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Preliminary Investigations into the Binding Interactions between Plasmodial and Host Proteins using Computational Approaches

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Abstract

Post-genomic scientists are left with large deposit of genomic and proteomic information such as peptides and protein residues for analysis. For example, one species of Plasmodium called *falciparum* has been recognized to have more than 4,600 peptides which are assembled into over 700 proteins, and human genome is identified to possess as much as 20,000-25,000 protein-coding genes. These proteins and peptides, acquired as a result of mutations require constant re-appraisal for purposes designing therapeutic interventions and improving on our wellbeing.

Clinical approaches to assessing these vast data are expensive, resource and time consuming, laborious, and arduous. As a result, computational approaches have become necessary as they will streamline, re-strategise and rationalize preliminary clinical assessment procedures that are being employed in the search for drugs and vaccines.

In this study, Plasmodial and their host target proteins are studied in order to find out if there exist correlation between established clinical findings and our computational outcomes. It was disclosed in this study that some computationally obtained results correlated with clinical findings. For example, the adhesive domain of the Circumsporozoite (CSP) and Importin alpha 3 which are clinically verified to interact are found to share the same Consensus Frequency computationally. On the other hand, some preliminary findings could not correlate with our outcomes. This could be as a result of the proteins engaged.

Our findings therefore appears to suggest that binding interactions can be computationally established and also recommend that precise proteins or peptides be engaged in order to obtain the desired computational results.

Keywords: Malaria; Plasmodial Proteins; Digital Signal Processing; Resonant Recognition Model

Introduction

Plasmodial species are the causative organisms for Malaria which are injected into the host blood stream by Anopheles Mosquitoes during a blood meal [1,2]. Malaria has remained an age-long disease which has defied complete cure as a result of repeated re-infection [3,4].

In Plasmodium species only, about 1543 proteins have been identified as being employed by the parasite for biological functionalities that include entry into the host, transmigration (gliding), infection, metabolism, immunogenicity and others [5]. Proteomic analysis of one Plasmodium specie, namely *falciparum* revealed 728 proteins which constitute 4611 peptides for these functionalities [5]. In human also, genomic analysis has revealed that about 20,000-250,000 protein-coding genes [6].

Living organisms and viruses change the amino acids compositions in their sequence (mutate) in an effort to resist drugs or improve biological functionalities. Therefore, they generate newer proteins and peptides. Consequently, the proteomic database has significantly increased. These proteins desired to be constantly investigated in the clinical laboratories for their engagement in the designing and developing therapeutic interventions. Clinical experimentation of all these huge datasets of proteins and peptides will burden the already over-stressed laborious, manual, clinical procedures. This therefore calls for the application of computational approaches to investigating these proteins and peptides. These computational assessments that will follow clinical verification is expected to help direct, streamline and complement clinical investigations and reduce cost.

The Plasmodial proteins already identified include Circumsporozoite Proteins (CSP) [7,8] Thrombospondin-Related Adhesive Protein (TRAP) [9], Merozoite surface Proteins (MSPs) [10], Apical Merozoite antigens (AMAs) [11], Sporozoite Threonine and Asparagine Rich Protein (STARP) [12], Sporozoite And Liver Stage Asparagine- Rich Protein (SLARP) [13,14], Secreted Ookinete Adhesive Protein (SOAP) [15], Knob-Associated Histidine-Rich Protein (KAHRP) [16], Liver Stage Antigens (LSAs) [17], and Sporozoite and Liver Stage Antigen (SALSA) [18]. Proteins which are utilized for host cell transmigration include Sporozoite microneme Protein Essential for Cell Traversal 1and 2 (SPECT 1 and SPECT 2) [19], and Cell Traversal protein for Ookinetes and Sporozoites (CelTOS) [20], Perforin-Like Proteins (PLPs) [21], Membrane Attack Ookinete Proteins (MAOPs) [15].

In this study, interactions between Plasmodial and the host proteins which have clinically been determined are analysed using computational methods. The aim is to find out if the computationally derived results correlate with preliminary clinical findings. This will help re-direct the expensive, resource consuming clinical experimentations to computational assessments. Resonant Recognition Model is used in this investigations. Consensus Frequencies (CF) of the Plasmodial and

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host protein residues are obtained and analysed. Proteins that share the same CF are known to bio-recognise and interact. Our results revealed that some computationally derived results correlated with preliminary clinically outcomes. It is also observed that some of our outcomes did not correlate with initial clinical studies. This may be as a result of the protein residues engaged. The methodologies engaged, the results obtained and inferences drawn as well as conclusions made are presented in the subsequent sections.

Methodology

Materials

In order to identify the materials in use for this investigations, preliminary clinical interactions that exist between proteins and peptides from Plasmodia and the plasmodial host target proteins are first briefly discussed. The amino acids sequences of these proteins and peptides are then retrieved from the UNIPROT [22] or literatures and further analysed using Resonant Recognition Model. The interactions are as follows

Circumsporozoite protein (CSP) and importin alpa-3: The principal Plasmodial sporozoite surface protein employed for attachment and other interactions with host proteins has been identified as Circumsporozoite Protein (CSP) [23,24]. The CSP has been acknowledged to binds effectively to Importin alpa-3, a binding interaction is found to be abrogated when the 9 amino acids residues that constitute the Nuclear Localization Signal (NLS) is removed [24]. The Plasmodium Export Element (PEXEL/VTS) motif is used to introduce the circumsporozoite (CS) protein into the hepatocyte cytoplasm [24,25] while the PEXEL is found to be sliced by Plasmepsin V [26].

Region 11 of CSP and laminin gamma-1: Amino acids domain analogous to the 18 protein residues (EWSPCSVTCGNGIQVRIK) which constitute has been identified and referred to as CSP Region 11 (CSP R11) [23,27]. This domain has been found to bind to Laminin gamma-1 [24,28]. This interaction is co-ordinated strongly by the peptide called P25 and weakly by P28 [28]. Laminin is the principal component of the basal lamina surrounding the midgut of the malaria plamodia [28].

PfEMP1 and host cytoadherence receptors: PfEMP1 is a Plasmodial protein expressed on the surface of the infected RBC as a 'knob-like' protrusion that affords binding to the Cytoadherence receptors [29]. It consist of several binding peptides and elicit numerous physiological features [30-33]. Receptors that bind to the PfEMP1 include Platet/Endothelial Adhesion Molecule (IPECAM-1) also known as CD51, Vascular Cell Adhesion Molecule 1 (VCAM-1), Thrombospondin, E-Selectin and P-Selectin [34-35]. The PfEMP1 is identified to also bind to the Knob-Associated Histidine-Rich Protein (KAHRP) [36]. Also, CD36 is noted to be involved in the sequestration of parasitized RBC [37], platet-mediated clustering of the parasitzed RBC which is linked to cerebral malaria development [38]. This activity is co-ordinated by interaction between PfEMP1and the CD36 with [31-33,37,39,40]. This interaction is mediated by CIDR1 of the PfEMP1 [41].

