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

1Joseph Mendy, 2Novel N Chegou, 3Harriet Mayanja-Kizza, 4Kim Stanley, 6Bonnie Thiel, 5Tom Ottenhoff, 6Stefan Kaufmann, 6Henry Boom, 7Gerhard Walzl, 1Jayne Sutherland.

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.

A TRANSLATIONAL PRECLINICAL PLATFORM TO ASSESS THE CHEMPROPHYLAXIS AND CHEMPREVENTION DOSE-RELATIONSHIP OF MALARIA DRUGS: THE CASE STUDY OF M5717

1Sofia Rebelo, 1Daniel Simão, 4Francisca Arez, 1Diana Fontinha, 3Marta Machado, 1Tatiana Martins, 1Christoph Fischli, 2Claude Oeuvray, 1Manuel Carrondo, 1Matthias Rottman, 4Thomas Spangenberg, 1Catarina Brito, 6Beatrice Greco, 6Miguel Prudencio, 1Paula M Alves.

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.