Structure-function relationship of the malaria sporozoite 6Cys proteins

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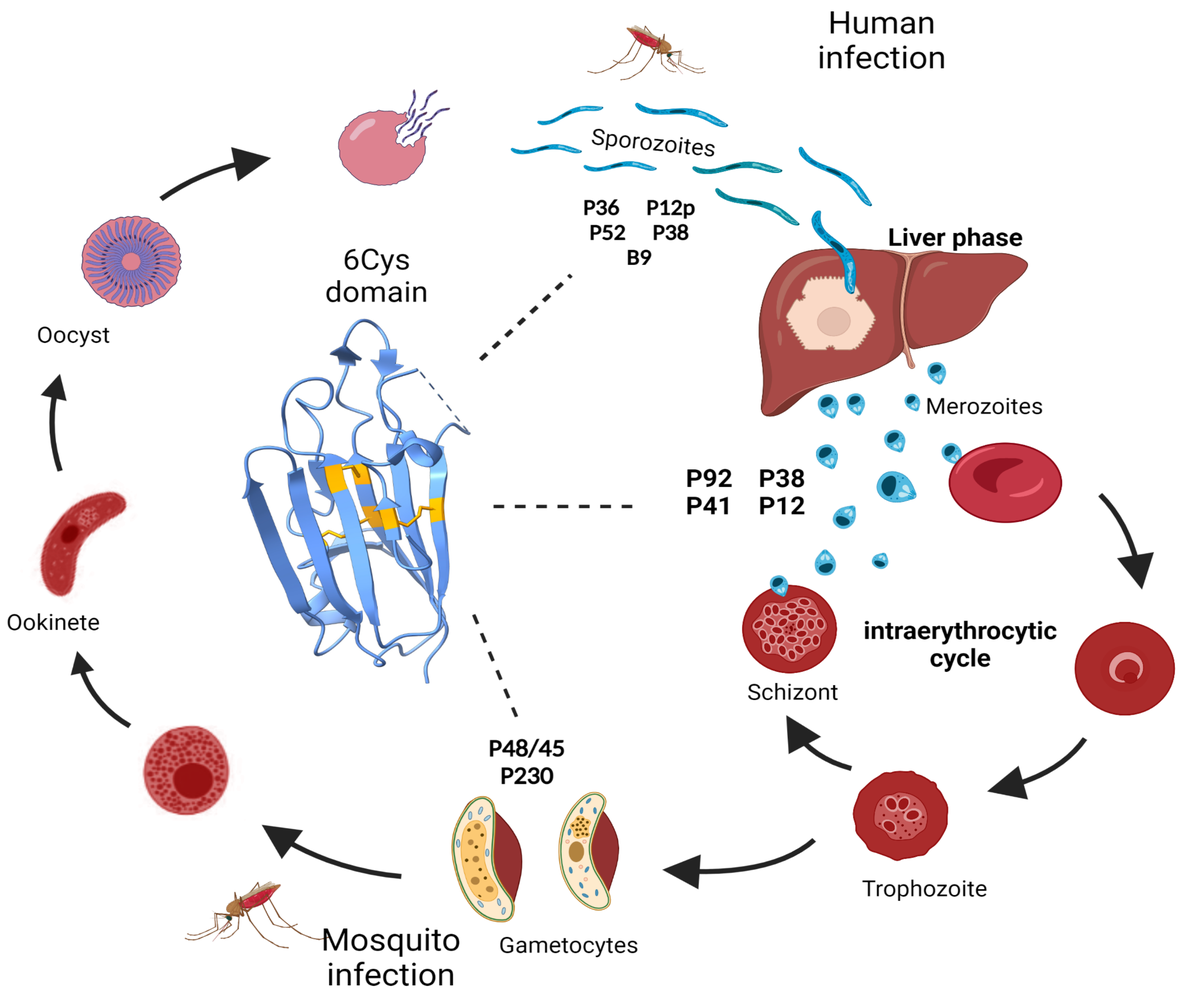
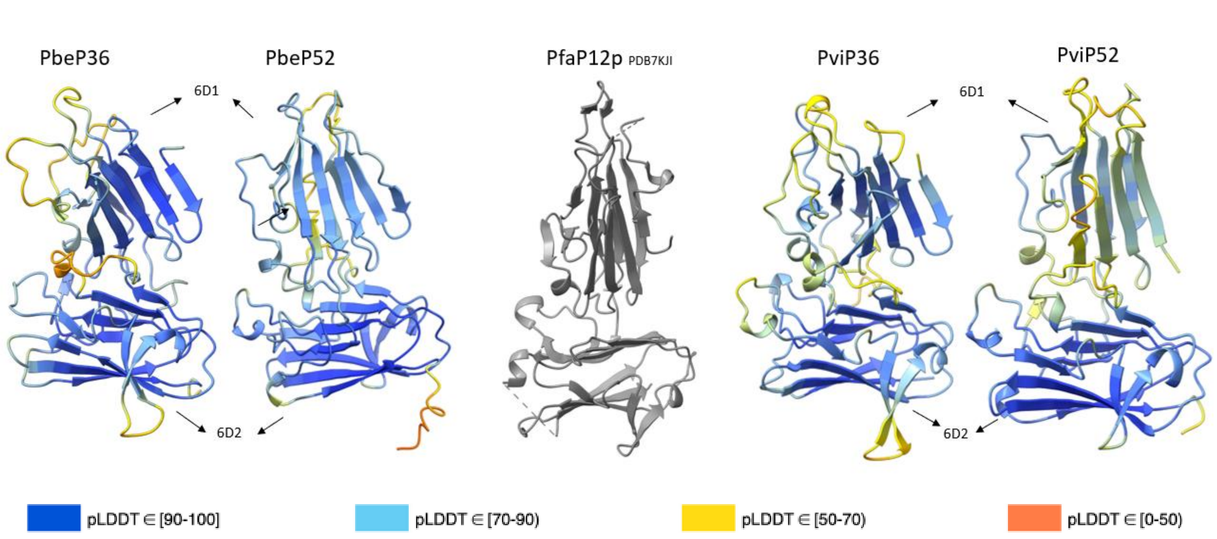
Introduction

