RESOURCE HUB *Correspondents*

BioMalPar XVI Conference "Biology and Pathology of the Malaria Parasite" - Virtual

Complete series

MESA Correspondents bring you cutting-edge coverage from the BioMalPar XVI Conference "Biology and Pathology of the Malaria Parasite"

18 - 19 May 2020

Virtual Conference

The MESA Alliance would like to thank Silvia Portugal (Heidelberg University Hospital, Germany) for providing senior editorial support.

The MESA Alliance would also like to acknowledge the MESA Correspondents Nathalie Amvongo Adjia (Institute of Medical Research and Medicinal Plant Studies, Cameroon), Manuela Runge (Northwestern University, USA) and Ntui Vincent Ntui-Njock (University of Buea, Cameroon) for their crucial role in the reporting of the sessions.

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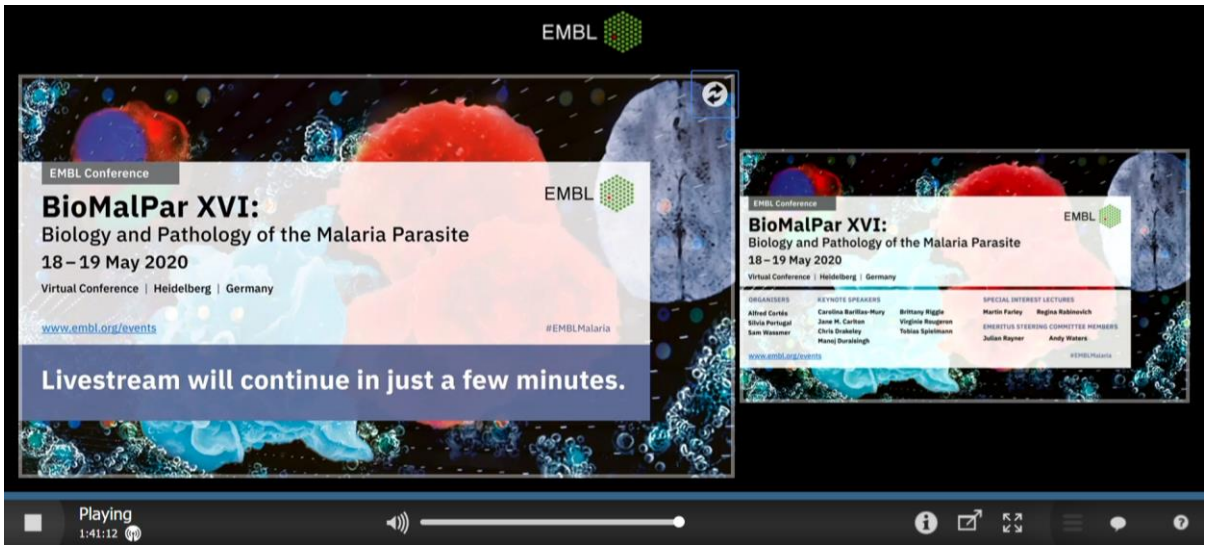
Day 1: 18th May 2020

Opening remarks

The first virtual BioMalPar conference started with the opening remarks by the scientific organizers. **Silvia Portugal** (Heidelberg University Hospital, Germany) highlighted the high numbers of registrations, almost 400, from around the world. 70 of them from malaria endemic countries. **Sam Wassmer** (London School of Hygiene and Tropical Medicine, LSHTM, UK) summarized the good practices for the following two days and encouraged attendees to participate in the virtual pub quiz happening at day 2. Finally, **Alfred Cortés** (Barcelona Institute for Global Health, ISGlobal, Spain) went over the program and suggested the use of the tools created to communicate among us during the conference.



Virtual Session 1 - Emerging Challenges and new tools

Laurent Dembele (University of Sciences, Techniques and Technologies of Bamako, Mali) presented his findings on the association between dormant rings and artemisinin (ART) drug resistance. Specifically, the focus laid on resistance induced ring stage dormancy in *P. falciparum* aiming to identify potential artemisinin partner drug candidates that are active against all ring stages including those with K13 mutation. The methodology included the evaluation of the in vitro drug sensitivity profile of normally developing *P. falciparum* ring stages and dihydroartemisinin (DHA)-pretreated dormant rings (DP-rings). Dembele presented on two compounds, KDU691 and GNF179. While KDU691 was found to be highly inhibitory against DP-rings and would be only useful after DHA exposure to eliminate dormant rings, GNF179 was found to be a suitable drug candidate, as it eliminated dormant parasites including those that break K13 mutations and are resistant. By combining compounds like GN179 with ART, novel antimalarial combination therapies would be created and may help preventing ART resistance spread to Africa.

