Structural delineation of malaria vaccine antigen Pfs230D1 binding to a potent transmission reducing human antibody

Wai Kwan Tang[1]

[1]N/A

tangwai@mail.nih.gov

Blocking the transmission of Plasmodium falciparum from the human host to the mosquito vector is an effective method to prevent malaria transmission. Pfs230 is a protein that presents on the surface of gametes and zygotes and plays an important role in sexual-stage development of the parasite within the mosquito. Here, we present the structure of Pfs230D1, containing part of the pro-domain and the first domain of Pfs230, in complex with a human monoclonal antibody LMIV230-01 isolated from Malian adults vaccinated with Pfs230D1. The structure of Pfs230D1 is comprised of beta strands organized in a five-on-four beta sandwich stabilized by two disulfide bridges and resembles a 6-cys domain fold. The human antibody LMIV230-01 binds with nanomolar affinity to a large conformational epitope of Pfs230D1 through hydrophobic interactions and hydrogen bonds. The antibody potently blocks transmission of parasites to mosquitoes as determined by the standard membrane feeding assay. Analysis of Pfs230D1 sequences reveals that polymorphisms are infrequent in the residues within the antibody epitope. Mutagenesis reveals these polymorphic variants can all bind to LMIV230-01 indicating the human monoclonal antibody is strain transcendent. Our data indicate that immunization with Pfs230D1 produces a potent transmission blocking antibody that engages a large and highly conserved conformational exposed epitope. This study provides a rational basis to improve vaccines and develop therapeutic antibodies for malaria control and elimination.