

Keystone: Malaria: Functional genomics to biology to medicine

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Pètra Mens, KIT Biomedical Research, Department of Parasitology

The Keystone symposium Malaria: Functional genomics to biology to medicine was held in Taos-New-Mexico from February 28 until the 5th of March.

The symposium covered a whole spectrum of subjects about *Plasmodium* in 8 sessions with 25 invited speakers and 1 workshop.

The symposium started with a keynote address from Mrs Rabinovich, who works at the Bill and Melinda Gates Foundation that financially supported the meeting. The oral presentations were grouped in 4 morning and 4 afternoon/evening sessions. The first session focused on system biology in which antigenic variation and epigenetics was discussed. Genome and transcriptome analysis was discussed in the second session. The following day the symposium continued with the session Genetic Diversity in the parasite host, which covered among other things the phylogenetic relationship of different *P. falciparum* isolates and lab strains. It was striking to hear that one of the most frequently used lab strains 3d7 formed its own group in phylogenetic trees thus making it a very distinct *Plasmodium* strain than from those found in the field.

Virulence factors and host immuno-pathology combined with pathogenesis was discussed in the afternoon session and in these sessions a lot of discussion focused on the transformation of these insights into control strategies such as new drug and vaccine targets. In the last sessions there was a lot of attention for the development of drugs and vaccines. Host immune responses and mosquito parasite interactions were discussed. Since resistance against artemisinin is already occurring in *P. chaboudi* lab strains, but recently also been found in the field, there is still an urgent need for new drugs and a good vaccine. The recent progress of the RTS,S vaccine, by some still considered as THE potential malaria vaccine, was reported but also new approaches such as the targeting of the food vacuole and thus inhibiting the haemoglobin degradation. Even though the majority of the presentations focused on *P. falciparum* there was also some interest for *P. vivax*. Jane Carlton from TIGR for example presented the completed *P. vivax* genome.

In the evening there were small poster sessions. Because these sessions were small, about 25 posters per evening, it was possible to see everything and have more detailed and personal discussions. I presented the work below in which I had the opportunity to discuss the project in more detail and even though the main theme of the symposium was molecular biology and basic research there was quite some good response to the poster.

Evaluation of a quantitative nucleic acid sequence based amplification (QT-NASBA) assay to predict the outcome of sulfadoxine-pyrimethamine treatment of uncomplicated *P. falciparum* malaria.

P.F. Mens^{1,3}, S.A. Omar², G.J. Schoone¹, A. Yusuf², J. Mwangi², S. Kaniaru², G.A.A. Omer¹, H.D.F.H. Schallig¹, P.A. Kager³

¹ KIT Royal Tropical Institute KIT Biomedical Research, Meibergdreef 39, 1105 AZ Amsterdam, The Netherlands

²Kenya Medical Research Institute, Centre for Biotechnology Research & Development, Nairobi, Kenya

³Academic Medical Centre, Division of Infectious Diseases, Tropical Medicine and AIDS, Amsterdam, the Netherlands

Background In view of widespread drug resistance of malaria parasites, laboratory techniques are becoming more important. Availability of a fast, sensitive, reliable and quantitative method to detect parasite survival during and after drug treatment would help clinicians to monitor and –if needed- adjust treatment regimen. Quantitative nucleic acid sequence based amplification (QT-NASBA) technology is an isothermal molecular diagnostic test that allows for the quantification of *Plasmodium* species in clinical samples.

Methods A quantitative nucleic acid sequence-based amplification (QT-NASBA) assay was studied for its predictive potential regarding the outcome of sulfadoxine-pyrimethamine (SP, Fansidar) treatment of uncomplicated malaria in children aged <6 years in an endemic region in Kenya. Success of treatment was assessed according to WHO 2003 guidelines. Blood samples were collected at initial diagnosis and during follow-up. Mutation-specific nested PCR methods to analyse DHFR (Arg-59) and DHPS (Glu-540) mutations that are associated with SP drug resistance were applied. Parasite genotyping on *m*sp1 and 2 and GLURP was performed in order to distinguish between re-infection and recrudescence. Findings Eighty-six patients were recruited of which 66 were available for followed up. Nine children were classified as early treatment failure (ETF), 13 cases were classified as late clinical failure (LCF), 32 as late parasitological failure (LPF) and only 12 children had an adequate clinical and parasitological response (ACPR). DHFR and DHPS mutations conferring SP resistance were abundant in the *Plasmodium* population. Blood samples obtained 7 days after treatment were used to see in retrospect if the outcome of SP treatment could have been predicted. QT-NASBA correctly predicted the outcome of treatment in 85.7% of the cases. Positive predictive value (PPV) of QT NASBA case was 95% (95% confidence interval = 88.3 – 100) and negative predictive value (NPV) was 63% (95% C.I. = 39.5 – 86.5). In contrast, microscopy correctly predicted outcome in only 37.5% of the cases. PPV of microscopy was 100% (95% C.I. = 73.9 - 100) and the NPV was 25.5% (95% C.I. = 13.0 – 38.0).

Interpretation The analysis of a day 7 blood sample with QT-NASBA allows for the prediction of late clinical or parasitological treatment failure in the majority of the cases analysed in the present study.