Plasmodium, the parasite causing malaria, has an extensive life cycle with different stages and a multitude of stage-specific surface antigens. Among these are the 6Cys proteins P36 and P52, expressed by the malaria sporozoite (SPZ). These proteins are crucial for productive hepatocyte invasion. However, the structural basis for P36-P52 complex formation and the molecular mechanisms underlying host-receptor binding and specificity remain poorly understood. We aim to fill this knowledge gap by establishing the structure-function relationship of the SPZ 6Cys proteins through a research approach including structural biology and functional parasitology.



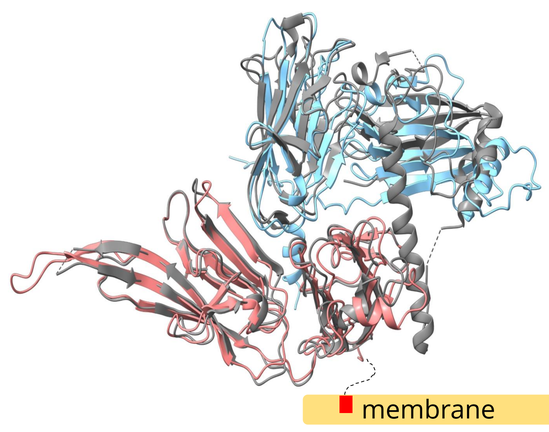
AF can predict the structures of individual SPZ 6Cys proteins with high confidence

- P12p is a SPZ 6Cys protein harboring two 6Cys domains and the crystal structure of *P. falciparum* P12p (PfaP12p) has been determined.
- The structures of *P. berghei* (rodent infective) and *P. vivax* (human infective) were predicted using AlphaFold2 and compared to the PfaP12p crystal structure.
- AlphaFold2 is capable of predicting structures of 6Cys proteins with two 6Cys domains with high confidence and the interdomain organization is consistent with the one observed for the PfaP12p crystal structure,

