significant diference ($p<0.05$) was observed in the IL-10 concentration, in were DHfertile had the highest concentration (116.6±73.2) compared to DHinfertile (34.2±21.4), HT (36.6±20.6), DS (28.2±17.6) and H (27.5±9.5).

CONCLUSIONS.
This results suggest that, rather than only a local immune response, hidatidosis and distomatosis plays an important role in the systemic immune response in cattle.

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APOPTOSIS IN ADVENTITIAL LAYER OF HYDATID CYSTS.

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INTRODUCTION.

Cystic Echinococcosis (CE) is a zoonotic infection with high prevalence in part of Eurasia, Africa, Australia, and South America that represents a major public health and economic burden in many countries. Fertile cysts are capable to generate protoscolex, while for unknown reason, some cysts are unable to produce (infertile hydatid cysts). Previous reports showed that apoptosis could be involved in a negative regulation of protoscoleces generation, leading to hydatid cyst infertility but no report are available about cell apoptosis in adventitial layer and the relationship with other parasitic disease like fascioliasis.

MATERIAL AND METHODS.

Animals were evaluated to characterize the presence of CE and fasioliasis (FS) in cattle slaughtered at abattoir in Santiago, Chile. Samples were processed for routine histology and stained with heamatoxylin/eosin. samples from animal with both fertile and infertile cyst from CE and with or without DS was included in this study, using 5 samples per condition. Histological samples were evaluated by immunofluorescence and TUNEL Assay; digital images were obtained using an Olympus BX 41 Microscope and analyzed with software for morphometric analysis (Image Pro-Plus, Media Cybernetics, USA). The adventitial layer apoptotic index was calculated as follows: apoptotic nuclear area in adventitial layer x 100/total nuclear area in adventitial layer. Kruskal-Wallis test was performed using IBM SPSS Statistics 22 (IBM Corporation) software, $p < 0.05$.

RESULTS.

The apoptotic index in infertile cysts (0.18 ± 0.35%) was significantly higher ($p = 0.032$) compared with fertile cysts (0.045 ± 0.068%), as the presence of co-infection with liver fluke, both fertile cysts as infertile has a lower apoptotic index without significant difference ($p > 0.05$).

CONCLUSIONS.

The highest index of apoptosis cells in the adventitia layer of hydatid cysts is related to infertility cysts. The presence of distomatosis decreases cell apoptosis.

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IMAGING FLOW CYTOMETRY FOR CHARACTERIZATION OF DRUG ACTIVITY IN VITRO: CYTOTOXICITY, PARASITE REDUCTION RATE, CIDAL VS STATIC ASSAY

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Background:
The increase in the prevalence of antimalarial-resistant Plasmodium falciparum has called for the discovery and development of new antimalarials. Due to this pressing need, approaches are now leaning more on high-throughput methods. This study sought to validate an imaging flow cytometry-based method that can be used to characterize candidate antimalarial drugs on the basis of IC50, parasite reduction rate (PRR), and cidal vs static activities.

Method:
Cytotoxicity, PRR, and cidal vs static assays were carried out using three antimalarial drugs, chloroquine, artemisinin, azithromycin, and atovaquone. Plasmodium falciparum FCR1/FVO7120 were maintained in vitro under constant exposure to drugs for up to 120 hrs. Samples of the cultures were taken every 24 hrs, stained with acridine orange, and analyzed using the Amnis Flow Sight™ flow cytometer. The machine was programmed to acquire 20,000 events (excluding debris), which were then gated in four successive steps. The gates were FOCUSED > SINGLE CELLS > INTERNALIZATION > BRIGHT DETAIL VS INTENSITY using the FITC and brightfield channels. Data were analyzed using the IDEAS 6.3 software by Amnis. The final gated data (bright detail vs intensity) showed four clusters (R1 to R4) distinct from non-parasitized RBCs. Cytotoxicity, PRR, and cidal vs static assays were calculated from each cluster, using procedures modified from the literature. Median inhibitory concentration (IC50) was calculated using CompuSyn™. PRR was calculated as change in parasitemia within several 48-hr intervals during continuous exposure to drug for up to 120 hrs. Cidal vs static activities were profiled based on the growth curve following removal of drug after exposure for 12-48 hrs.