DBPR11 of the *Plasmodium vivax* and *knowlesi* and DARC: In the P. *vivax*, ligand-receptor interaction between the plasmodial protein called Duffy Binding Protein (DBP) found on the merozoites and the host receptor site in the Red Blood Cell (Erythrocyte) called Duffy Antigen Receptor Chemokines (DARC) is recognized to bring about plasmodial invasion of the Erythrocytes and Liver [42,43]. DARC in *Plasmodium vivax* and *Plasmodium knowlesi* shares same physiological characteristics as CCR5 in HIV. It has been recognized that as individuals who inhabit HIV but lack chemokine co-receptor called CCR5 are refractory HIV progression to AIDS. In the same manner, persons who are deficient in DARC are recognized to be unresponsive to *P. vivax* infestation [44,45]. This interaction has been found to occur between the conserved cysteine-rich Duffy Binding Protein Region 11 (DBPR11) which has about 330 amino acids residues and the DARC [44,45].

Duffy Binding-like families of the *Plasmodium falciparum*: Plasmodial invasion by the *Plasmodium falciparum* requires association of numerous receptor-lignand interactions [46], involving the Duffy Binding-like families (DBL) and the Reticulocyte Binding Homologues (RH) [42]. The DBL family consists of 5 *Plasmodium falciparum* homologues of the *Plasmodium vivax* (Pv) called PvDBP including EBA- 175, EBA-140 (BAEBL), EBA-181 (JESEBL), EBL-1 and EBA-160 (PEBL) [47]. Similarly, the Reticulocyte Binding Homogues (PfRH) family encompasses the six homologues of the *Plasmodium vivax* (Pv) Reticulocyte Binding Proteins (RBP) which include PfRH1, PfRH2a, PfRH2b, PfRH3, PfRH4, PfRH5 [42,47,48]. Interaction between the Plasmodial Erythrocyte Binding Antigen (EBAs) and Reticulocyte Binding Homogues (RH) with the host RBC has been identified as Salic Acid independent which is facilitated by the Complement Receptor Type 1 [49].

Apical merozoite antigens (AMAs) and RON proteins: Apical membrane antigen 1 (AMA-1) has been identified as a well protected apical organelle protein engaged during receptor-ligand interaction that results in the merozoite invasion of the Red Blood Cells before DBL-EBPs bio-recognition and binding interaction by their receptors [50]. Like other Apicomplexan parasites, Plasmodium species engage a group of proteins referred to as Rhoptries Neck (RON proteins) to interact with micronemal protein Apial Membrane Antigen-1 (AMA-1). This interaction results in a formation of a complex called Moving Junction (MJ) [51-55]. In *Plasmodium falciparum,* three RONs namely PfRON2, PfRON4 and PfRON5 are found to interact with the *Plasmodium falciparum* AMA-1 (PfAMA-1) to form Moving Junction. The Moving Junction assist merozoite in attacking the Erythrocytes [54].

Merozoite Surface Antigen 3 (MSA-3) and Acidic Basic Repeat Antigen (ABRA): Plasmodial merozoite antigens include Merozoite Surface Antigens 1-5. MSA-3 of the *Plasmodium falciparum* is a well-protected protein residues identified to be involved in the movement of proteins onto the merozoite surface via interaction with the Acidic Basic Repeat Antigen (ABRA), also referred to as Merozoite Surface Protein 9 (MSP 9) [10].

Sporozoite Surface Protein (SSP2) and CD8 T Lymphocytes: SSP2 has been defined as a TRAP homologue from *P.yoelli* [34,42,55]. SSP2 is another surface protein found in the oocyst sporozoite of the Plasmodium which has a region with about 200 amino acids length called A-domain and analogue of CS region 11 [67]. Sporozoite Surface Protein 2 (SSP2) is reported to target CD8 T Lymphocytes [3]. This activity has been reported to have led to the elimination of *Plasmodium yoelii* from the hepatocytes of the mice, offering SSP2 opportunity for incorporation into the clinical Human Malaria Vaccine [58]. This clinical interaction between TRAP and CD8 as well as with CD4 has been confirmed by field studies carried out in Gambia [58].

Plasmodial transmigration proteins: Plasmodial transmigration into the host cells involves Cell Entry and Trasverval processes. Numerous proteins have been implicated in both Plasmodial cell entry and trasverval. They include Sporozoite microneme Protein Essential for cell Trasversal (SPECT) [19,59], Perforin-like Protein 1 (PLP1) also known as SPECT 2 which is found to embody a perforin-like domain found in mammals called Membrane Attack Complex (MAC) [19], Cell Trasversal protein for Ookinetes, Sporozoites (Celtos) [20], Membrane Attack Ookinete Protein (MAOP) [15], Phospholipases (PL) like PLP2, PLP3, PLP4 and PLP5 [21] and the TRAP-Like Protein (TLP) [60,61]. It has been reported that SPECT-2 shares sequence similarity with both Human Perforin and Complement Receptor Type 9 [19]. This similarity is found to be higher that obtained in the Human Perforin and Complement Receptor Type 9. Both Human Perforin and Complement Receptor Type 9 are pore-forming proteins. Perforin and Complement Receptor Type 9 are spore-forming proteins of the Plasmodial hosts involved in the disruption of the cell membrane of the viruses and micro-organisms [62], UNIPROT [22].

The Plasmodial Host Receptors and Intermediates: These constitute the host proteins that serve as receptors or intermediates. Mechanism of immune protection offered by xx was reported to have involved CD8 T-cells, IFN-c, IL-12, iNOS and natural killer (NK) as in the case of BALB/c mice or CD4 Tcells as in the case of C57BL/6 mice [14]. Investigations confirming the functions of CD8 cells, CD4 T-cells, gamma delta (gd) T-cells, NK , NKT-cells, Stellate (Ito) cells as well as immune mediators which include Interleutin 1, Interleutin-6, and Interleutin-12, Interferon-gamma (IFN-g), O_2, NO radicals and NO synthase in the Plasmodial invasion have been reported [63]. Sporozoite entry into the PV is found to have been mediated by least two hepatocyte surface molecules of the host, the tetraspanin CD81 and Scavenger receptor B1 (SRB1) [14,64]. It has also been observed that the sporozoite mutant that lack the migratory capacity are eaten up by CD11b [14]. Some of the parasites that successfully traverse into the bloodstream are also sucked into the lymphatic nodes and phagocytized by the CD11c [14]. While transmigrating some are reported to have been lost in the Kupffer cells (KCs) by phagocytosis [14].

Inhibitory activities of melanoma growth stimulatory activity (MGSA) and IL-8: Chemokines which are found to interact with the DARC are also discovered to have inhibitory activity on the adhesion of the PvDBP to the EBP of the human erythrocytes. This inhibitory Activity arises from competitive antagonism which is achieved through 35 amino acids residues. They are therefore regarded as blockers of Red Blood Cell plasmodial invasion [65] in the Duffy-positive phenotypes [44,66]. These Chemokines include Interleutin-8 (IL-8) and Melanoma growth stimulatory activity (MGSA) [65].

