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Topic: Computational Simulation of Candidate Ligands Inhibiting Binding of *Var*2csA Encoded *Pf*EMP1Protein to Placental Chondroitin Sulfate A.

INTRODUCTION

Malaria is one of the leading causes of death in tropical, underdeveloped countries throughout the world. Upon infection, the life cycle of the *Plasmodium sp.* begins and ends in the bloodstream where erythrocytes are infected and consequently destroyed, causing symptoms such as anemia, respiratory sequelae, cerebral malaria, metabolic acidosis, and eventually organ failure, leading to death (Achidi et al. 2012). However, before the total destruction of erythrocytes occurs, there seems to be a mode by which the parasitized red blood cells (pRBCs) become sequestered or adhered in particular sites throughout the vascular system (Sein K.K et al., 1993).

Plasmodium falciparum erythrocyte membrane protein 1 (*Pf*EMP1) mediates adhesion of infected erythrocytes (IE) to various host cells on the vascular lining, during the blood stage of malaria infection (Baruch D.I et al., 1995, pp. 77-87., Su X.Z, et al., 1995, pp.89-100., Kraeme S.M & Smith J.D, 2006., Su et al. 1995). *Pf*EMP1is a family of proteins encoded by approximately 60% variable genes (*var* genes) which are situated in subtelomeric regions close to other variant antigen – encoding genes such as the *rif* and *stevor* gene families, while the remaining approximately 40% are found centrally in the chromosomes (Thomas S., Rask et al., 2010 p.1., Matthew K, 2008.). Proteins of the *Pf*EMP1mediate this adhesion through specific binding to multiple endothelial cell (EC) receptors, including domain cassette (DC)36, DC31also known as platelet endothelial cell adhesion molecule 1 (PECAM – 1) or cluster of differenciation 31 (CD31) (Kalinowska A, Losy J (2007), DC13, DC8, intercellular adhesion molecule -1 (ICAM – 1), E-selectin, endothelial protein C receptors, Duffy antigen receptor for chemokines (DARC), and placental chondroitin sulfate A (CSA). Binding to endothelium results in widespread sequestration of IEs and hence their reduced clearance from the blood stream by the spleen (William C. Aird et al., 2011p. 163).

BACKGROUND TO THE STUDY

Plasmodium falciparum evade splenic clearance by sequestering infected red blood cells to host's receptors by means of specific proteins deposited on the surface of infected erythrocytes. These proteins are a family of proteins derived from approximately 60 variable genes which code *Pf*EMP1protein.

Each individual parasite
expresses a single *var* gene at a time, maintaining all other *var*
genes in a transcriptionally silent state. Almost all members of the
var family are classified into one of 3 major groups (A, B, and C)
based on a combination of chromosomal location, transcription
direction, and upstream promoter sequence(William C. Aird, Laurent O. Mosnier,& Rick M. Fairhurst, 2013, p.163).
In this study, attention will be focused on pregnancy malaria which is mediated by *Var*2csA proteins of *Pf*EMP1 binding to placental chonroitin sulfate A.

Identifying and application of safe and potent inhibitors to the *Pf*EMP1 proteins will contribute immensely to winning the war against malaria. The spleen handles the role of clearing the parasite using the host's immunologic machinery.

JUSTIFICATION FOR THE STUDY

Malaria during pregnancy is a major cause of maternal morbidity worldwide and leads to poor birth outcomes. Pregnant women are more prone to complications of malaria infections than non pregnant women. Some of the consequences of malaria in pregnancy include miscarriage, preterm delivery, fetal growth restriction, perinatal death (stillbirth / neonatal death) as well as low birth weight and congenital malaria infection. Others are increased susceptibility to malaria during infancy, impaired response to paediatric vaccine, and infant mortality (Blair W, 2018.)

The increasing menace of resistant *Plasmodium species* has inspired this study. Since the parasite has the ability to mount resistance against all available therapeutic agents, it has become urgent to develop an alternative remedy which does not depend on parasite's physiologic manipulation to deal with the malaria issue.

In many severe cases of malaria, occlusion of vessels seems to further complicate the overall severity of the disease. Cerebral malaria (CM), possibly the most severe type, is synonymous with its specific location of impairment, evidenced by the sequestration of parasitized red blood cells (pRBCs) mainly in the central nervous system (CNS). The consequent occlusion of brain

microvasculature can lead to convulsions and coma, and death is reported often (Beare et al. 2009).

RESEARCH QUESTION

With the parasite being resistant to all the chemotherapeautic agents in the market, should we continue to rely on the use of these agents even though they are rerely effective?

AIM

This study is aimed at using computer to predict and design a non parasitic analog which can competitively inhibit binding of the *var*2csA protein to placental chondroitin sulfate A (CSA).

OBJECTIVES

In this study, there will be :

- structural simulation of the *ver*2csA ligand and the CSA receptor;
- a library of *ver*2csA analogs will be generated; and
- virtual screening of the analogs to isolate the ligand with the best energy conformations in the binding pockets of CSA.

SCOPE OF THE RESEARCH

The following are critical to the study: Ligand binding sites to csa by the *var*2csA protein will be identified., Binding pockets from csa will be selected, Ligand docking will be done using MolSoft ICM software (Molsoft, 2018), or any other suitable software. Candidate ligands may be edited to suit conformation; then, there will be virtual screening of the candidate ligands using MolSoft ICM software or any other suitable software. There will also be extensive use of information from protein data bank (PDB) in the aspect of ligand and receptor structures and other protein information that may be required.

LIMITATION

The limitations to this study include non availability of efficient internet service and erratic power supply.

ASSUMPTIONS

It is assumed that at the end of the research high efficient and safe ligands to CSA binding pockets will be generated.

OUTCOMES

Library of selected suitable ligands will be developed. Alternative binding pockets which may alter the structure of the receptor may be identified. Information on possible structural modification of *Var2csa* may also be obtained. Energies of conformation of the ligands will be obtained from the docking analysis. *Var*2csA protein may have affinity for other molecules, the library of these molecules may also be generated.

METHODS

1. **Structure:** 3D structures of the ligand (*var*2csA protein) and other candidate ligands from the PubChem, https://pubchem.ncbi.nlm.nih.gov/, and protein databases will be extracted;
2. **Docking**: ligand – receptor docking using molsoft ICM software will be carried out;
3. **Screening:** virtual screening of candidate ligand to csa receptor; and
4. virtual screening of other ligands that may have affinity for *var*2csA protein will be done.

ANALYSIS TECHNIQUE

Ligand binding sites to csa by the *var*2csA protein will be identified., Binding pockets from csa will be selected, Ligand docking will be done using MolSoft ICM software (Molsoft, 2018), or any other suitable software. Candidate ligands may be edited to suit conformation; then, there will be virtual screening of the candidate ligands using MolSoft ICM software or any other suitable software. There will also be extensive use of information from protein data bank (PDB) in the aspect of ligand and receptor structures and other protein information that may be required.

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