Result:
Microscopy suggested that R2 consists mainly of trophozoites whereas R3 and R4 consist mainly of schizonts. Analysis using R2 counts produced sigmoid curves and expected results for chloroquine IC50 (121.03 ng/mL) that are consistent with previous determinations using microscopy (DAPI staining). The IC50 for artemisinin (22.19 ng/mL), also consistent with previous determinations using microscopy, suggests that FCR1 is a resistant strain. The PRRs for the drugs are consistent with literature; in particular, the value for artemisinin at a concentration 16X the IC50 (-99% reduction rate) is consistent with artemisinin being the most rapidly acting antimalarial drug available. Azithromycin and atovaquone were correctly profiled as static whereas artemisinin and chloroquine were profiled as cidal, consistent with their known activities.

Conclusion:
This study was able to establish a gating strategy for the imaging flow cytometry that gave reliable indications of drug action. The sensitivity, specificity, and speed of the system combined with a 96-well autosampler make it a highly feasible high-throughput platform for antimalarial drug discovery and development.

IMMUNOGENICITY OF A *PLASMODIUM VIVAX* CIRCUMSPOROZOITE ANTIGEN-BASED PROTEIN PRODUCED IN YEAST *PICHIA PASTORIS* AS CANDIDATE FOR A UNIVERSAL VACCINE AGAINST MALARIA.

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Human parasitic diseases caused by vector-borne transmitted protozoa remain a major concern in public health. In the particular case of malaria, so far there is not a commercial vaccine available. The most advanced formulation (Mosquirix®, currently in clinical phase 4) is based on the circumsporozoite protein (CSP) from *Plasmodium falciparum*. If approved, this vaccine would be unable to protect against *Plasmodium vivax*, the most common type of malaria outside the African continent. Recently, using bacterial recombinant proteins based on the *P. vivax* CSP, we demonstrate that it is possible to elicit strong antibody mediated immune responses to each of the three allelic forms of this antigen (VK210, VK247 and Vivax-like). However, the solubilization and purification processes of these proteins produced in *E. coli* were time-consuming and the final product may contain LPS residues. In this work, a chimeric recombinant protein based on *P. vivax* CSP was successfully produced as soluble secreted protein in the yeast *Pichia pastoris* and highly purified by affinity and ionic exchange chromatography. Protein purity, secondary conformation, freeze-drying stability and protein sequence were assayed by HPLC, circular dichroism, lyophilization-rehydration and mass spectrometry analyses, respectively. The purified protein was used for experimental immunization of C57Bl/6 mice in the presence of Poly I:C, a TLR3 ligand as adjuvant and tested for its capacity to elicit antibody mediated immune responses. Our results establish that it is possible to elicit high (>10^5) antibody titers to all three different allelic forms of *P. vivax* CSP using this formulation. This recombinant protein expressed from *P. pastoris* could be a good candidate for clinical trials aiming at the development of a universal vaccine against *P. vivax* malaria.

MOLECULAR SURVEILLANCE OF DRUG RESISTANCE GENES IN IMPORTED CASES OF PLASMODIUM FALCIPARUM IN QATAR.

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Background
Imported malaria is a great challenge for public health in Qatar due to large number of immigrant workers from Indian subcontinent and Sub-Saharan Africa. Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today. Chloroquine (CQ), sulphadoxine-pyrimethamine (SP) and artemisinin (ACT) drug resistance in Plasmodium falciparum (Pf) is associated with polymorphisms in Pfcrt/Pfmdr-1, Pfdhfr/Pfdhps and PfATPase6 respectively. Monitoring parasite haplotypes that predict susceptibility to major anti-malarials can guide treatment policies. The present study is conducted to determine polymorphic regions of antimalarial drug resistance genes in imported malaria cases in the State of Qatar.

Method:
During September 2013 to September 2015, a total of 79 Pf microscopically positive uncomplicated malaria samples were collected from Hamad General Hospital, Qatar and confirmed by molecular assay. Nested-PCR, Restriction Fragment Length Polymorphism to detect alleles of pfcrt and pfmdr1 and DNA sequencing were used for Pfdhfr, Pfdhps and PfATPase6.