Liver stage antigen-3 (LSA-3) and inferon gamma: Clinical experiments have demonstrated that Inferon-gamma inhibit Liver Schizogony of the *Plasmodium falciparun* [63]. Vaccine preparation using human *P.falciparun* Liver Stage Antigen 3 (LSA-3) has demonstrated that Interferon-gamma (IFN-g) provided the protection experienced in the pre-eryhrocyctic stage, suggesting interaction between the LSA-3 peptide and the paratope that produced Interferon-gamma (IFN-g) [63]. Result shows AMA-1 0.4078 and Inferon gamma, 0.406.

Lipoprotein receptor-related protein (LRP) and CSP: Apart from binding to the HSPGs, CSP are identified to adhere to low-density Lipoprotein Receptor-Related Protein (LRP) [7,14].

Human leukocyte antigen (HLA)-DR types 2: A protected sequence from the CSP is identified to bind with many Human Leukocyte Antigen (HLA)-DR Type 2 including those with Uniprot Protein ID Q9GIY3, Q5Y7A7, P01903, P20039, P04229, P79483, Q30154, Q29974, Q95IE3, P01920, P13760, P13761, Q9TQE0, Q30134, P04440, P13762, P01911, P01912 [58].

Experimental procedures

Resonant recognition model (RRM): Resonant Recognition Model (RRM) is used in this experiment. The procedure is briefly described here. The RRM procedure involves three main steps: (1) the translation of the alphabetic code of amino acids sequences into numerical values using the Electron Ion Interaction Potential (EIIP) amino acids parameter. Thereafter, the numerical sequences are upsampled or padded using zero values so as to bring them to same window length. These two procedures result in the transformation of the amino acids sequences into signals of equal length. (2) They are then decomposed using the Discrete Fourier transform (DFT) to reveal the biological functionalities as Spectral Characteristics. The x-axis (Frequency) defines the position of the bio-recognition and binding interaction. The y-axis (Amplitude) symbolises the contributions of the sequences in terms of their binding interaction. (3) Cross-spectral (CS) analysis which is the point-wise multiplication of the DFT-decomposed signals are then executed to disclose the common information contained in these protein residues [67]. This common biological activity can be symbolized by Consensus Frequency (CF) which is produced by the region of the sequence that contributes to the functionality under investigation.

Above procedure is employed in the analysis of xx Plamodial and host proteins in order to obtain the position of common biological activity called Consensus Frequency (CF). Proteins that share common CF have been recognised to bio-recogise and bioattach [68]. The CF all the Plamodial proteins are studied against those of the host. The outcome of our experiment on the proteins that share common CF, which appear to suggest that they interact are correlated with preliminary clinical findings.

Results and Discussions

In presenting the result of this investigation, the Consensus Frequencies (CFs) of all the Plasmodial and host proteins are first derived as shown in Tables 1 and 2. Some Plasmodial proteins share similar CF. They include RESA (0.250), PfRH4 (0.276), AMA- 1 (0.276), EBA-165 (0.214), MSA-4 (0.246), PfRON4 (0.288). These are similar to those obtained in the host proteins Interleukin (0.258), Complement Receptor 8 (0.258), CD11b (0.249), Importin alpha-1 (0.260), DARC (0.270) and Lamin gamma-1 (0.284). Other group of Plasmodial proteins with similar CF are CSPR11 (0.368), MSA-1 (0.327) and SPECT- 2 (0.347) possess similar CF with the host proteins including Importin alpha-3, CD36 (0.346) and Follistain (0.350). Also, CD8 alpha (0.290), CXCR1 (0.300), Human Leukocyte Antigen DR types 2 (0.306) and CCR4 (0.312) are host proteins that have similar CF with the Plasmodial proteins like SPECT Trasversal (0.290).

Another group of Plasmodial proteins which have CF that bear resemblance are EBA- 175 (0.180), EBA-140 (0.192), and STARP (0.199). Host proteins which possess CF similar to the above-

S/N	Protein	Position	N	CF	S/N	Protein	Position	N	CF
1	AMA1	165	598	0.276	23	PfEMP1	40	178	0.225
2	Papain	39	630	0.062	24	PfRH2	49	533	0.092
3	MSA-4	67	272	0.246	25	PfRH4	458	1716	0.267
4	CelTOS	78	196	0.398	26	PfRON2	332	2189	0.152
5	CSP	19	53	0.359	27	PfRON5	333	1156	0.288
6	CSP R 11	7	19	0.368	28	PPLP5	256	676	0.3787
7	DARC	57	336	0.170	29	RESA	251	1008	0.25
8	DBP11	52	392	0.133	30	SOAP	2	202	0.0099
9	EBA-140	118	616	0.192	31	SPATR	37	274	0.135
10	EBA-165	141	659	0.214	32	STARP	120	604	0.199
11	EBA-175	104	579	0.180	33	Vivapain 1	92	630	0.146
12	EBA-181	65	673	0.097	34	Vivapain 2	184	487	0.378
13	Facipain	38	595	0.077	35	Vivapain 3	87	495	0.176
14	MSA-3	1	354	0.003	36	Vivapain 4	144	484	0.298
15	HDP(P.vinkei)	39	205	0.190	37	SPECT (MACPF)	382	810	0.472
16	KAHRP	46	623	0.074	38	SPECT (Trasversal)	70	241	0.290
17	LSA	203	493	0.412	39	SPECT microneme	27, 85	245	0.11, 0.347
18	MJ P.f	92	1201	0.077	40	Plasmepsin V	167	597	0.280
19	MOAP	364	815	0.4466	41	HIV gp120	18	508	0.0354
20	MSA-1	567	1733	0.3272	42	HIV gp160	154	836	0.185
21	MSA-2	5	320	0.0156					
22	MSA-5	33	387	0.085					

Table 1: Consensus Frequencies and Spectral Features of the Plasmodial Proteins.

S/N	Protein	Position	N	CF	S/N	Protein	Position	N	CF
1	CXCR1	105	351	0.300	17	Interferon	64	170	0.375
2	CCR2	32	360	0.089	18	Sequestrin	245	652	0.376
3	LRP3	150	734	0.204	19	IL-8	23	79	0.291
4	CCR4	112	359	0.312	20	HLA	81	266	0.306
5	CCR5	149	352	0.424	21	CX3CR1	16	358	0.045
6	CCR8	4	356	0.0112	22	Eselectin	103	589	0.175
7	C R1	164	1998	0.082	23	Follistatin	110	315	0.350
8	C R8 gamma	47	182	0.258	24	ICAM1	6, 32, 79, 158	518	0.152
9	C R 9	109	574	0.178	35	Importin a-1	141	542	0.260
10	CD4	18	482	0.034	26	Importin a-3	173	521	0.332
11	CD8 Beta	75, 4	192	0.397, 0.026	27	Spectrin A	116	2477	0.0468
12	CD8 Alpha	64	220	0.291	28	Spectrin B	985	2564	0.384
13	CD11b	287	1153	0.249	29	CXCR2	32	360	0.089
14	CD11c	217	1161	0.187	30	Pselectin	141	789	0.179
15	CD36	163	471	0.346	31	PECAM	124	713	0.174
16	CXCR1	105	351	0.300	32	Perforin	104, 78	555	0.187, 0.141

Table 2: Consensus Frequencies and Spectral Features of Host Proteins.

mentioned are PECAM (0.174), Peselectin (0.179), Eselectin (0.175), DARC (0.170), Perforin (0.187), CD11c (0.187), and LRP12 (0.184).