The special lecture by **Regina Rabinovich** (Harvard TC Chan School of Public Health; Barcelona Institute for Global Health, ISGlobal, Spain) about the COVID-19 and malaria interface started with a review of the history of the fight against malaria, from the Global Malaria Eradication program to the scale up of interventions following increased global funding, the increased data availability, and the evolution of the global malaria agenda. The World Health Organization (WHO) was already tackling the plateau in malaria progress prior to COVID in 2020. The Strategic Advisory Group on malaria eradication, established by the Director General of the WHO, was asked to address likelihood of future malaria eradication taking into account a variety of determinants such as climate change, economic development and other megatrends. However, a pandemic was not included as a potential threat. Malaria endemic countries face challenges with the novel COVID-19 pandemic, especially in Africa, and this may add additional challenges to progress in achieving malaria goals. Rabinovich reviewed lessons learned from other diseases on the eradication agenda, emphasizing the need to continue "research and development even beyond eradication". A 6-step strategy was proposed including: planification, innovation, research affordability, fundraising, generation of data and community engagement. Malaria urgency and burden in endemic countries is clear, but translating the culture of urgency from COVID-19 where collaboration, funding and efforts to accelerate translation to the field are evident, to malaria, is a critical component of the interface between the pandemic and the global malaria program.

Virtual Session 2 - Parasite biology

The keynote from this session addressed the very intriguing process of how parasites escape the lockdown in red blood cells. **Manoj Duraisingh's** (Harvard T.H. Chan School of Public Health, USA) mentioned how the depletion of *Plasmodium falciparum* protein phosphatase 1 (*Pf*PP1) gene, related to the egress of *Plasmodium falciparum* parasites, was the central question around the presented experiments. Early and mid *Pf*PP1 depletion resulted in abnormal schizogony and DNA replication; mid-stage depletion in atypical nuclear division; while late-stage depletion revealed an essential function on post-replicative egress. Further studies with *Pf*PP1 depleted suggested that the inability to activate protein kinase G could be responsible for the block in egress. A more 'intriguing result' was the strong synergy with a phosphodiesterase-inhibitor, indicating a potential negative feedback loop preventing premature egress. *Pf*PP1 has an essential role in schizogony and coordinates multiple signals early in egress. Finally, the progress of parasites escaping red blood cells is regulated by intrinsic signals associated with *Pf*PP1, but also by exogenous lipids.

Virtual Session 3 - "Omics" approaches & evolution

Jane Carlton (New York University, USA) was in charge of the keynote of the session on "*How Evolutionary genomics plays an important facet of malaria studies in India*?". Carlton incorporated *Plasmodium falciparum (Pf)* and *Plasmodium vivax (Pv)* isolates from India into a global sequencing map that provided evidence of widespread genomic admixture within and between *Pf* parasite's populations of the European, African, and Asian continents. Indian *Pv* isolates showed higher polymorphic lineage than that of *Pf* or other isolates being hybrid of the Old World and New World and therefore increasing the difficulty of *Pv* elimination. The analysis and findings demonstrated the

use of evolutionary genomics as an informative approach to trace parasitic populations' history in a highly diverse country where submicroscopic and asymptomatic infections are increasing. Carlton ended her talk with a call for more sequencing data to capture the diversity of *Pf* and *Pv* parasites in the context of shifting malaria epidemiology, especially genome sequence data in India.

** MESA only reported the talks that had the approval of the speaker.*

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Day 2: 19th May 2020

Virtual Session 4 - Epidemiology & surveillance

Mario Recker (University of Exeter, UK) presented malaria infection data from a longitudinal, systems-immunological cohort study conducted in a study site in Kenya between 2010 and 2018. He defined an immune response pattern that distinguishes children with frequent malaria episodes and those with an average number of episodes. After describing the time-spatial trends in cumulative malaria exposure (year of birth), Recker investigated whether malaria susceptibility could be predicted. The data showed high heterogeneity in the rate at which children experience clinical malaria and no persistent hotspots were found within the study area. The rate of acquired clinical episodes was similar between older and younger individuals and the number of experienced episodes seemed to depend more on the year of birth rather than age. Against their expectation, the probability of clinical episodes in the upcoming transmission season increased with previous exposure while no geographic trend could be determined. From these findings, Recker concluded that there might be differences in susceptibility phenotypes in the population and raised the concern that the high inter-annual and inter-individual heterogeneity likely affect results from 'epidemiological snapshots'.

