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ORIGINAL ARTICLE

Epitope prediction for $MSP1_{19}$ protein in *Plasmodium yeolii* using computational approaches

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Abstract Malaria disease is caused by the transmission of *Plasmodium*, through the bite of a female *Anopheles* mosquito. Although the *Plasmodium* life-cycle has been extensively characterized, relatively little is known about sporozoite interaction with host organelles and proteins. Individuals that survive continuous exposure to infection do eventually develop clinical immunity, suggesting that a vaccine against asexual blood stage of the parasite is achievable. The merozoite surface protein ($MSP1_{19}$) of *Plasmodium yoelii* was considered as the target protein for epitope prediction using the computational approaches. The T-cell and B-cell epitopes for $MSP1_{19}$ were predicted using a variety of computational tools. Out of these predicted epitopes, the epitopes being expressed by the protozoa were identified. The 3D structures of T-cell epitopes (MHC-I and MHC-II) were modeled by homology modeling method followed by validation using the SAVES server. Further, the MHC molecules were identified and their 3D structures were retrieved from the Protein Data Bank. The protein–protein docking of modeled epitopes with respective MHC molecules were also carried out. Total Six T-cell epitopes ('ELSEHYYDRY', 'LLIITIVFNI', 'MMYHIYKLK', 'IYQAMYNVIF', 'SEEDMPADDF', 'YVLLQNSTI') for $MSP1_{19}$ have been identified as promising vaccine candidates. Furthermore, six B-cell epitopes ('QPTET', 'SEETE', 'SDKYNKKKP', 'KEKKKE', 'CKKNKA', 'THPDNT') have also been identified as potential epitopes. In future, these predicted epitopes might be exploited in vaccine development against malarial infection.

Keywords Malaria · Merozoite surface protein · Epitope · Major histocompatibility complex · Docking

1 Introduction

Malaria, the most widespread disease throughout the globe is also caused by transmission of *Plasmodium yeolii* which is a rodent strain of malarial parasite, i.e., *Plasmodium* (Chauhan 1996). The malarial parasite maturation occurs within the erythrocyte (Orengo et al. 2008). In the final phase, a large plasmodial protein becomes a significant surface protein of merozoite which is synthesized in all malarial species (Schwartz et al. 2012). Studies on *P. yoelii* has shown that protein is found in a processed form on the merozoite surface, as a result of proteolytic cleavage of the large precursor molecule, hence called Merozoite surface protein ($MSP1_{19}$) (Holder et al. 1992; Blair and Carucci 2005). This disease is spread across the globe causing hundreds of millions of clinical infections and at least a million deaths per annum. An effective way to control and finally eradicate malaria is by developing cheap and effective vaccines (Brady et al. 2001; Giles 2005). Previous studies established a strong association between this population's antibody responses to Merozoite surface protein-1 (antigens) against malarial parasite in humans (Woehlbier et al. 2010). Therefore, antigenic $MSP1_{19}$ protein can be exploited for the epitope prediction, and, consequently, vaccine development against malaria. Epitopes are the immunologically active regions of an immunogen that binds to the antigen-specific membrane receptor on lymphocytes

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to secret antibodies. The T-cells and B-cells recognize different epitopes on the same antigenic molecule.

Thus, epitopes against $MSP1_{19}$ protein could be predicted using the computational techniques (Yadav and Rana 2011; Yadav and Mishra 2012) that might further become good candidate(s) for the vaccine development against malaria (Doolan et al. 2003). A HLA supertype allowed the identification of epitopes capable of binding multiple HLA molecules and offered the prospect of designing broadly reactive epitope based vaccines (Sette and Sidney 1998). An arsenal of eight major supertypes (HLA-A1, -A2, -A3/-A11, -A24, -B7, -B44, -DR, and -DRB) protected the coverage of more than 99 % of any human population, at the level of both MHC class-I and class-II molecules (Southwood et al. 1998). Over the past few years to investigate the potential candidates for vaccine development, epitope-based predictions have been enormously used (Sette and Peters 2007; Yadav et al. 2011; Purcell et al. 2007). The merozoite surface protein ($MSP1_{19}$) of *P. yoelii* is a rodent malarial immunogenic protein (Carlton et al. 2002). The aim of the present study was to predict T-cell and B-cell epitopes for $MSP1_{19}$, respectively, using the computational techniques, and to predict the 3D structures of the best predicted epitopes (small peptides) followed by protein–protein docking study with respective MHC alleles of *Homo sapiens*.