A survey of the clinically experimented binding characteristics of these proteins reveals that some of them which are reported to bind to each other share similar CF. For example, Complement component such as C6, C7, C8 and C9 which are involved in the perforation of target cells, as well as the pore-forming lytic proteins from the lymphocytes called Perforin, are known to contain similar sequences

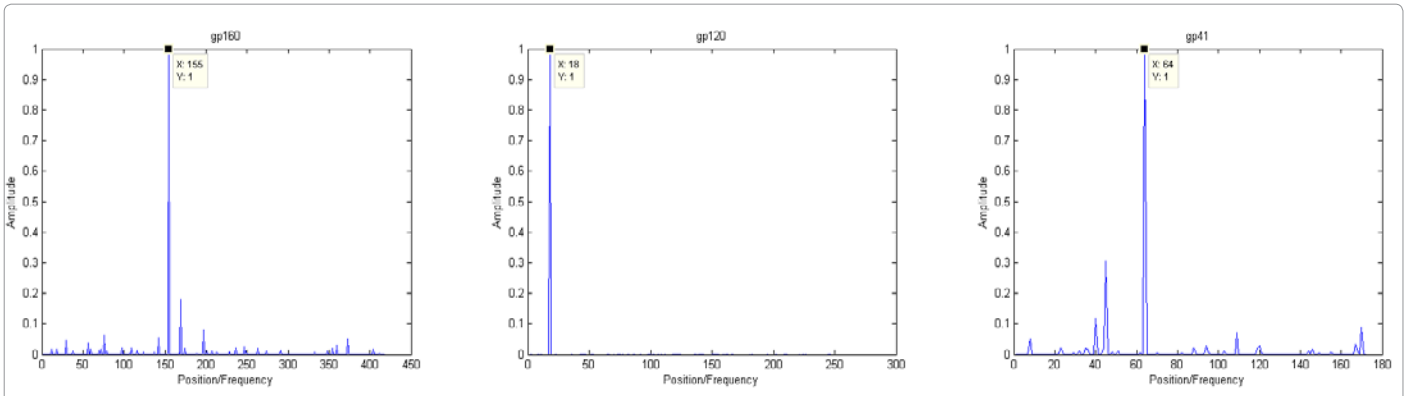

Figure 1: The results of the CS analyses of the gp160 showing CF at Position 155 (CF=0.185), the gp120 at Position 18 (CF=0.0354) and the gp41 at Position 64 (CF=0.186).

[69]. Our findings demonstrate that the CF of the Perforin (0.187) and that of the Compliment Component Receptor 9 (0.178) as shown in Figure 3 are similar. These proteins are known to share common biological functionality referred to as perforation of target cells and are known to target common proteins [21]. They therefore demonstrate affinity and binding interaction for similar proteins. AMA-1 is known to interact with RON complexes such as xx in both plasmodium and gondii during tacyzoite and merozoite invasion has been recognised [46,70]. Our findings revealed the CF of the AMA-1 (0.276) and that of

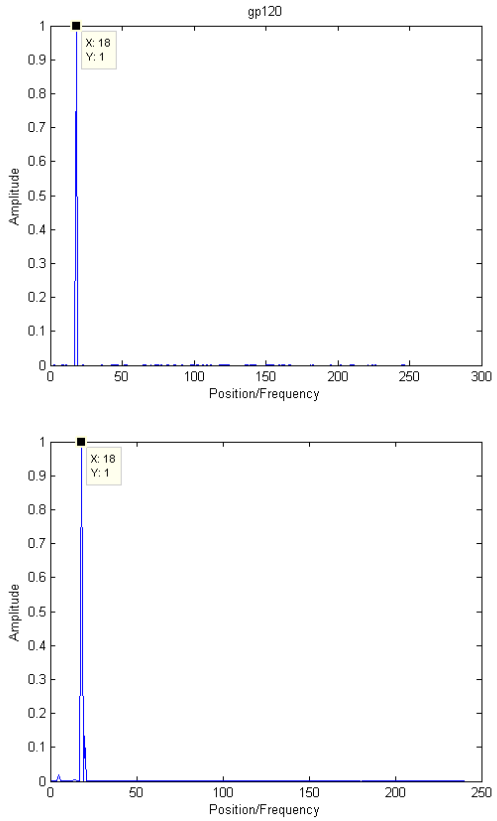

Figure 2: The results of the CS analyses of the HIV gp120 showing CF at Position 18 or (CF=0.0354) and Host CD4 showing CF at Position 18 or (CF=0.0373).

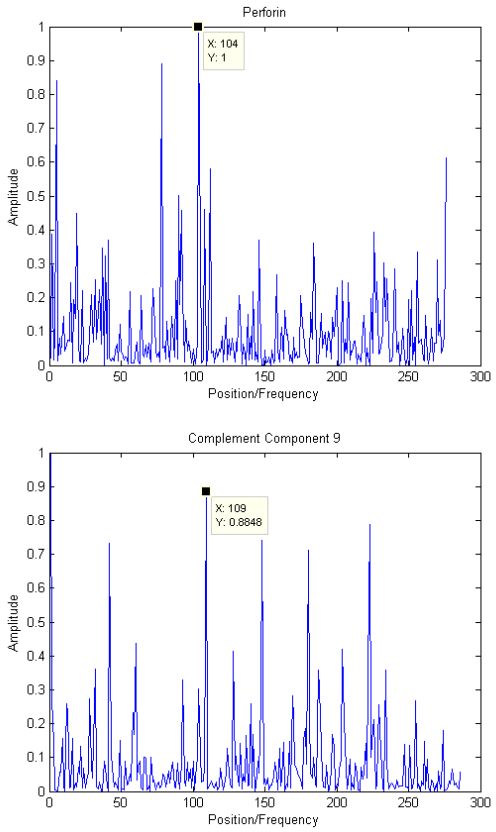

Figure 3: The results of the CS analyses of the Perforin showing Amplitude of 1.0 each at the CF of Position 104 (CF=0.187) and Complement Component Receptor 9 at Position 109 (CF=0.178).