Manuella Carrasquilla (Harvard T.H. Chan School of Public Health, USA) highlighted the important aspects of malaria epidemiology in a study area in the Pacific coast of South America, Guapi. The *de novo* emergence of *PfKelch13* C580Y mutation in Guapi, a regional hotspot of drug resistance, suggests high level of mutation occurring in local *Pf* populations. Carrasquilla performed whole-genome sequencing of 151 *Pf* clinical samples from the locality of Guapi. Population structure analysis was performed with all allele frequencies revealing five distinct ancestral populations. This is driven by the history of antimalarial selection, human migration and neutral drift. Also, identity-by-descent (IBT) analysis showed variation in the level of relatedness and a large number of clonal clusters in Guapi. Spatial and temporal dynamics of clonal clusters reveal mining sites as main drivers of malaria transmission. The impact of selection antimalarial on population structure showed dihydrofolate reductase (DHFR) haplotypes, possible ongoing antifolates selection, and migration. Ultimately, Carrasquilla pointed out evidence of transfer of *Pf*mdr1 haplotype between clonal clusters in addition to an increasingly level of recombination events with time.

Reduction in malaria burden has been associated with increased control interventions as shown by prevalence and cases estimates over time. **Simon Kigozi** (London School of Hygiene and Tropical Medicine, UK) evaluated the age distribution of malaria cases in order to determine the progress of control interventions. To address this issue, Kigozi compared routine surveillance data over a period of about ten-years (January 2009 – July 2018) from four sentinel health districts (HDs) in Uganda. These HDs have undergone mass distribution of LLINs and/or IRS during the study period. Over the study period, Kigozi observed an overall change in the age distribution of suspected and confirmed malaria cases with a shift from younger to older age groups. Age distributions were very similar to baseline data for not suspected and negative malaria patients with a marginal decline across the intervention period. These findings are therefore indicative of immunity, behavioural, occupational factors and the success of control interventions.

Virtual Session 5 - Pathogenesis & immunology

In Africa, most malaria case fatalities in pediatric patients are caused by *Plasmodium falciparum* (*Pf*) cerebral infections and failure in response to available therapeutics. **Brittany Riggle** (National Institutes of Health, USA), in charge of the keynote of the session, investigated the role of CD8+ T cells in this severe disease form. Using a mouse model, Riggle induced a similar pathogenesis as observed during pediatric cerebral malaria (CM) and noted a significant expression of *Pf* specific CD8+ T cells in the brain following a DON (6-Diazo-5-oxo-L-norleucine) treatment administered to experimental mice 4 to 8 days' post-infection, however, CD8+ T cells were not found in peripheral tissues. Similar observations were made in post-mortem brains from pediatric patients with or without CM and with known HIV status engaging CD3+ and CD8+ into cerebro- and perivasculature. These data provide a rationale for investigating CD3+ CD8+ T cells as the target of an adjunctive therapy for cerebral malaria.

Carola Schaefer (Seattle Children's Research Institute, USA) developed a unique humanized mouse model to investigate the transition of *Pv* infection to blood stages and to test blood stage interventions. In the model, human liver-chimeric FRGN huHep mice were infected with *P. vivax* sporozoites and infused with human reticulocytes. The model demonstrated successful parasites developed into all asexual stages (erythrocytic forms within their physiological 48-hour life cycle *in vivo*). A successful expression of gametocyte antigen Pvs16 was also detected. The developed model was found adequate to test blood stage interventions and provides a proof of principle that gametocytes mature and can be transmitted to mosquitoes. A promising step towards maintaining a whole life-cycle in the lab.

Virtual Session 6 - Transmission biology

The findings of **Dennis Klug's** (INSERM, France) "cast new light" on the interactions between malaria parasites, their vectors and the interplay of factors during mosquitoes' immune response of. In his talk Klug focused on the role of the Thioesther-containing protein 12 (TEP12) in the early phase of immune response of Anopheles against *Plasmodium* infection and compared it with TEP1, the most studied protein and major anti-parasitic factor across the TEP family. Several experiments were carried out using *Anopheles stephensi* and *A. coluzzi*, infected with *Plasmodium berghei* or *Plasmodium falciparum*. When TEP12 was knocked down, some increase in parasite load was observed in *A. stephensi* infected by *Plasmodium berghei*. When an engineered *A. coluzzi* strains was used, results indicated that absence of TEP12 also allowed for increase in *P. berghei* infections, but the opposite effect was observed in *P. falciparum* where knocked down of TEP12 led to a decrease in mosquito infection. Finally, TEP 12 was the first anti-plasmodial TEP present in all sequenced *Anopheles* species.

The closing remarks by the emeritus steering group of the EMBL Virtual BioMalPar 2020 were moderated by **Julian Rayner** (Wellcome Sanger Institute, UK) who gave the floor to **Andy Walters** (University of Glasgow, UK) for a brief *In Memoriam* talk, remembering Shahid Khan for his brilliant contributions in characterizing malaria parasite using OMICs tools. Rayner further thanked the organizing committee for their invaluable commitment and 'superhuman efforts' to make the virtual event possible and the great experiment they did with this first virtual BioMalPar. Finally, he thanked all conference participants for the wonderful experience shared and active communication.

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