OC 8405 IDENTIFICATION OF AN MTB-SPECIFIC SOLUBLE HOST SIGNATURE FOR RISK OF DEVELOPMENT OF ACTIVE TB IN HIV-POSITIVE MTB-EXPOSED CONTACTS

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Background With 2 billion people infected with *Mycobacterium tuberculosis* (Mtb) worldwide, identification of those most at-risk of progressing to active disease would provide a targeted, cost-effective approach for preventative therapy strategies. The GC6–74 project recruited Mtb-exposed HIV-positive (HIV+) contacts from 5 African countries with the aim of identifying molecular and protein signatures for identification of 'at-risk' subjects by comparing those who progressed to active disease (progressors) to those who remained asymptomatic (controls).
Methods For this arm of the project, we analysed longitudinal samples from 12 HIV +progressors and 28 HIV +matched controls from Uganda (Makerere University, MAK) and South Africa (Stellenbosch University, SUN). Diluted whole blood was stimulated for 7 days with 7 Mtb-specific antigens plus controls. Supernatant was collected and a 38-plex multiplex assay performed following identification of confirmed progressors and controls.
Results The median time to progression to active disease was 510 days for SUN and 425 days for MAK participants. Baseline CD4 counts were 163 cells/µl for progressors and 154 cells/µl for controls. Baseline responses showed significantly lower IL-4 production in progressors following ESAT-6/CFP-10 (EC) stimulation ($p=0.0309$) and significantly higher macrophage-derived chemokine (MDC) following both Rv3019 and TB10.4 stimulation. For the time-point closest to progression, IL-10 production following EC stimulation and IFN-γ production following Rv3019 stimulation were significantly higher in progressors than controls ($p=0.0024$ and $p=0.0028$ respectively). A combination of 12 analytes following EC and TB10.4 stimulation gave 84.4% and 91.1% correct classification respectively.
Conclusion We have defined a soluble signature for detecting likely progression to active TB in HIV +subjects 1 year prior to progression. Following validation in other cohorts, this could be exploited for development of a field-friendly test for targeted interventional therapy.

OC 8415 A TRANSLATIONAL PRECLINICAL PLATFORM TO ASSESS THE CHEMOPROPHYLAXIS AND CHEMOPREVENTION DOSE-RELATIONSHIP OF MALARIA DRUGS: THE CASE STUDY OF M5717

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Major progress has been made in the control of malaria leading to significantly reduce the number of cases and deaths. However, to reach the elimination stage, new tools will be needed, including combination of drugs capable of blocking the spread of malaria through chemoprophylaxis.

M5717 is a first-in-class compound that targets the *Plasmodium* Eukaryotic translation Elongation Factor 2, essential for protein synthesis. M5717 is highly potent against all developing stages of *Plasmodium* parasites and has a long half-life suggesting that a single dose development may be possible for cure, prophylaxis and transmission blocking activities. *In vivo* preclinical PK/PD data indicates an increased exposure in the portal vein compared to peripheral circulation translating into a prophylactic activity at a lower dose than the curative one. M5717 is currently completing first-in-man studies with the objective of initiating clinical prophylactic development in 2019. Additional data to model the human prophylactic dose will be needed prior to initiate the studies to demonstrate clinical efficacy (phase 2).

We recently established a human cell-based platform for drug screening against *Plasmodium* liver-stage infection relying on human hepatic 3D cultures in bioreactors supporting rodent *P. berghei* infection with similar rates of infection and parasite development compared to existing models. The platform was validated by assessing the activity of currently used antimalarial drugs.

Here we report the data of a dose response experiment to establish the liver stage efficacious concentration of M5717 compared to atovaquone in *Plasmodium*-infected hepatic 3D cultures. The data obtained with this new model were confirmed using the *in vivo* model of *P. berghei* sporozoite-induced infection in mice, demonstrating the validity of the *Plasmodium*-infected hepatic 3D cultures as an enabling technology for malaria drug development. These data are also providing additional evidence that M5717 should be developed as a chemoprophylactic agent for the prevention of malaria.

OC 8431 CLINICAL RESEARCH AND SUSTAINABLE DEVELOPMENT IN SUB-SAHARAN AFRICA: THE IMPACT OF NORTH-SOUTH PARTNERSHIPS

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Background The European legislation introduced in 2004 (under article 58) a collaboration tool to increase access to high quality and effective medicines in low- and middle-income countries. The European Medicines Agency (EMA) can provide scientific opinions on medicines intended for significant public health needs, in partnership with the World Health Organisation (WHO) and the relevant 'target' non-EU regulatory authorities. This EU-Medicines4all (EU-M4all) initiative contributes to the broader Global Health Mandate of the EU.
Methods We contacted the pharmaceutical companies holding 'article 58' scientific opinions and compiled the number of actual approvals based on these opinions.
Results Nine medicines have been assessed so far, most of them for HIV/AIDS, tuberculosis, malaria and maternal/newborn health. Although this figure may appear low, the impact of the corresponding scientific opinions is much wider. Approvals were granted in 66 different countries worldwide, 38 of which are in Africa, based on these opinions.

