The first human monoclonal antibody against gamete stage of *Plasmodium falciparum*

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Malaria transmission-blocking vaccines (TBVs) induce antibodies against proteins expressed by the parasite in the mosquito midgut and are an innovative approach to reduce parasite transmission and contribute to malaria elimination. Antibodies against Pfs230, a protein on the surface of *Plasmodium falciparum* gametes*,* can block parasite transmission, and Pfs230 vaccine candidates are currently in clinical trials. Antibody repertoire analyses, performed by B cell receptor (BCR) sequencing, have been employed to evaluate responses to other vaccines and to identify sequences of neutralizing antibodies. Here, we used a Pfs230 tetramer to sort Pfs230-specific single B cells (CD3-, CD14-, CD56-, CD19+, CD20+, CD27+, Pfs230+) generated after the fourth dose of Pfs230-EPA/Alhydrogel® in Malian adults. We sequenced both heavy and light antibody chains from these cells and identified paired BCR from nine vaccinees. The resulting sequences indicated expansion of clonotypes using IGHV1-69 (heavy chain) in 8 subjects and using IGKV4-1 (light chain) in 7 subjects. The IGHV1-69 clonotypes were characterized by high mutational rates with at least ten mutations per sequence in CDR1 and CDR2 regions, suggesting proliferation and selection in response to the vaccine. We developed and applied a method to rapidly generate Fab fragments by cell free expression; individual BCR of interest were identified based on repeated frequency on the plate, again suggesting clonal selection. Five paired heavy, and light chains were PCR amplified from selected wells. Using overlap extension PCR, all necessary elements for in vitro transcription and translation and either the CH1 or C-kappa-domain were added to both the 5’ and 3’ ends of the single cell VDJ. After in vitro transcription and translation, four out of five tested Fab fragments demonstrated binding through a colorimetric ELISA assay. To assess complement-dependent function, we generated a human IgG1 antibody in HEK cells using the same VDJ sequence. This new antibody, LMIV230-01, bound to Pfs230D1 recombinant protein in ELISA, to extract of female gametocytes in Western blot and to the surface of both female gametes and parasites in early developmental stages isolated from midguts three hours post-feeding. The antibody reduces parasite burden in the mosquito midgut in more than 85%. These results will be fundamental for design and improvement of TBV strategies to induce potent antibody responses against mosquito stage parasites.