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Abstract: Acute-phase Trypanosomiasis: Role of parasite surface glycoprotein and DNA in immune response dysregulation

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Trypanosomiasis due to *Trypanosoma brucei* and *Trypanosoma congolense* remains a threat to human and animal lives in tsetse-infested pockets of Sub-Saharan Africa. The fundamental hallmark of the disease is immune dysregulation owing to severe inflammation and overstimulation of antibody responses in the acute phase and immunosuppression in the subsequent chronic stage. Three mouse strains A/J, Balb/c and C57BL/6 varying in genetic susceptibility to Trypanosomiasis have been identified as appropriate animal models.

Gene expression dynamics in the host during the acute phase of *Trypanosoma congolense* infection were investigated by transcriptional profiling of tolerant (C57BL/6), moderately susceptible (Balb/c) and susceptible (A/J) mice. The mice were infected with with *T.congolense* parasites over a 17-day timecourse. Total RNA from liver tissues was hybridized to Affymetrix GeneChip Mouse Genome 430 2.0 oligonucleotide arrays. Pathway analysis of differentially-expressed genes revealed significant perturbation of the toll-like receptor, NF-κβ, MAPK and inflammation pathways with an expression signature akin to the endotoxic shock response elicited by the bacterial endotoxin, lipopolysaccharide (LPS). This observation was suggestive of *T.congolense*-specific pathogen associated molecular patterns (PAMPs) that mimicked bacterial LPS in induction of an inflammatory immune response.

Follow-up studies in an immunologically naïve mouse macrophage culture system using *E.coli* LPS as a positive control showed that *T.congolense* variant surface glycoprotein (VSG) and DNA activated macrophages to a classical phenotype characterized by increased secretion of pro-inflammatory cytokines and chemokines, particularly by macrophages from the tolerant mouse model, C57BL/6.

Using cutting edge functional genomics tools coupled with traditional cell culture system, we have demonstrated that *T.congolense* VSG and DNA are the key mediators of a bacterial LPS-like inflammatory response in the acute phase of Trypanosomiasis. This response may be beneficial to the host for effective parasite clearance but also sets stage for severe pathologies as anaemia and cachexia. These findings harness our knowledge on the immunological mechanisms underlying pathology and host

tolerance to Trypanosomiasis. They also provide insights on management of the acute phase of Trypanosomiasis drawing from known therapeutic interventions against bacterial sepsis in order to influence favorable disease outcomes.