PfRON5 (0.288) are observed in this experiment to be similar (Figure 5). AMA-1 is also known to interact with Interleukin 9 [71] and in this study they both share similar CF as AMA-1 has CF at 0.276 while the CF of Interleukin is at 0.258 (Figure 4). It has been identified that the conserved region (EWSQCNVTCGSGIRVRKRK) of the TSP found in the CSP Region 11 (CSPR11) is known to be responsible for the interaction with the Cluster of Differentiation36 (CD36) [72]. In this investigation also, it is shown that the CF of CSPR11 is 0.368 and that of CD36 is 0.346 (Figure 7).

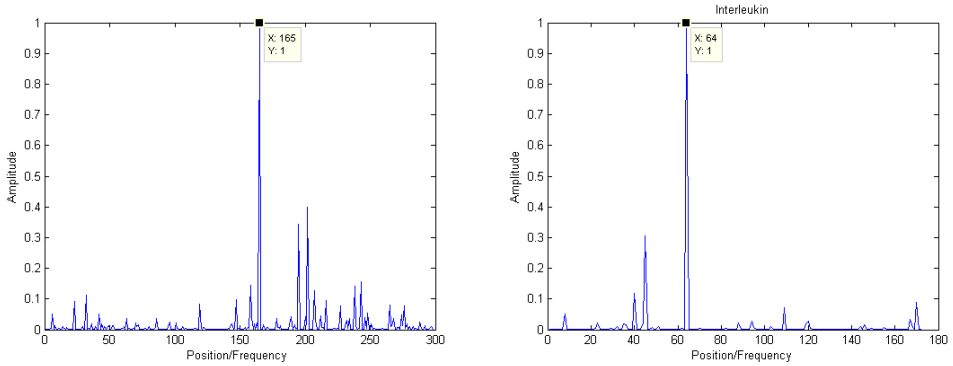

Figure 4: The results of the CS analyses of the AMA-1 showing CF at Position 165 (CF=0.276) and Interleukin showing CF at Position 64 (CF=0.258.

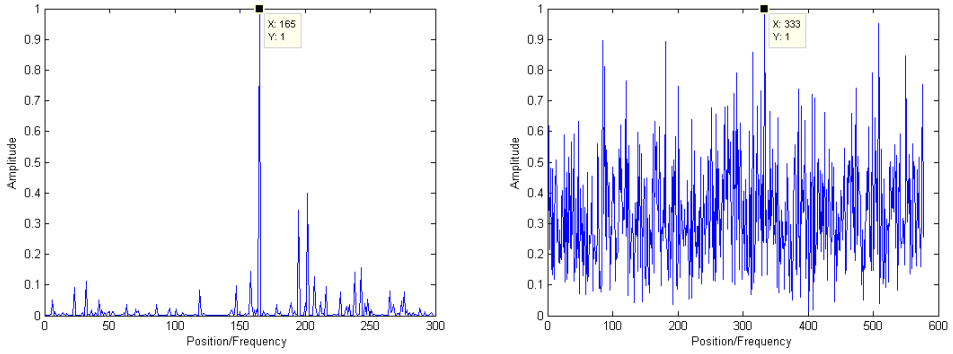

Figure 5: The results of the CS analyses of the AMA-1 showing Amplitude of 1.0 each at the CF of Position 165 (CF=276) and PfRON5 at Position 333 (CF=0.288)

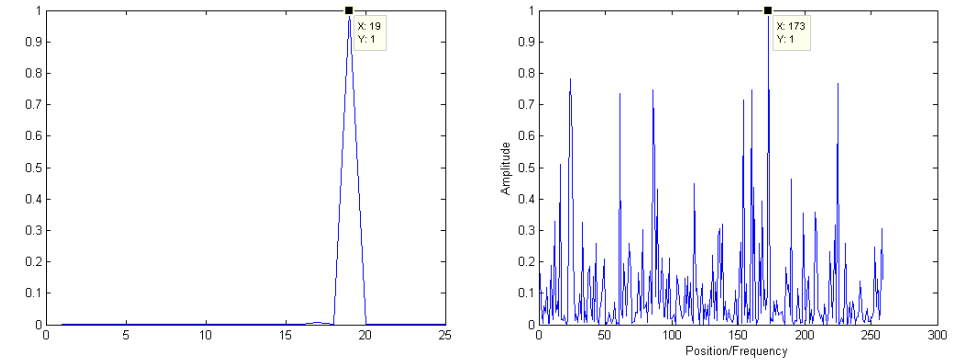

Figure 6: The results of the CS analyses of the CSP Region 11 showing Amplitude of 1.0 at the CF of Position 19 (CF=0.359) and Importin alpha-3 at Position 173 (CF=0.332).

Some proteins, which have clinically been identified to interact with one another are also found in this study to display different CFs. For example, the interaction between the Ring-infested Erythrocyte Surface Antigen (RESA) and Spectrin has been recognized [73,74] yet, the CF RESA and that of the neither Spectrin-Alpha nor Spectrum-Beta (Figure 8) are observed to at different positions. This may be as a result of the protein residues engaged. Engagement of the appropriate protein residues that is involved in the clinical experiment is vital in obtaining the right result. For example, it is known [75] and demonstrated in this study 2 that the HIV gp120 and host CD4 interact with each other as they share same CF. However, the HIV Envelope protein (gp160) which embodies the gp120 has a different CF (0.185) as shown in Figure 1. HIV Envelope Protein consists of the Surface Protein (gp120) and the Transmembrane protein gp41. The CS analysis of the HIV gp120 demonstrates a CF at 0.0354 (position 18) while that of the gp41 is 0.186 or position 64 (Figure 1). While the gp120 which interacts with the CD4 of the host shares common CF, the gp160 which is the parent protein has different CF. This applies to the proteins studied here. This appears to demonstrates that clinically, specificity in proteinprotein interaction which also need to be considered in the computational

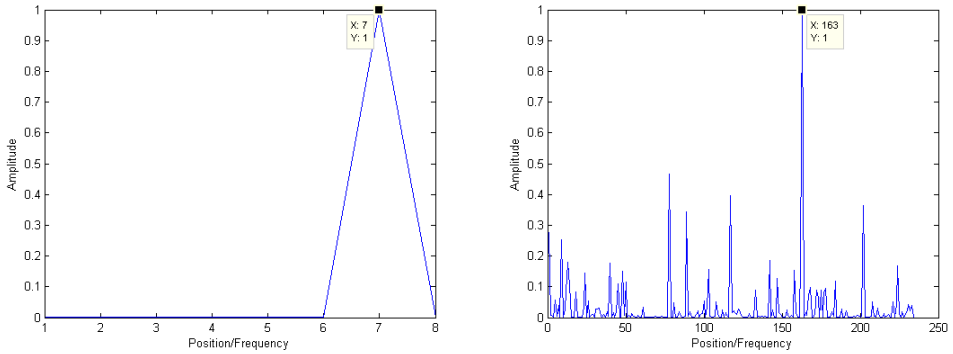

Figure 7: The results of the CS analyses of the CSP Region 11 (conserved region) showing Amplitude of 1.0 at the CF of Position 7 (CF=0.368) and CD36 at Position (CF=0.346).

