

## PROTOZOAN ASSOCIATE MOLECULAR PATTERNS AND TOLL-LIKE RECEPTORS (TLRS): NEW MICROBIAL ADJUVANTS FOR IMMUNOLOGICAL INTERVENTIONS?

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Infection with protozoan parasites is a major human health issue, causing vast morbidity and mortality that, particularly in developing countries, contributes to political, social and economic instability. There are no vaccines available to prevent these devastating infections, and drug resistance in protozoan parasites is a growing problem (<http://www.who.int/tdr/diseases/default.htm>). Therefore, there is urgent need for the development of new strategies to approach prophylaxis and therapy of patients infected with this class of pathogens. We have taken two main strategies to enhance the efficacy of vaccines against protozoan parasites, i.e. (i) use of recombinant non-replicative/attenuated virus encoding protozoan antigens as vaccine; and (ii) define new TLR agonists that could enhance protective immunity elicited by recombinant parasite antigens. In our studies, we defined that MyD88 (an adaptor molecule for TLRs) is critical for eliciting the production of pro-inflammatory cytokines during infection with protozoan parasites. In the case of *T. cruzi* TLR9 was shown critical for induction of IL-12 and IFN- $\gamma$  and in conjunction with TLR2 mediated resistance to acute infection with this protozoan parasite. Further, during acute episodes of malaria in mice, MyD88 was shown to mediate induction of pro-inflammatory cytokines and development of sepsis related symptoms that are mediated by cytokines such as TNF- $\alpha$  and IFN- $\gamma$ . Consistently, we have identified glycosylphosphatidylinositol (GPI) anchors and CpG containing oligonucleotides (ODN) as major *Protozoan Associated Molecular Patterns* that activate TLR2 and TLR9, respectively. Studies are currently being performed, in order to evaluate these microbial compounds as immunological adjuvants that may be used for the development of therapeutic and/or prophylactic vaccines.