

Naturally acquired immunity as a tool for therapeutic target discovery in pediatric *falciparum* malaria

P. falciparum malaria is a leading cause of morbidity and mortality in developing countries, infecting hundreds of millions of individuals and killing over 620,000 in sub-Saharan Africa this past year ¹³. Children suffer the greatest morbidity and mortality from malaria- yet this age group has not been targeted at the target identification stage of vaccine development. New antigen candidates and formulations are urgently needed, but strategies to identify novel antigens are limited.

In holoendemic areas, some, but not all, children develop naturally acquired resistance to *P. falciparum* which manifests first as decreased incidence of severe malaria and later as decreased intensity and risk of infection. Using data and samples from longitudinal cohort studies in Tanzania and Kenya, we have developed methods to identify the parasite proteins recognized by antibodies expressed by children who are resistant to malaria. Importantly, we prioritize candidates that are not recognized by antibodies produced by susceptible children.

Using this approach, we have identified several vaccine candidate antigens, including PfSEA-1, PfGARP and PfGBP130. In parasite growth assays, anti-PfGARP antibodies significantly inhibit parasite growth in the absence of immune effector function and vaccination of non-human primates with nanoparticle encapsulated mRNA encoding PfGARP confers significant protection against *P. falciparum* challenge. Based on its surface localization, we have also developed small molecules targeting PfGARP and these compounds demonstrate low nanomolar killing of parasites *in vitro* and are effective in *in vivo* models.

Together, these results highlight the importance of dissecting naturally acquired protective immune responses as tools for therapeutic target discovery in malaria, with potential application to a broader range of infectious pathogens.