2 Materials and methods

2.1 T-cell and B-cell epitope prediction

The protein sequence of merozoite surface protein ($MSP1_{19}$) of *P. yoelii* was retrieved from the UniprotKB database (ID: P13828) (http://www.uniprot.org) (Magrane and UniProt Consortium 2011). A variety of tools/servers were used for T-cell epitope predictions which include: (1) IEDB analysis tool based on Artificial Neural Network (ANNs) (http://tools.immuneepitope.org) (Neilson et al. 2003). (2) ComPred based on combination of Artificial Neural Networks (ANNs) and Quantitative Matrices (QM) (http://www.imetech.res.in/reghav/nhlapred/comp.html) (Lata et al. 2007). (3) SMM based on linear programming (http://zlab.bu.edu/SMM/) (Peters et al. 2003). (4) SVMHC based on the support vector machine (SVM) (http://www.sbc.su.se/svmhc/new.cgi) (Doones and Elofsson 2002). (5) SYFPEITHI based on peptide binding motif (http://www.uni-tuebingen.de/uni/kxi/) (Rammensee 1999). The B-cell epitopes were also predicted using two methods, i.e., the Bepipred linear epitope prediction method (Larsen et al. 2006) and Emini surface accessibility prediction method (Emini et al. 1985) (http://tools.iedb.org/bcell/). For each method, top 5 scoring predicted epitopes were selected. The step-wise selection of supertypes and peptides are depicted in Fig. 1.

2.2 Population coverage and allergenicity prediction

For the analysis of population coverage for the MHC class-I and class-II alleles of the selected epitopes, IEDB-Population Coverage Calculation tool was used (Bui et al. 2006). To predict the allergenicity of antigenic $MSP1_{19}$ protein in advance stage, the web-based AllerHunter server was also used (Muh et al. 2009), so that risk of failure can be avoided.

2.3 Modeling and docking of predicted epitopes

The 3D structures of top scoring epitopes (small peptides) for MHC-I and MHC molecules were modeled and predicted using the Pepstr server (http://www.imitech.res.in/

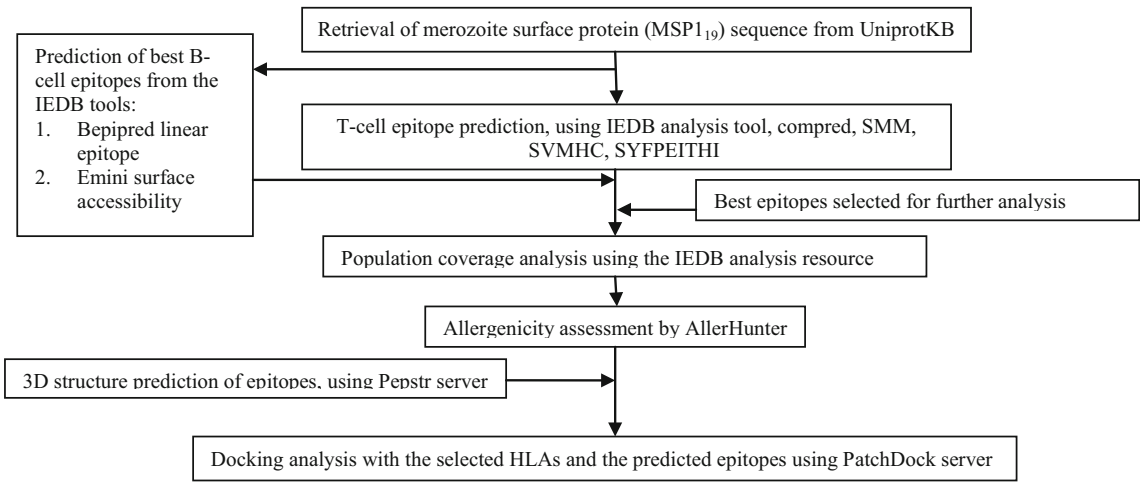

Fig. 1 *Flow chart* representing the complete protocol of epitope prediction

Table 1 T-cell epitopes interacting with their respective MHC-I and MHC-II alleles