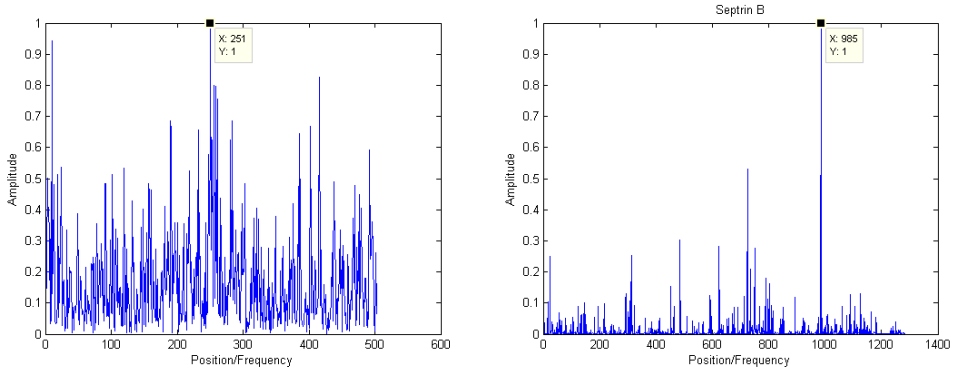

Figure 8: The results of the CS analyses of the Ring-infested Erythrocyte Surface Antigen (RESA) showing CF at Position (CF=0.25), the Spectrin B at Position 985 (CF=0.382).

assessment. Therefore, it is pertinent that the protein residues engaged be that which is involved in the clinical interaction.

Conclusion

Post-genomic Bioinformaticans now face the problem of analysing millions of protein residues arising from the mutations by micro-organisms and viruses for purposes of therapeutic interventions. This problem is helped by the fact that clinical approaches are labour-intensive, cost-, time- and resource wasting. Clinical assessment of these millions of protein residues is unachievable. Therefore initial computational approaches are necessary to streamline and re-organize clinical confirmation. In this study, a Digital Signal Processing technique called Resonant Recognition Model was applied to several Plasmodial proteins and the host target proteins in order to find out if preliminarily clinical findings can be correlated with our computational outcomes.

It was observed that some of our computational results correlated with initial clinical findings while others did not. This could be as a result of the protein residue used in the experiment. It is important to note that computational assessment of biological functionalities requires the use of appropriate protein residues. As noted in this study, the HIV Envelope protein (gp160) which consists of HIV Surface protein (gp120) and HIV Transmembrane protein (gp41) is found to have different CF from the gp120 and gp41. The HIV gp120 is known to and also demonstrated in this study to interact with the CD4. Both have a common prominent peak called Consensus Frequency (CF) at 0.035 as shown in Figure 1.

As a result, computational assessment of interaction between the gp160 (which harbours the gp120) and the CD4 will not yield the desired outcome as the protein involved in the interaction is the gp120. The specificity of the protein-protein interaction as observed in the clinical experimentation is required to be adhered in the computational analysis. Therefore, it is recommended that engagement of the appropriate protein residues are required to obtain the desired results as demonstrated by means of HIV Envelope, Surface and Transmembrane proteins. It is also recommended that other procedures such as Informational Spectrum Method (ISM) for assessing interactions be engaged to computationally examine these proteins and their outcome be used to correlate clinical findings so as to rationalize the evaluation of the physiological properties of proteins. This will also provide quick, cheap characterization of the organisms from which the proteins are derived from.

References

1. Lensen AH, Bolmer-Van de Vegte M, van Gemert GJ, Eling WM, Sauerwein RW (1997). Leukocytes in a Plasmodium falciparum-infected blood meal reduce transmission of malaria to anopheles mosquitoes. Infect Immun 65: 3834-3837.

2. Smith TG, Serghides L, Patel SN, Febbraio M, Silverstein RL, et al. (2003) CD36-mediated nonopsonic phagocytosis of erythrocytes infected with stage I and IIA gametocytes of Plasmodium falciparum. Infect Immun 71: 393- 400.

3. Khusmith S, Sedegah M, Hoffman SL (1994) Complete protection against Plasmodium yoelii by adoptive transfer of a cd8+ cytotoxic t cell clone recognizing sporozoite surface protein 2. Infect Immun 62: 2979-2983.

4. Hoffman R, Welton ML, Klencke B, Weinberg V, Krieg R (1999) The significance

of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys 44: 127-131.