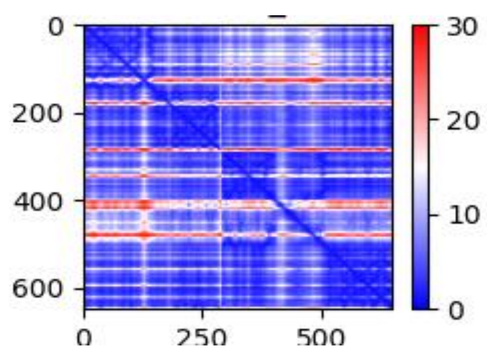


AF - multimer can predict the structures of 6Cys protein heterodimers

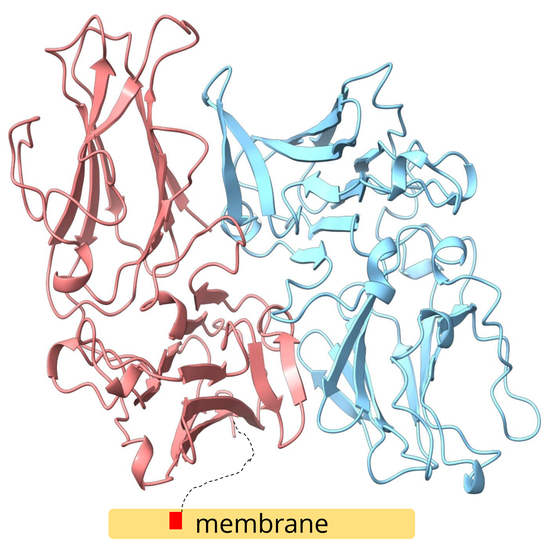
PfaP12-PfaP41



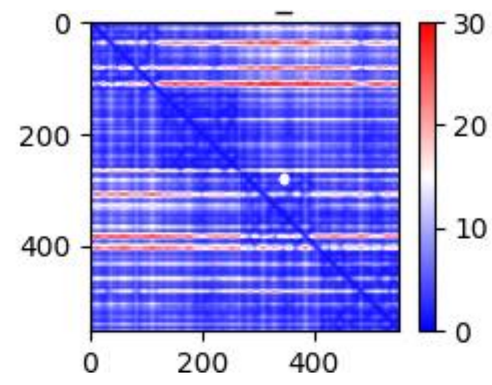
Model structure of the PfaP12-PfaP41 complex with the MX structure coloured grey, P12 in light coral and P52 in light sky blue.



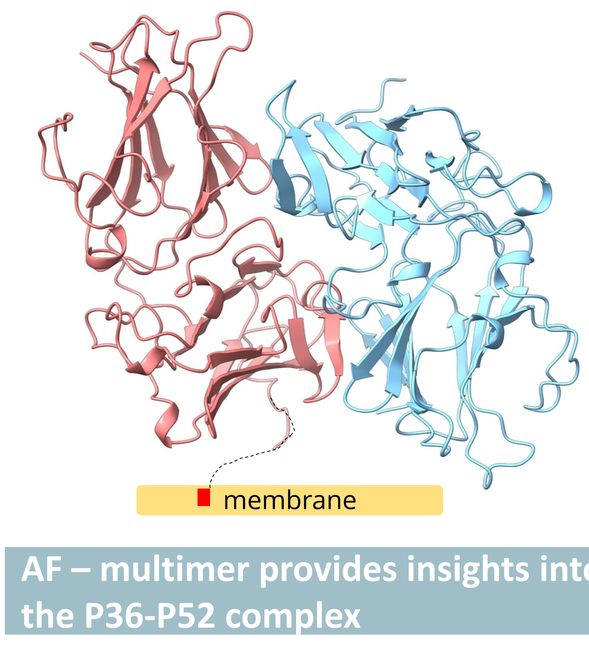
PviP36-PviP52



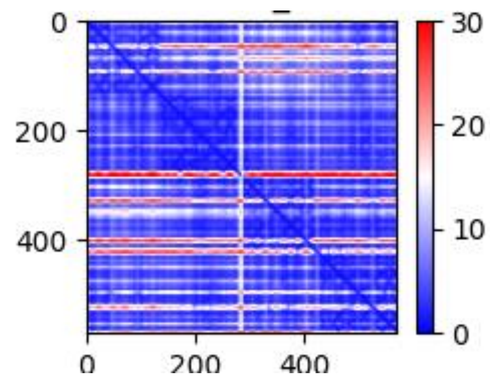
Predicted structure of the PviP36-PviP52 complex with P52 in light coral and P36 in light sky blue.