Rank	Predicted epitopes	Docked energy (KJ/mol)
MHC class-I HLA-A*01:01 allele		
1	**ELSEHYYDRY**	**−430.50**
2	KTELNTCEY	−426.10
3	NTDMLLKYY	−423.57
4	FSNKKKELQY	−413.31
5	FVDPIELEY	−409.20
MHC class-I HLA-A*02:01 allele		
1	**LLIITLIVFNI**	**−496.01**
2	LMHAINFYYDV	−475.83
3	LLFSFVFFAI	−472.92
4	NMDGMDLLGV	−421.32
5	YVSGGLHHV	−417.01
MHC class-I HLA-A*03:01 allele		
1	**MMYHIYKLK**	**−579.41**
2	RLKKNINLGK	−497.48
3	AMYNVIFYKK	−487.41
4	RLGSTYKSLK	−487.36
5	KLYYLEKLQK	−474.40
MHC class-I HLA-A*24:02 allele		
1	**IYQAMYNVIF**	**−375.63**
2	YYLEKLQKF	−309.42
3	KYYKARTKYF	−298.81
4	RYGVKYLI	−255.40
5	FYILNGYVNF	−248.22
MHC class-I HLA-B*44:02 allele		
1	**SEEDMPADDF**	**−388.56**
2	SEFTNESLY	−387.05
3	SETIIPLTI	−384.84
4	TEFNQQKTPF	−382.75
5	SELDVLLAI	−365.18
MHC class-IIHLA-DRB1*0101 allele		
1	**YVLLQNSTI**	**−424.77**
2	FYILNGYVN	−406.78
3	YVIRNPYQL	−399.59
4	LSILKARLL	−392.42

Epitopes shown in bold have lowest docking energy score for respective MHC allele

raghava/pepstr/) (Kaur et al. 2007). Subsequently, protein–protein docking was carried out for the top scoring epitopes with their respective human MHC receptors. The molecular docking algorithms based on the shape complementarity principles were used by PatchDock server (http://bioinfo3d.cs.tau.ac.il/Patchdock) (Duhovny et al. 1997). The 3D structures of the MHC alleles, i.e., HLA-A*01:01 (pdb id:1W72), HLA-A*02:01(pdb id: 1AKJ), HLA-A*03:01 (pdb id: 2XPG), HLA-A*24:02 (3VXN), HLA-B*44:02 (pdb id: 1SYS), and HLA-DRB1*0101 (pdb id: 3S5L) were retrieved from the Protein Data Bank (http://www.rcsb.org/pdb) (Jardetzky et al. 1994). To perform the protein–protein docking with these MHC alleles, the receptors were prepared by removing all HETATOMs and solvents from the pdb files. The 3D structures of epitopes modeled by Pepstr server were docked with their respective MHC allele (s) in 10 conformations (Berman 2008). Out of these 10 conformations, the conformation with the minimum-binding free energy score was selected as the most stable MHC-epitope complex (Vajda and Kozakov 2009). All the docked complexes were visualized in 3D space using the CHIMERA tool (Pettersen et al. 2004).

3 Results and discussion

3.1 Epitope prediction

In the present work, several potential epitopes have been predicted for the Merozoite surface protein ($MSP1_{19}$) in *P. yoelii* which has been reported as potential antigenic protein (Holder et al. 1992; Blair and Carucci 2005; Woehlbier et al. 2010). For the T-cell, five epitope prediction algorithms (methods), and for the B-cell, two prediction methods were employed, respectively (Table 1).

