Malaria causes high morbidity and mortality and limit economic development worldwide, especially in Sub-Saharan Africa. Development of an efficacious vaccine or antibodies that can prevent and ultimately eradicate malaria is urgently needed. We recently reported the isolation of a highly neutralizing monoclonal antibody (mAb), CIS43, from a subject immunized with an attenuated Plasmodium falciparum (Pf) whole-sporezoite (SPZ) vaccine (Sanaria PfSPZ Vaccine). Passive transfer of CIS43 conferred sterile protection against malaria infection in two separate mouse models of malaria infection (Kisalu, N.K. et al. (2018). "A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite." Nature Medicine, volume 24, pages 408–416). CIS43 prevented proteolytic cleavage of PfCSP on PfSPZ, an essential step for the hepatocyte invasion by the sporozoite. Biophysical analysis of CIS43 binding to PfCSP showed that there are two sequential multivalent binding events within the repeat region of PfCSP. The first binding event occurs on a unique ‘junctional’ epitope located between the N terminus and the central repeat region of PfCSP; the second binding event is multivalent. Crystal structures of the CIS43 antigen-binding fragment in complex with the junctional epitope revealed the molecular interactions of binding and showed the conformational flexibility of the epitope. Although CIS43 confers sterile protection in preventing malaria infection, the mechanisms by which this mAb protects still need to be elucidated. To understand whether the Fc (constant) region mediates the protective effect of CIS43, mutations have been introduced in the Fc domain to abolish binding to the Fc gamma receptor on immune cells. This loss-of-function Fc mutant has been used to investigate the requirement of the Fc domain for the CIS43’s efficacy. To advance CIS43 into clinical testing, the “LS” mutations have been introduced into the Fc domain to prolong the half-life of this mAb. CIS43 and CIS43LS have been administered in macaques to assess the biodistribution and PK pharmacokinetics in macaques. Data generated in the pre-clinical studies have been used to model future clinical trials. CIS43LS is undergoing a Phase 1 clinical trial to assess the safety, efficacy and PK parameters in humans. The demonstration that CIS43 is highly efficacious for malaria prevention has potential application for use in travelers, military personnel and elimination campaigns and identifies a new and conserved site of vulnerability on PfCSP for next-generation rational vaccine design.