THE MALARIA VACCINE DILEMMA:

NOVEL APPROACHES TO ADENOVIRAL VECTORED MALARIA VACCINES

By

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Despite the discovery more than 30 years ago that artificial or “unnatural” protection against malaria is achievable, a practical protective malaria vaccine has yet to be realized. Recent developments in sub-unit malaria vaccine platforms are bridging the gap between high levels of protection and feasibility. However, the current leading sub-unit vaccine, RTS,S, has only demonstrated the ability to induce protection from malaria infection in up 56% of RTS,S vaccinees. Though encouraging, these results may fall short of protection levels generally considered to be required to achieve eradication of malaria. The uses of viral vectored vaccine platforms have recently been pursued to further improve the efficacy of malaria vaccines. Adenovirus serotype 5 (Ad5) based vaccine platforms have demonstrated potent anti-malaria immune responses, although it is clear more potent Ad5-induced immune responses are required if Ad5-based malaria vaccines are to confer protection. Through explication of Ad interactions with the innate immune system we have uncovered multiple targets that could be exploited to improve the immunogenicity of Ad-based malaria vaccines. We have also attempted to overcome an oft cited difficulty with use of Ad5 in malaria vaccine platforms, namely the high seroprevalence of Ad5. We sought to improve Ad-induced immunogenicity in Ad5 immune patients by the use of an alternative serotype of Ad (Adenovirus serotype 4 (Ad4)) in heterologous prime boost regimens with Ad5. Instead, we uncovered a previously unknown cross-reactivity between these two Ad serotypes that resulted in severely ablated immunogenicity. We then tested the utility of various immunomodulators expressed from Ad

vectors to stimulate innate immune system responses and ultimately improve adaptive responses to Ad-expressed malaria antigens. We found a promising immunomodulator in a SLAM receptor adaptor protein (EAT-2). Co-injection of an Ad5 vaccine expressing EAT-2 with an Ad5 vaccine expressing a malaria antigen (Circumsporozoite protein (CSP)) improved CSP specific CD8+ T cell responses and in vivo cytotoxicity. Currently, we are testing the ability of this immunomodulator to improve protection against a mouse malaria challenge model. Our research has unearthed multiple valuable advancements in Ad-based vaccine technology that can be utilized in malaria and non-malaria vaccine platforms alike.