3.2 Population coverage and allergenicity prediction

The population coverage of the MHC alleles (class-I and II) of the predicted epitopes were also calculated (Fig. 2).

Different *Plasmodium yeolii* affected regions were selected for the evaluation of the population coverage of the proposed epitopes. It calculated that the 73.73 fraction of east-Asian, 50.60 fraction of Indian, 92.41 fraction of Europeans, and 82.51 fraction of north-American individuals were responded to epitopes with selected MHC restrictions. The sequence-based allergenicity prediction was also carried out using the AllerHunter tool, which predicted the query sequence as a non-allergen with score of 0.0. [(sensitivity) SE = 91.6 %, (specificity) SP = 87.1 %].

3.3 Modeling and docking of predicted epitopes

Subsequent to T-cell epitope (MHC-I and MHC-II) prediction, the 3D structures of high ranking epitope was modeled which are prerequisite for the protein–protein docking studies. The binding free energy scores (docked energy) with MHC class-I and class-II molecules, respectively, were calculated using the PatchDock server. The T-cell epitopes identified against different alleles of MHC class-I and class-II molecules along with their docking energies (KJ/mol) are shown in Table 1.

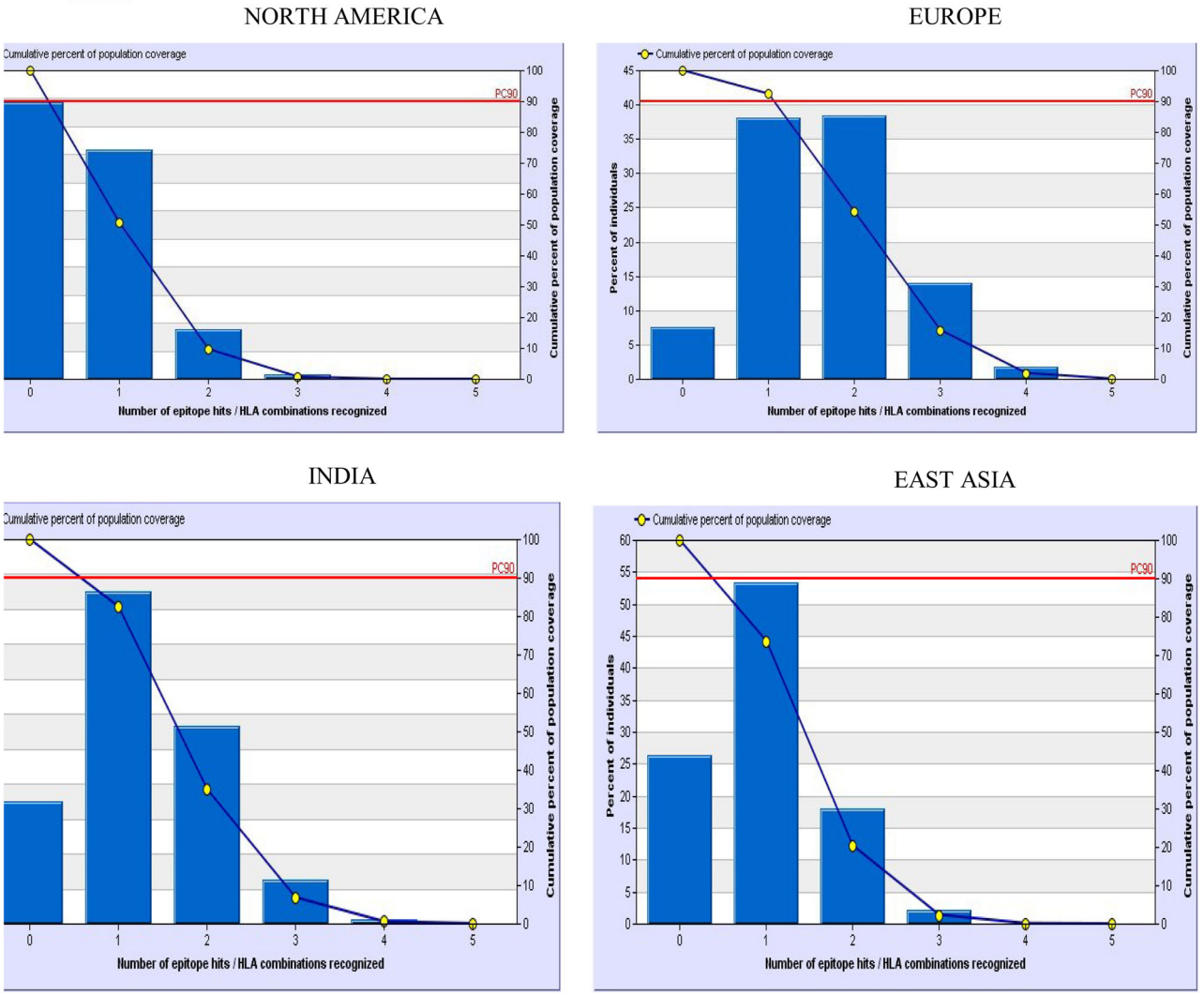

Fig. 2 Population coverage based on MHC-I restriction data [The *line* (–o–) represents the cumulative percentage of population coverage of the epitopes; the *bars* represent the population coverage for each HLA allele]

After docking the highest ranked epitopes with HLA-A*01:01 allele (PDB ID: 1W72), it was found that the epitope 'ELSEHYYDRY' showed least energy score (−430.50 kJ/mol) which shows highest binding affinity for the MHC class-I receptor (Fig. 3).

For MHC class-I allele HLA-A*02:0, the most potential epitopes were docked with the receptor (PDB ID: 1AKJ), and it was found that 'LLIITLIVFNI' epitope was possessing highest binding affinity towards the MHC-I receptor (−496.01 kJ/mol) (Fig. 4).

The 3D structure of 'MMYHIYKLK' epitope was docked with MHC class-I receptor (HLA-A*03:01 allele) (PDB ID: 2XPG) which showed the lowest docking energy of -579.41 kJ/mol. The lower docking energy reveals higher binding affinity for HLA-A*03:01 allele (Fig. 5).

The highest ranked epitope 'IYQAMYNVIF' for MHC class-I HLA-A*24:02 allele was docked with the receptor

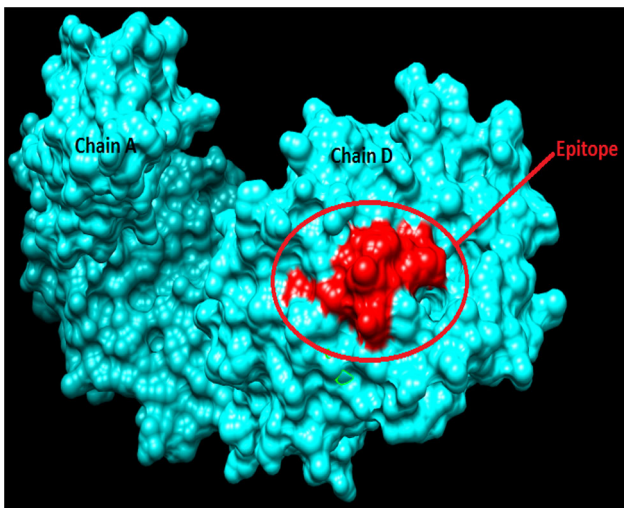

Fig. 3 Docked complex of epitope 'ELSEHYYDRY' and MHC-1 receptor (1W72)