5. van Gemert G, Mair GR, Vermunt AM, Douradinha BG, van Noort V, et al. (2008). Proteomic profiling of plasmodium sporozoite maturation identifies new proteins essential for parasite development and infectivity. PLoS Pathog 4: e1000195.
6. International Human Genome Sequencing Consortium (2004). Finishing the euchromatic sequence of the human genome. NATURE 431: 931-945.
7. Frevert U, Galinski MR, Hugel F, Allon N, Schreier H, et al. (1998) Malaria circumsporozoite protein inhibits protein synthesis in mammalian cells. EMBO J 17: 3816-3826.
8. Ying P, Shakibaei M, Patankar MS, Clavijo P, Beavis RC, et al. (1997) The malaria circumsporozoite protein: Interaction of the conserved regions I and II-plus with heparin-like oligosaccharides in heparan sulfate. Exp Parasitol 85: 168-182.
9. Robson KJ, Naitza S, Barker G, Sinden RE, Crisanti A (1997) Cloning and expression of the thrombospondinrelated adhesive protein gene of Plasmodium berghei. Mol Biochem Parasitol 84:1-12.
10. Polley SD, Tetteh KK, Lloyd JM, Akpogheneta OJ, Greenwood BM, et al. (2007) Plasmodium falciparum merozoite surface protein 3 is a target of allele-specific immunity and alleles are maintained by natural selection. J Infect Dis 195: 279-287.
11. Rodriguez LE, Urquiza M, Ocampo M, Suarez J, Curtidor H, et al. (2000) Plasmodium falciparum EBA-175 kDa protein peptides which bind to human red blood cells. Parasitology 120: 225-235.
12. Karnchaisri K, Seethamchai S, Hongsrimuang T, Kanbara H, Jongwutiwes S, et al. (2008) Positive selection on the Plasmodium Falciparum sporozoite threonine-asparagine-rich protein: analysis of isolates mainly from low endemic areas. Gene 410: 139-146.
13. Silvie O, Goetz K, Matuschewski K (2008) A sporozoite asparagine-rich protein controls initiation of plasmodium liver stage development. PLoS Pathog 4: e1000086.
14. Matuschewski K, Hafalla JC, Silvie O (2011) Cell biology and immunology of malaria. Immunol Rev 240: 297-316.
15. Matsuyama T, Chinzei Y, Yuda M, Kadota K, Ishino T (2004) Essential role of membrane-attack protein in malarial transmission to mosquito host. Proc Natl Acad Sci U S A 101: 16310-16315.
16. Pei X, An X, Guo X, Tarnawski M, Coppel R, et al.. (2005) Structural and functional studies of interaction between Plasmodium falciparum knob-associated histidine-rich protein (KAHRP) and erythrocyte spectrin. J Biol Chem 280: 31166-31171.
17. Cifuentes G, Vanegas M, Martinez NL, Pirajan C, Patarroyo ME (2009) Structural characteristics of immunogenic liverstage antigens derived from P. falciparum malarial proteins. Biochem Biophys Res Commun 384: 455-460.
18. Puentes A, Garcia J, Vera R, Lpez R, Suarez J, et al. (2004) Sporozoite and liver stage antigen Plasmodium falciparum peptides bind specifically to human hepatocytes. Vaccine 22: 1150-1156.
19. Yuda M. Ishino T, Chinzei Y (2005) A plasmodium sporozoite protein with a membrane attack complex domain is required for breaching the liver sinusoidal cell layer prior to hepatocyte infection. Cell Microbiol 7: 199-208.
20. Kariu T, Ishino T, Yano K, Chinzei Y, Yuda M (2006) CelTOS, a novel malarial protein that mediates transmission to mosquito and vertebrate hosts. Mol Microbiol 59: 1369-1379.
21. Carruthers VB, Kafsack BF (2010) Apicomplexan perforin-like proteins. Commun Integr Biol 3:18-23.
22. Jain E, Bairoch A, Duvaud S, Phan I, Redaschi N, et al. (2009) Infrastructure for the life sciences: design and implementation of the UniProt website. BMC Bioinformatics 10: 136.
23. Sultan AA (1999) Molecular mechanisms of malaria sporozoite motility and invasion of host cells. Int Microbiol 2: 155-160.
24. Singh AP, Buscaglia CA, Wang Q, Levay A, Nussenzweig DR, et al. (2007) Plasmodium circumsporozoite protein promotes the development of the liver stages of the parasite. Cell 131: 492-504.
25. Marti M, Good RT, Rug M, Knuepfer E, Cowman AF (2004). Targeting malaria virulence and remodeling proteins to the host erythrocyte. Science 306: 1930-1933.
26. Russo I, Babbitt S, Muralidharan V, Butler T, Oksman A, et al. (2010) Plasmepsin V licenses Plasmodium proteins for export into the host erythrocyte. Nature 463: 632-636.
27. Rathore D, McCutchan TF (2000). Role of cysteines in Plasmodium falciparum circumsporozoite protein: Interactions with heparin can rejuvenate inactive protein mutants. Proc Natl Acad Sci U S A 97: 8530-8535.
28. Vlachou D, Lycett G, Siden-Kiamos I, Blass C, Sinden RE, et al. (2001) Anopheles gambiae laminin interacts with the P25 surface protein of Plasmodium berghei ookinetes. Mol Biochem Parasitol 112: 229-237.
29. Henrich PP, Kraemer SM, Avril M, Vigan-Womas I, Mercereau-Puijalon O, et al. (2010) Identification of a role for the PfEMP1 semi-conserved head structure in protein trafficking to the surface of Plasmodium falciparum infected red blood cells. Cell Microbiol 12: 1446- 1462.
30. Smith JD Kraemer SM (2006) A family affair: var genes, PfEMP 1 binding, and malaria disease. Curr Opin Microbiol 9: 374-380.
31. Smith JD, Robinson BA, Welch TL (2003) Widespread functional specialization of Plasmodium falciparum erythrocyte membrane protein 1 family members to bind cd36 analysed across a parasite genome. Mol Microbiol 47: 1265- 1278.
32. Baruch DI, Ma XC, Singh HB, Bi X, Pasloske BL, Howard RJ (1997) Identification of a region of pfemp1 that mediates adherence of Plasmodium falciparum infected erythrocytes to CD36: Conserved function with variant sequence. Blood 90: 3766-3775.
33. Kotaka M, Niang M, Gao X, Iyer JK, Lescar J, et al. (2008) The C-terminal segment of the cysteine-rich interdomain of plasmodium falciparum erythrocyte membrane protein 1 determines cd36 binding and elicits antibodies that inhibit adhesion of parasite-infected erythrocytes. Infect Immun 76: 1837-1847.
34. Winograd E, Sherman IW, Eda S (2003) Cytoadherence and sequestration in Plasmodium falciparum: defining the ties that bind. Microbes Infect 5: 897-909.
35. Kanchan K, Anand P, Jha GN, Pati SS, Mohanty S, et al. (2008) Variations in host genes encoding adhesion molecules and susceptibility to falciparum malaria in india. Malar J 7: 250-258.
36. Waller KL, Nunomura W, Cooke BM, Mohandas N, Coppel RL (2002) Mapping the domains of the cytoadherence ligand plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) that bind to the knob-associated histidine-rich protein (KAHRP). Mol Biochem Parasitol 119: 125-129.
37. Roberts DJ, Urban BC, Willcox N (2001) A role for CD36 in the regulation of dendritic cell function. Proc Natl Acad Sci USA 98: 8750-8755.
38. Kai O, Urban BC, Lowe B, Marsh K, Roberts DJ, et al. (2001) Platelet-mediated clumping of Plasmodium falciparum-infected erythrocytes is a common adhesive phenotype and is associated with severe malaria. Proc Natl Acad Sci USA 98: 1805-1810.
39. Baruch DI, Ma XC, Pasloske B, Howard RJ, Miller LH (1999) CD36 peptides that block cytoadherence define the CD36 binding region for plasmodium falciparum-infected erythrocytes. Blood 94: 2121-2127.
40. Elliott SR, Spurck TP, Dodin JM, Maier AG, Voss TS, et al. (2007) Inhibition of dendritic cell maturation by malaria is dose dependent and does not require Plasmodium falciparum erythrocyte membrane protein 1. Infect Immun 75: 3621-3632.
41. Su HP, Makobongo MO, Moore JM, Singh S, Miller LH, et al. (2008) The cysteine-rich interdomain region from the highly variable plasmodium falciparum erythrocyte membrane protein-1 exhibits a conserved structure. PLoS Pathog 4: e1000147.
42. Sahar T, Reddy KS, Bharadwaj M, Pandey AK, Singh S, et al. (2011) Plasmodium falciparum reticulocyte binding-like homologue protein 2 (PfRH2) is a key adhesive molecule involved in erythrocyte invasion. PLoS One, 6: e17102.

43. Xainli J, Adams JH, King CL (2000) The erythrocyte binding motif of plasmodium vivax duffy binding protein is highly polymorphic and functionally conserved in isolates from Papua New Guinea. Mol Biochem Parasitol 111: 253-260.

44. Ntumngia FB, McHenry AM, Barnwell JW, Cole-Tobian J, King CL, et al. (2009) Genetic variation among plasmodium vivax isolates adapted to non-human primates and the implication for vaccine development. Am J Trop Med Hyg 80: 218-227.

