Document heading: Research Article

State of the art for Linear B-cell epitope in *Plasmodium falciparum* according to a bibliographical investigation

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Received: 18-09-2018 / Revised: 19-10-2018 / Accepted: 20-11-2018

Abstract

The goal of this investigation is to analyze the bibliographical references that are registered in the IEDB database regarding the linear B-cell epitopes responsible for *Plasmodium falciparum* malaria in humans during the temporal period 1984 to 2018. The geographical origin of the samples and the relevant journals were obtained for the linear B-cell epitopes in *Plasmodium falciparum* according to the Similarity Index. This methodology can be applied to another disease.

Keywords: B cell, Plasmodium falciparum, malaria, Similarity Index.

Introduction

Malaria is transmitted by the protozoan *parasite Plasmodium* and it is transmitted among humans by the female mosquitoes *Anopheles gambiae*. Plasmodium belongs to the phylum Apicomplexa and the *Plasmodiidae* family. Only five species affect humans where four of them are anthroponotic *(Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale*) and one by zoonotic that also affects primates (genus Macaca).

In 2016, approximately 216 million cases of malaria (or paludism) were reported worldwide according to the World Malaria Report 2017 [1], and of all of them, *P. falciparum* is responsible for most of the clinical manifestations throughout the world (90% of the fatal cases). They mainly occurred in Africa, while that *P. vivax* is the principal species that is found in America.

At the present time, there is a vaccine that is currently in phase III of clinical trials and it is the pre-erythrocytic vaccine called RTS,S (Mosquirix™) [2].

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It's effectiveness has yet to be demonstrated totally. For this reason, we reviewed the scientific literature of all the scientific studies presented in the database called IEDB [3] and delayed including it until September, 2018 and focused only on the availability of vaccines. In fact, this type of study allows one to create new vaccines based on B cell epitopes against malaria caused by *Plasmodium falciparum* such as [4-7]

The Immune Epitope Database (abbreviated IEDB and available at iedbr.org) which issponsored by the National Institute of Allergy and Infectious Diseases (NIAID) for the last 14 years [3]. It is a repository of epitope of emerging diseases as well as in the bioterrorist threat. Until November 2018, this has included more than 19,818 publications and 471,390 B cell papers. In addition, only publications appearing in peer-reviewed journals, patents or patent applications, and registered items are considered. For this reason, this work will analyze all the publications concerning linear epitopes B cells in humans in *Plasmodium falciparum* from 1984 until September 2018.

Material & methods

We select publications in the IEDB by *P. falciparum* based on linear B cells epitope whose host is human, and we determined: (1) the geographical origin of the samples, (2) the journals where the results were published, (3) the years of publication, (4) the antigens, and (5) the consensus of linear B cell epitope according

to the methodology published in the scientific literature. The consensus selection will be the one with the highest value of the "Similarity Index".This index is calculated when aligning each of the epitopes present in each antigen, and we count the frequency at the positions of the amino acids in each epitope, divided by the total length of the epitope.The range of values is from zero (there is no consensus defined in all positions of the amino acids that make up the epitope) to 10.0 (identical).

Geographic origin

Results

We obtained a file in CSV format (*ie* separated by a comma) from the IEDB database where 146 scientific journals with linear B cell epitopes whose host was a human in *Plasmodium falciparum*, which allow us to determine:

Figure 1 shows the geographic origin of the samples by continents where the majority of events comes from Africa (83.48%), followed by South America (6.63%), Asia (4, 94%), and so on. Finally, North America is the continent with the lowest number of samples registered by *Plasmodium falciparum*.