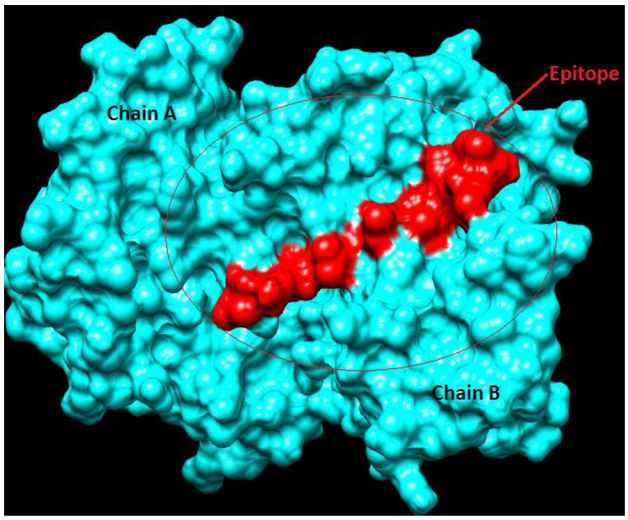

Fig. 4 Docked complex of epitope 'LLIITLIVFNI' and MHC-1 receptor (1AKJ)

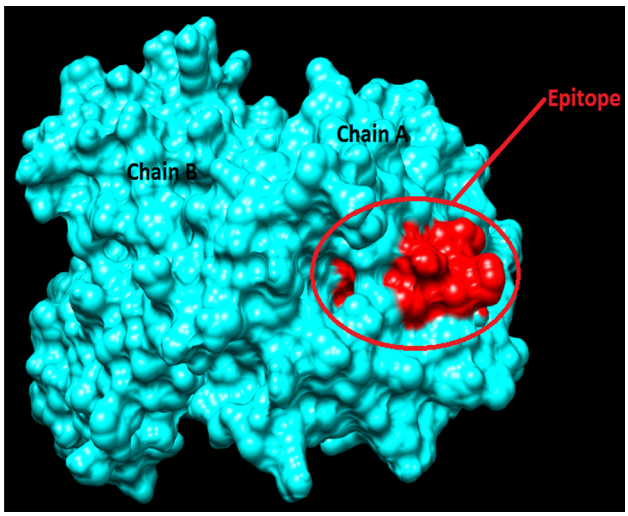

Fig. 6 Docked complex of epitope 'IYQAMYNVIF' and MHC-1 receptor (3VXN)

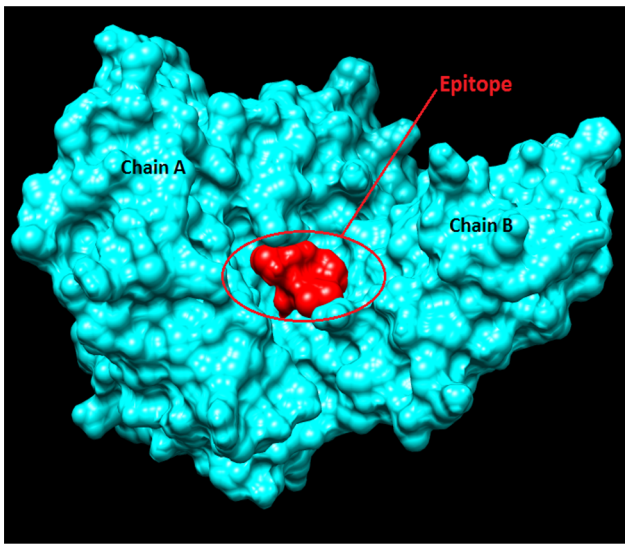

Fig. 5 Docked complex of epitope 'MMYHIYKLK' and MHC-1 receptor (2XPG)

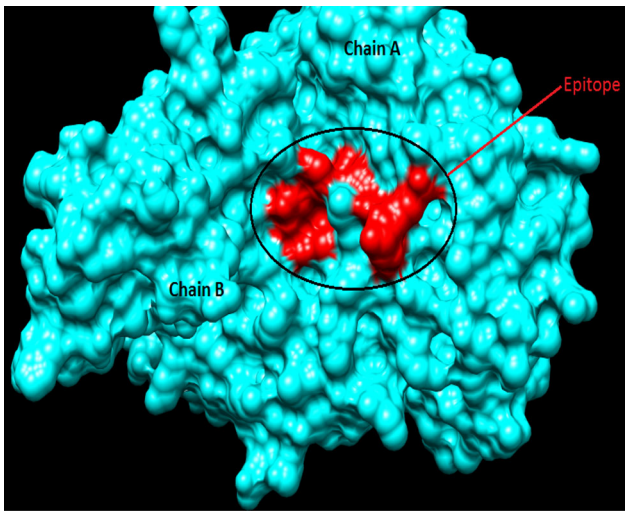

Fig. 7 Docked complex of epitope 'SEEDMPADDF' and MHC-1 receptor (1SYS)

(PDB ID: 3VXN), and the docking energy was found to be −375.63 kJ/mol (Fig. 6).