Result:
Out of 79 uncomplicated malaria cases, the majority of patients were from East Africa followed by Indian Sub-continent and West & Central Africa. Molecular genotyping at codon 86 of pfmdr1 showed that 60.7% had wild, 26.6% mutant and 11.4% mixed alleles. However, prevalence of Pfcrt mutant, wild and mixed alleles was 72.1%, 22.8% and 5% respectively. In Pfdhps and Pfdhfr, we found 4 (436,437,540,581) and 3 (51,59,108) mutations respectively. However, no mutation was seen in PfATPase6.

Conclusion:
Molecular surveillance strategy based on imported malaria cases can be used to detect and track drug-resistant malaria. The data presented here might be helpful for enrichment of molecular surveillance of antimalarial resistance and will be useful for developing and updating antimalarial guidance for non-immune imported cases in State of Qatar.

Key words: Plasmodium falciparum, Imported malaria, Drug resistance, Qatar

CARDIAC COMPLICATIONS OF MALARIA : LITERATURE REVIEW

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Abstract: Studies of malaria complication have been conducted over last several years, particularly in the endemic area. Malaria, especially falciparum malaria, can cause various complications involving various systems of the body, such as cerebral malaria, severe anemia, acute kidney injury, acute lung injury, multiple seizure, circulatory collapse, and also cardiac function. But, the involvement cardiac in severe malaria has not received sufficient attention. Previous study has been showed that there was a rising of cardiac enzymes in complicated malaria. Other study has showed a significantly reduced ejection fraction by its echocardiography result during hospital admission. The objective of this review is to critically evaluate the potential complication of severe malaria to heart, as one of the most important organ in human body. As result, complicated malaria is more commonly caused by Plasmodium falciparum and it is rarely caused by other malarial parasites. On the other hand, some cases reported the parasite could affect heart condition, like ventricular fibrillation, acute heart failure, acute myocarditis, and myocarditis unknown. In order to investigate another potential pathologic condition of the heart caused by malaria, further study need to be conducted to prevent all the possibility of heart diseases.

Keywords: malaria, cardiac, complication

IMMUNOGENICITY OF A RECOMBINANT *PLASMODIUM VIVAX* CIRCUMSPOROZOITE PROTEIN PRODUCED IN YEAST *PICHIA PASTORIS* AS CANDIDATE FOR A UNIVERSAL VACCINE AGAINST MALARIA.

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Human parasitic diseases caused by vector-borne transmitted protozoa remain a major concern in public health. In the particular case of malaria, so far there is not a commercial vaccine available. The most advanced formulation (Mosquirix®, currently in clinical phase 4) is based on the circumsporozoite protein (CSP) from *Plasmodium falciparum*. If approved, this vaccine would be unable to protect against *Plasmodium vivax*, the most common type of malaria outside the African continent. Recently, using bacterial recombinant proteins based on the *P. vivax* CSP, we demonstrate that it is possible to elicit strong antibody mediated immune responses to each of the three allelic forms of this antigen (VK210, VK247 and Vivax-like). However, the solubilization and purification processes of these proteins produced in *E. coli* were time-consuming and the final product may contain LPS residues. In this work, a chimeric recombinant protein based on *P. vivax* CSP was successfully produced as soluble secreted protein in the yeast *Pichia pastoris* and highly purified by affinity and ionic exchange chromatography. Protein purity, secondary conformation, freeze-drying stability and protein sequence were assayed by HPLC, circular dichroism, lyophilization-rehydration and mass spectrometry analyses, respectively. The purified protein was used for experimental immunization of C57Bl/6 mice in the presence of Poly I:C, a TLR3 ligand as adjuvant and tested for its capacity to elicit antibody mediated immune responses. Our results establish that it is possible to elicit high (>10^5) antibody titers to all three different allelic forms of *P. vivax* CSP using this formulation. This recombinant protein expressed from *P. pastoris* could be a good candidate for clinical trials aiming at the development of a universal vaccine against *P. vivax* malaria.

