Characterisation of a host receptor for *Plasmodium falciparum*-infected erythrocyte rosette formation

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P. falciparum rosetting, the binding of two or more uninfected erythrocytes to an infected erythrocyte, is a key virulence factor associated with severe malaria. Rosette formation is mediated by *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) expressed on the surface of infected erythrocytes. Several molecules have been proposed as host rosetting receptors (such as Blood Group A antigen and Complement Receptor 1), but none of these can account for rosetting interactions across all parasite strains, suggesting that major host receptors remain unidentified. The Wright^{b} blood group antigen, which is formed by a physical interaction between Band 3 and Glycophorin A, has been identified by the Rowe lab as a potential novel rosetting receptor. Antibody fragments targeting Wright^{b}, disrupt rosettes in several *P. falciparum* strains, but the mechanism of action of this antibody is largely unknown. This study aimed to characterise this key receptor-ligand interaction implicated in rosetting and determine if a rosette-disrupting antibody to Wright^{b} is active against a range of *P. falciparum* strains, suggesting therapeutic potential.

To determine whether the Wright^{b} antigen or Band 3 is a rosetting receptor, we tested the ability of Band 3-transfected K562 cells and naturally occurring Glycophorin null cells to form rosettes with purified *P. falciparum*-infected erythrocytes. Our results showed that Band 3-transfected cells (expressing the Wright^{b} antigen) form rosettes with two parasite strains, whereas wild type K562 cells (expressing Glycophorin A alone) do not. Rosette frequency and rosette size did not vary across the glycophorin genotypes examined, showing that Glycophorin A is not essential for rosetting for the parasite strains tested. Further, we revealed that anti-Wright^{b} antibody fragments show variable activity against a panel of rosetting culture-adapted *P. falciparum* strains and clinical isolates. Thus, our data suggest that Wright^{b} could be a potential anti-rosetting therapeutic target, but that, due to the complexity of rosetting mechanisms, multiple host receptors may need to be targeted to obtain an intervention effective against all P. falciparum strains.