PbeP36-PviP52

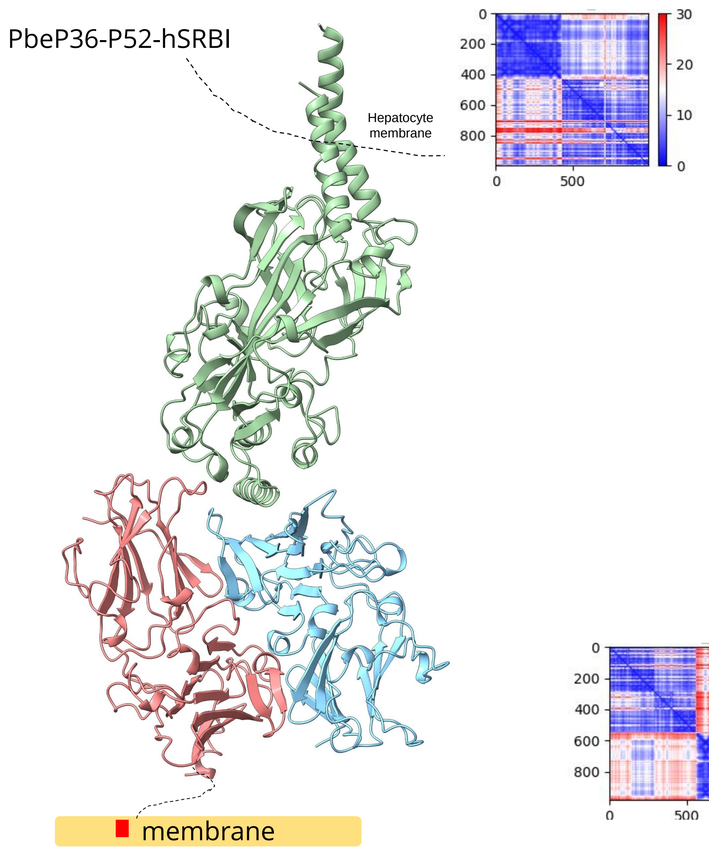


Predicted structure of the PbeP36-PviP52 complex with P52 in light coral and P36 in light sky blue.

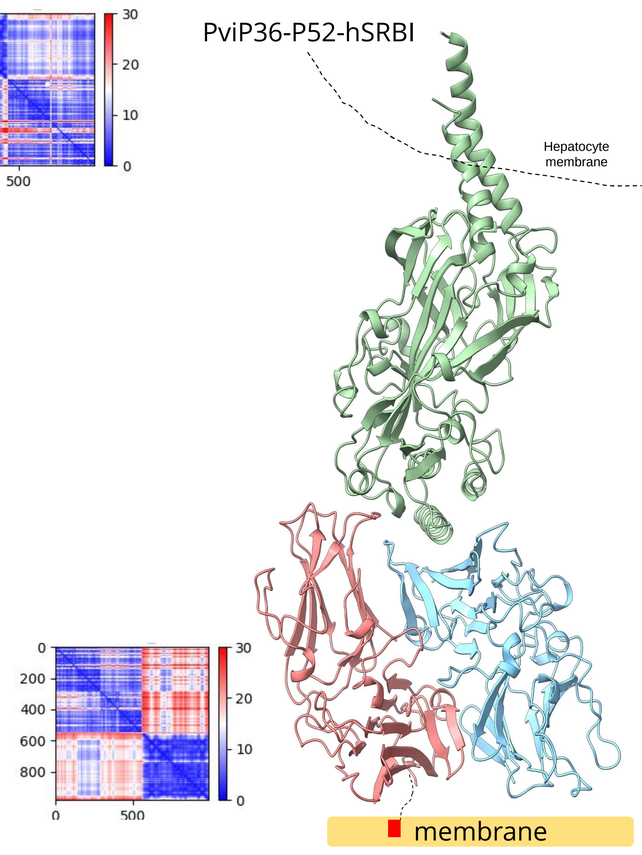


AF – multimer provides insights into host-receptor recognition by the P36-P52 complex

PbeP36-P52-hSRBI



PviP36-P52-hSRBI



Conclusion and perspectives

The information obtained through this thorough sequence and structure analysis will be employed to rationally guide further parasitological experiments in which P36 and P52 will be mutated at specific sides to validate the AlphaFold2 models.

The eventual goal is to further supplement hitherto performed work with **biochemical**, **biophysical**, **parasitological and structural data** such to determine the structure-function relationship of P36, P52 and B9 through a multidisciplinary, integrative approach.

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Biorender was used to create images