IDENTIFICATION OF BIOMPHALARIA SNAILS AND SCHISTOSOMA MANSONI TRANSMISSION IN KOME ISLAND, LAKE VICTORIA, TANZANIA

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In order to investigate intestinal schistosomiasis transmission by Biomphalaria snails in Kome island, Lake Victoria, Tanzania, Biomphalaria snails were collected at lakeshores and examined morphologically and molecular biologically. Morphological identification of Biomphalaria snails revealed B. sudanica type and B. choanomphala type. Unlike those of B. sudanica type, shell size and shape of B. choanomphala type are variable. Most of cytochrome oxidase subunit I (COI) sequences of the collected Biomphalaria snails were similar to the sequences of previously reported Lake Victorian Biomphalaria snails. Eighteen unique COI sequences were identified and named as KCOI-1 to KCOI-18. Molecular phylogenetic tree revealed close relationships between B. sudanica and B. choanomphala types. About seven percent of examined Biomphalaria snails were infected with Schistosoma mansoni. These results support the insistence that the different morphological forms of Lake Victorian Biomphalaria snails may be ecophenotypes of one species. More evidences on the species-related susceptibility of Biomphalaria snails to S. mansoni infection are required.

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MOLECULAR BASIS FOR THE DEFORMABILITY AND LOCALIZATION OF PLASMODIUM FALCIPARUM MATURE GAMETOCYTES

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Plasmodium falciparum, the malarial parasite, alternates between two hosts-human and mosquito. The transmission from human to mosquito occurs via the sexual form of parasite called gametocytes. Gametocytes develop and mature in human red blood cells (RBCs). Interestingly, immature gametocyte-infected RBCs (iRBCs) are localized in the bone marrow and only mature gametocyte-iRBCs are found in the circulation. Previous studies have suggested that this differential localization of gametocytes occurs due to stage-dependent differences in iRBC mechanical properties. Immature gametocytes are more rigid and get sequestered in the bone marrow tissue, while mature gametocytes are deformable and easily pass into the circulation. Higher rigidity of the immature gametocytes has been correlated to the presence of the STEVOR protein on the iRBC surface. Conversely, the increased deformability of mature gametocytes is associated with the absence of STEVOR from the iRBC surface. We demonstrate that during the transition from immature to mature gametocytes, STEVOR protein is cleaved from the iRBC surface by a serine protease. Furthermore, in the presence of a serine protease inhibitor, mature gametocytes are more rigid compared to the control-treated gametocytes. They fail to undergo the shape change that is characteristic of mature gametocytes. Using the P. falciparum transcriptome database, Plasmodb.org, we identified four serine proteases belonging to the rhomboid protease family that were highly expressed during the late gametocyte stage. Each of these rhomboid proteases (PfROM3, PfROM4, PfROM7, and PfROM10) was tested for its ability to cleave STEVOR in a heterologous mammalian transection assay. Using this assay, we found that PfROM4 is capable of shedding STEVOR protein. Further studies using a PfROM4 conditional knockout parasite strain will be done to demonstrate the role of PfROM4 in STEVOR processing. Taken together, these findings shed light on the critical role of PfROM4 in gametocyte maturation and localization, and help identify possible new ways to prevent gametocyte transmission.

DISCOVERY OF SYNTHETIC FLAVONOIDS AS POTENT ANTI-LEISHMANIAL AGENTS

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Naturally-occurring flavonoids have been reported to have weak anti-leishmanial activity. Here we report the design, synthesis and characterization of a library of synthetic flavonoids with potent anti-promastigote and anti-amastigote activity. The most potent compound FM09 has an in vitro IC50 of less than 1 µM. FM09 has a low toxicity towards peritoneal elicited macrophages with IC50 of 42 µM; giving it a selective index of higher than 42. We have performed detailed pharmacokinetic study in Balb/C mice. After intravenous administration at 10 mg/kg, FM09 was found to have a short half-life. In vitro metabolism studies using human liver microsomes demonstrated that FM09 is rapidly metabolised by N-dealkylation at the carbon between the pyridine ring and nitrogen. Structural modification is underway to slow down such metabolism pathway in order to increase its half-life. We have also investigated the mechanism of action by which FM09 exerts its anti-leishmanial effect. We demonstrated that, using DCFDA assay, that FM09 can induce reactive oxygen species (RO) in amastigotes. ROS scavengers like N-acetyl cysteine (NAC) can rescue promastigotes from the killing effect of FM09.

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