Structural delineation of human antibody responses against malaria transmission-blocking vaccine antigen Pfs25

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Transmission blocking vaccines have been proposed as a critical strategy for malaria protection and outbreak control. These vaccines are proposed to function by inhibiting parasite development in the *Anopholes* mosquito, thus preventing subsequent human infections. Molecular characterization of humoral responses to Pfs25, a leading candidate antigen for *Plasmodium falciparum* transmission blocking vaccines, has largely been limited to pre-clinical model organisms. Our study presents an in-depth structural, biophysical, and gene usage delineation of human immune responses to Pfs25 vaccination. We report four crystal structures of elicited human antibodies bound to Pfs25, across both previously described, and novel epitopes. We also describe the crystal structure of a cross-species reactive antibody elicited by Pfs25 vaccination, which is able to bind the P25 protein of four species of *Plasmodium,* including *Plasmodium vivax.* Our structural analysis defines at 2.9 Å resolution the most potent transmission-blocking epitope on Pfs25 targeted by a human antibody described to date, and a detailed analysis of its affinity maturation pathway. This work provides specific molecular details for designing improved immunogens and intervention strategies against malaria.