Finally, the highest ranking epitope 'SEEDMPADDF' MHC class-I HLA-B*44:02 allele was docked with the receptor (PDB ID: 1SYS), and the energy score was found to be −388.56 kJ/mol, which shows highest binding affinity for the MHC-I receptor (Fig. 7).

The HLA-DRB1*0101 allele of MHC class-II is lone allele whose 3D structure was present in the PDB database. The epitopes for above allele were predicted using the SVMHC tool which implements SYFPEITHI algorithm. For HLA-DRB1*0101 allele, top four predicted epitopes were carefully chosen as being the most suitable for further analysis. The 3D structures of all these epitopes were predicted followed by receptor-peptide docking. Out of four predicted epitopes, 'YVLLQNSTI' epitope was having lowest docking energy score (−424.77 kJ/mol) as compared to others. The lower energy score reveals highest binding affinity for the MHC-II receptor (PDB ID: 3S5L). The docked complex of epitope 'YVLLQNSTI' with HLA-DRB1*0101 allele of human HMC Class-II receptor are depicted in Fig. 8.

The B-cell epitopes for the $MSP1_{19}$ were also predicted using two methods, i.e., Bepipred linear epitope prediction method and Emini surface accessibility prediction method, respectively.

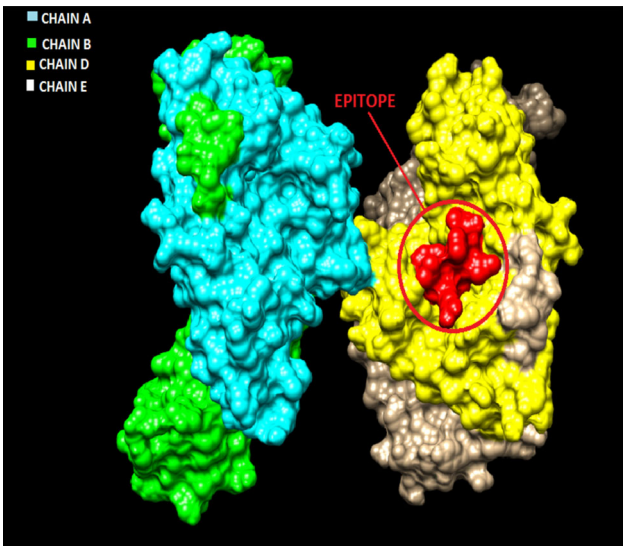

Fig. 8 Docked complex of epitope 'YVLLQNSTI' and MHC class-II receptor (3S5L)

The BepiPred predicts the location of linear B-cell epitopes using a combination of a hidden Markov model and a propensity scale method. The epitopes are ranked according to their peptide score (Table 2).

Using the Emini surface accessibility method, the B-cell epitopes for $MSP1_{19}$ were again predicted for the hydrophillic antigenic epitope (Table 3). In this method, the calculation was based on surface accessibility scale on a product instead of an addition within the window.

All the B-cell epitopes predicted by the Bepipred linear epitope prediction and Emini surface accessibility prediction methods were further analyzed. After comparing all the B-cell epitopes predicted from above two methods, it was found that the small peptides 'QPTET', 'SEETE', 'SDKYNKKKP', 'KEKKKE', 'CKKNKA', and 'THPDNT' were commonly predicted potential B-cell epitopes for $MSP1_{19}$ against *P. yoelii* (Table 4).

