ORAL ABSTRACTS

128. A whole-blood transcriptional signature predicts parasite control and protection from malaria fever during natural *Plasmodium falciparum* infection

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Session: 37. Immune Response to Microbial Infection
Thursday, October 9, 2014: 10:30 AM

Background. Understanding the host response to natural malaria infection can aid in the rational design of a highly effective vaccine. Antibody-mediated immunity that confers non-sterile protection from febrile malaria is acquired gradually through repeated *P. falciparum* blood-stage infections. However, the nature of cellular immune responses at the onset of clinically apparent versus clinically silent blood-stage infections in children remains to be elucidated.

Methods. In a prospective study in Mali, we collected whole-blood RNA, PBMCs and plasma from healthy, uninfected children aged 6-11 years (n = 78) before the 6-month malaria season and from the same children during their first *P. falciparum* infection of the ensuing season. First infections were detected retrospectively through bi-weekly active surveillance by PCR. We used RNA-seq to compare whole-blood transcriptomes of children whose clinically silent infections never progressed to fever (immune, n = 20), children whose infections progressed to fever within 2-14 days (late fever, n = 32) and children who were febrile at the time of infection (early fever, n = 26).

Results. Baseline transcription profiles before the malaria season distinguished children whose future *P. falciparum* infections either progressed to fever or not. Transcription profiles induced by the first-detected *P. falciparum* infection of the season revealed upregulation of innate, pro-inflammatory responses in immune children but not in late fever children, despite both groups having similar levels of parasitemia and the clinical absence of fever initially. In addition, this early upregulation of innate, pro-inflammatory responses was associated with slower subsequent parasite growth rates *in vivo*. In ongoing work, we are correlating transcription profiles with *P. falciparum*-specific antibody profiles before, during and after the first infection using *P. falciparum* protein microarrays.

Conclusion. Molecular and cellular signatures that predict protection from clinical malaria and biologically relevant outcomes are yielding novel insights into the mechanisms underlying naturally acquired immunity to malaria. The resulting datasets may inform the development of interventions that prevent or mitigate malaria disease.

Disclosures. **All authors:** No reported disclosures.

Open Forum Infectious Diseases 2014;1(S1):S1–65

DOI: 10.1093/ofid/ofu051