45. Bolton MJ, Garry RF (2011) Sequence similarity between the erythrocyte binding domain 1 of the Plasmodium vivax Duffy binding protein and the V3 loop of HIV-1 strain MN reveals binding residues for the Duffy antigen receptor for chemokines. Virol J 8: 45-55.

46. Lopaticki S, Maier AG, Thompson J, Wilson DW, Tham W, et al. (2011). Reticulocyte and erythrocyte binding-like proteins function cooperatively in invasion of human erythrocytes by malaria parasites. Infect Immun 79: 1107-1117.

47. Miller LH, Gaur D, Mayer DC (2004) Parasite ligand-host receptor interactions during invasion of erythrocytes by Plasmodium merozoites. Int J Parasitol 34: 1413-1429.

48. Renia L, Snounou G, Preiser PR, Iyer J, Gruner AC (2007) Invasion of host cells by malaria parasites: a tale of two protein families. Mol Microbiol 65: 231-249.

49. Spadafora C, Awandare GA, Kopydlowski KM, Czege J, Moch JK, et al. (2010) Complement receptor 1 is a sialic acid-independent erythrocyte receptor of Plasmodium falciparum. PLoS Pathog 6: e1000968.

50. Fraser TS, Blair PL, Adams JH, Kappe SH, Noe AR (1998) A family of chimeric erythrocyte binding proteins of malaria parasites. Proc Natl Acad Sci U S A 95: 1230-1235.

51. Papoin J, Roques M, Vulliez-Le Normand B, Morlon-Guyot J, Dubremetz JF, et al. (2011) The RON2-AMA1 interaction is a critical step in moving junction-dependent invasion by apicomplexan parasites. PLoS Pathog 7: e1001276.

52. Cao J, Kaneko O, Thongkukiatkul A, Tachibana M, Otsuki H, et al. (2009) Rhoptry neck protein ron2 forms a complex with microneme protein AMA1 in Plasmodium falciparum merozoites. Parasitol Int 58: 29-35.

53. Curtidor H, Patino LC, Arevalo-Pinzon G, Patarroyo ME, Patarroyo MA (2011) Identification of the Plasmodium falciparum rhoptry neck protein 5 (PfRON5). Gene 474: 22-28.

54. Takeo S, Thongkukiatkul A, Otsuki H, Torii M, Tsuboi T et al (2011). Plasmodial ortholog of Toxoplasma gondii rhoptry neck protein 3 is localized to the rhoptry body. Parasitol Int 60: 132-138.

55. Straub KW, Cheng SJ, Sohn CS, Bradley PJ (2009) Novel components of the Apicomplexan moving junction reveal conserved and coccidia-restricted elements. Cell Microbiol 11: 590-603.

56. Menard R. Lacroix C (2008) Trap-like protein of plasmodium sporozoites: linking gliding motility to host-cell traversal. Trends Parasitol 24: 431-434.

57. Morahan BJ, Wang L, Coppei RL (2009) No TRAP, no invasion. Trends Parasitol 25: 77-84.

58. Wang R, Charoenvit Y, Corradin G, De La Vega P, Franke ED, et al. (1996) Protection against malaria by Plasmodium yoelii sporozoite surface protein 2 linear peptide induction of CD4+ T cell- and IFN-gamma- dependent elimination of infected hepatocytes. J Immunol 157: 4061-4067.

59. Mota MM, Pradel G, Vanderberg JP, Hafalla JC, Frevert U, et al. (2001) Migration of plasmodium sporozoites through cells before infection. Science 291: 141-144.

60. Kumar S, Daly TM, Bergman LW, Matuschewski K, Heiss K, et al. (2008) Functional characterization of a redundant Plasmodium TRAP family invasin, TRAP-like protein, by aldolase binding and a genetic complementation test. Eukaryot Cell 7: 1062-1070.

61. Moreira CK, Templeton TJ, Lavazec C, Hayward RE, Hobbs CV, et al. (2008) The plasmodium trap/mic2 family member, trap-like protein (tlp), is involved in tissue traversal by sporozoites. Cell Microbiol 10: 1505-1616.

62. Praper T, Sonnen A, Viero G, Kladnik A, Froelich CJ, et al. (2011) Human perforin employs different avenues to damage membranes. J Biol Chem 286: 2946-2955.

63. Perlaza B, Sauzet J, Brahimi K, BenMohamed L, Druilhe P (2011) Interferon- γ, a valuable surrogate marker of Plasmodium falciparum pre-erythrocytic stages protective immunity. Malar J 10: 27-35.

64. Amino R, Giovannini D, Thiberge S, Gueirard P, Boisson B, et al. (2008) Host cell traversal is important for progression of the malaria parasite through the dermis to the liver. Cell Host Microbe 3: 88-96.

65. Chitnis CE, Sharma A (2007) Targeting the Plasmodium vivax Duffy-binding protein. Trends Parasitol 24: 29-34.

66. Chitnis CE, Miller LH (1994) Identification of the erythrocyte binding domains of Plasmodium vivax and Plasmodium knowlesi proteins involved in erythrocyte invasion. J Exp Med 180: 497-506.

67. Vaidyanathan PP (2004) Genomics and proteomics: A signal processors tour. IEEE Circuits and Systems Society 4: 6 - 29.

68. Cosic I (1994) Macromolecular bioactivity: Is it resonant interaction between macromolecules?-Theory and applications. IEEE Trans Biomed Eng 41: 1101-1114.

69. Stanley KK, Tschopp J, Masson D (1986) Structural/functional similarity between proteins involved in complementand cytotoxic T-lymphocyte-mediated cytolysis. Nature 322: 831-834.

70. Riglar DT, Chan JA, Foley M, Baum J, Ralph SA, et al. (2010) Interaction between Plasmodium falciparum apical membrane antigen 1 and the rhoptry neck protein complex defines a key step in the erythrocyte invasion process of malaria parasites. J Biol Chem 285: 14815-14822.

71. Coley AM, Gupta A, Murphy VJ, Bai T, Kim H, et al. (2007) Structure of the malaria antigen AMA1 in complex with a growth-inhibitory antibody. PLoS Pathog 3: 1308-1319.

72. Heimer E, Nachman RL, Asch AS, Silbiger S (1992) Thrombospondin sequence motif (csvtcg) is responsible for cd36 binding. Biochem Biophys Res Commun 182: 1208-1217.

73. Da Silva E, Foley M, Dluzewski AR, Murray LJ, Anders RF, et al. (1994) The plasmodium falciparum protein RESA interacts with the erythrocyte cytoskeleton and modifies erythrocyte thermal stability. Mol Biochem Parasitol 66: 59-69.

74. Foley M, Tilley L, Sawyer WH, Anders RF (1991) The ring-infected erythrocyte surface antigen of Plasmodium falciparum associates with spectrin in the erythrocyte membrane. Mol Biochem Parasitol 46: 137-147.

75. Cosic I (2001) Analysis of HIV proteins using DSP techniques. Proc of IEEE Eng Med Biol Soc 3: 2886 - 2889.