The linear B-cell epitopes typically vary 5–20 amino acids in length (Morris 2007). All the predicted B-cell epitopes possessing less than 5 amino acids were filtered out. In Table 3 (S. No. 4, 10), two epitopes are having exceptionally high number of amino acid residues, but they possess common epitope(s), such as 'SDKYNKKKP' and 'THPDNT', respectively, predicted by the Emini surface accessibility method. Since these two epitopes were commonly predicted by both methods, therefore they have also been considered as potential B-cell epitope.

All the top ranked predicted epitopes for MHC-I as well as MHC-II might be synthesized in wet laboratories, which can be exploited for vaccine development. Interestingly, all six commonly predicted epitopes for B-cells are also promising vaccine candidates against malarial infections.

Table 2 B-cell epitopes predicted by BepiPred linear epitope prediction method

S. no.	Start position	End position	Predicted epitope	Length
1.	56	65	TQPTETIDPF	10
2.	150	157	KISEEETE	8
3.	169	175	PIENIQD	7
4.	202	228	TKKIQPEGNEDCNDASCDSDKYNKKKP	27
5.	260	265	LKKNDA	6
6.	355	361	TLTLEEK	7
7.	398	407	KEKKKESCNL	10
8.	411	419	SCKKNKASE	9
9.	429	443	PNGISYPLPENDVYN	15
10.	446	476	ANNAAETTYGDLTHPDNTPLT GDLATNEQAR	31
11.	488	492	KAEEK	5
12.	499	504	TNYDNK	6
13.	506	518	TEFNQQKTPFKEA	13
14.	541	548	TKRDEYMT	8
15.	556	560	CEYGN	5
16.	665	675	KTYGNEGKPEP	11
17.	842	848	LTSEEDK	7
18.	902	907	KDENPS	6
19.	1087	1092	IDGNNT	6
20.	1193	1200	REAEKQYV	8

Table 3 B-cell epitopes predicted by the Emini surface accessibility method

S. no.	Start position	End position	Predicted epitope	Length
1	56	61	TQPTET	6
2	152	158	SEEETEM	7
3	200	206	EETKKIQ	7
4	220	228	SDKYNKKKP	9
5	394	403	EYFKKEKKKE	10
6	412	417	CKKNKA	6
7	458	463	THPDNT	6
8	485	495	KKIKAEEKKLE	11
9	497	504	LKTNYDNK	8
10	508	515	FNQQKTPF	8
11	525	531	SKFRNKL	7
12	538	552	KFKTKRDEYMTKKTE	15
13	592	599	FSNKKKEL	8
14	655	660	AQLKDK	6
15	666	675	TYGNEGKPEP	10
16	701	707	KEKERME	7
17	727	739	SSTDRSTQSSTSS	13
18	769	775	PSTEASE	7
19	782	789	TTQETQPS	8
20	888	894	ELYEKEM	7

Table 4 Predicted common B-cell epitopes

Result of B-cell epitope prediction				
Rank	Start position	End position	Epitope	Size
1	57	61	QPTET	5
2	152	157	SEEETE	6
3	220	228	SDKYNKKKP	9
4	398	403	KEKKKE	6
5	412	417	CKKNKA	6
6	458	463	THPDNT	6

4 Conclusion

The T-cell (MHC-I and MHC-II) and B-cell epitopes for $MSP1_{19}$ of *P. yoelii* were predicted using various tools/servers. After 3D structure prediction of top ranked predicted epitopes followed by receptor-peptide docking studies, it was found that the epitope 'IYQAMYNVIF' was possessing highest binding affinity for MHC-I receptor. On the other hand epitope, 'YVLLQNSTI' has shown highest binding affinity for MHC-II receptor. For the B-cell, six small peptides 'QPTET', 'SEETE', 'SDKYNKKKP', 'KEKKKE', 'CKKNKA', and 'THPDNT' were predicted as most promising epitope. In future, these predicted epitopes can be synthesized in wet laboratory and might be exploited as potential candidate(s) for the vaccine development against malaria.

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Compliance with ethical standards

Conflict of interest Authors declare that there is no conflict of interest.

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