Discussion Such scientific opinions on the quality, safety and efficacy of the medicines are provided by the EMA's Committee for Medicinal Products for Human Use (CHMP). Prior to this, it is recommended to agree on the data to be generated through scientific advice. The opinions are based on the same standards as used for those approved for Europe, with considerations for local conditions of use. To promote reliance on EMA scientific outputs and awareness of the procedure, two training events with regulators from Southern and from Western Africa are organised in partnership with WHO, NEPAD and local regulators in June 2018.
Conclusion We have shown that this 'article 58' procedure has a true impact and we encourage applications by companies developing medicines, aimed to prevent or treat diseases of significant public health interest, to be marketed outside the EU. This will ensure timely access of medicines by patients in target countries all over the world.

OC 8432 EVALUATION OF AN ANTIBODY-DETECTING POINT-OF-CARE TEST FOR THE DIAGNOSIS OF *TAENIA SOLIUM* TAENIASIS AND NEUROCYSTICERCOSIS/CYSTICERCOSIS IN AN ENDEMIC AREA

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Background *Taenia solium* taeniasis/(neuro)cysticercosis is a neglected parasitic zoonosis with significant economic and public health impacts. Neurocysticercosis is responsible for 30% cases of acquired epilepsy in endemic areas. Diagnosis and case management of neurocysticercosis/taeniasis in resource-limited endemic countries is challenging. Reliable, inexpensive and easy to use diagnostic tools with sufficient sensitivity and specificity are currently not available. A new point-of-care (POC) test based on recombinant rT24H and rES33 proteins developed by the Centre for Disease Control in Atlanta (US) which combines diagnosis of taeniasis and cysticercosis has been developed, however, its performance at community level is not known. The aim of this study is therefore, to evaluate the diagnostic performance of this test in a community setting.
Methods The study site is Mtandaza community, Sinda district, Eastern Province of Zambia. The diagnostic accuracy is being evaluated for taeniasis and (neuro) cysticercosis in 1200 randomly selected participants in a community-based study. The performance characteristics (sensitivity and specificity) for neurocysticercosis will be computed by cross-tabulating of POC results with those of the 'neurocysticercosis diagnosis' while a Bayesian approach will be used for cysticercosis and taeniasis to compare the performance of the index test with reference tests (enzyme-linked immuno-electrotransfer blot (EITB), B158/B60 Ag-ELISA, Ab-ELISA, Copro-Ag ELISA, PCR).
Results Preliminary results of 505 POC tests so far conducted show that 0.8% were positive for taeniasis, 9.1% for cysticercosis and, 4.6% were invalid or unclear. Except for Copro-Ag and B158/B60 Ag-ELISA for taeniasis and cysticercosis respectively, reference tests are yet to be conducted.
Conclusion Results will show the diagnostic value of the POC test and its applicability for use at community level in endemic areas. If successful, implementation of the tool will enable early detection of taeniasis and suspected neurocysticercosis cases and lead to improved patient management and treatment outcomes.

OC 8435 MULTI-BIOMARKER TEST STRIP FOR POINT-OF-CARE SCREENING FOR ACTIVE TUBERCULOSIS: A FIVE-COUNTRY MULTI-CENTRE TEST EVALUATION

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Background Inexpensive rapid screening tests that can be used at the point-of-care (POC) are vital to combat tuberculosis. Particularly, less invasive non-sputum-based biomarker tests for all TB forms can help controlling transmission. Availability of such tests would significantly accelerate and streamline diagnostic approaches, improve cost-efficiency and decrease unnecessary costly GeneXpert referrals.
Methods Multi-biomarker test (MBT) devices measuring levels of selections of up to six serum proteins simultaneously on a single lateral flow (LF) strip were produced. The strip contains individual capture lines for a biomarker selection allowing discrimination of TB-patients from other respiratory diseases (ORD). Only biomarkers successfully evaluated with singleplex strips (single biomarker tests) were applied to the MBT device. Quantitative signals are recorded with a low-cost handheld reader compatible with the applied luminescent up-converting particle (UCP) label. Biomarker selection and algorithms used to distinguish potential-TB and ORD are flexible.
Results Results obtained with MBT strips containing multiple test lines correlate well with singleplex LF strips. Using LF tests for 5 selected biomarkers a sensitivity of 94% and specificity of 96% could be achieved with a confirmed South African selection of 20 TB and 31 non-TB samples. Patients were designated TB positive when scoring a value above the cut-off threshold for at least 3 out of 5 biomarkers. Serum samples of potential TB patients collected at five medical research institutes (Ethiopia, Namibia, South Africa, The Gambia, Uganda) were tested locally with MBT strips comprised of CRP, SAA, IP-10, Ferritin, ApoA-I and IL-6 and results analysed to obtain an overall pan-Africa applicable signature.
Conclusion Evaluated POC applicable UCP-LF devices detecting serum biomarker signatures can help to distinguish active TB from other respiratory diseases and as such can prioritise highest-risk patients for further care. Ongoing prospective studies evaluate the MBT strip with fingerstick blood and do not require a laboratory or trained phlebotomist anymore.

OC 8450 ABSENCE OF MINORITY HIV-1 DRUG-RESISTANT VARIANTS FOLLOWING MOTHER-TO-CHILD TRANSMISSION DOES NOT PREDICT VIROLOGIC SUCCESS OF FIRST-LINE ANTIRETROVIRAL THERAPY

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