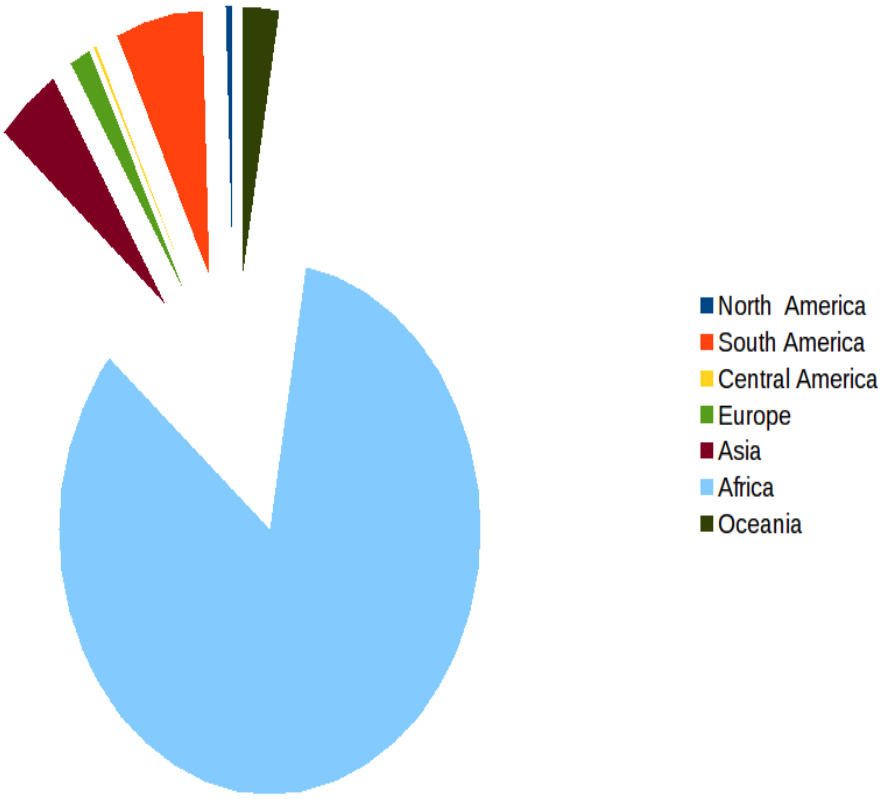

Fig. 1: Geographic origin of the samples according to IEDB

Scientific journals

The next analysis was to examine the scientific journals where the results are published with the condition being that three or more papers appear in same journal (Fig. 2). The majority of the papers were published in the journal "Infection and Immunity" (total of 27 papers), followed by "The American Journal of Tropical Medicine and Hygiene" (17 papers), "Parasite Immunology" (12 papers), "The Journal of Immunology" (9 papers), and so on.

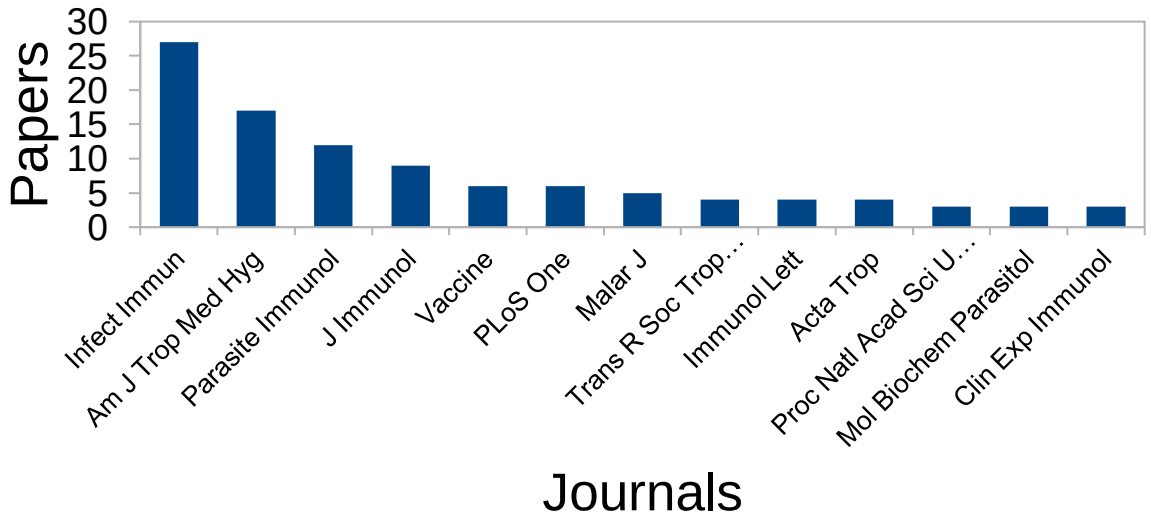

Fig. 2: Scientific journals with three or more papers have been published in malaria by *Plasmodium falciparum* in IEDB

Year of publications

The number of scientific publications per year is shown in Figure 3 during the period 1984 to September 2018. This figure shows an increase in 1991 and then the number fluctuates but decreases over time. From 2014 until the present time, the number of papers that are published per year is constant.

There is no one trend per year of scientific publications on *P. falciparum* malaria. In fact, in 1991, papers appeared in the following journals: Transactions of the Royal Society of Tropical Medicine and Hygiene, Parasite Immunology, Molecular and Biochemical Parasitology, The Journal of Immunology, Journal of Clinical Microbiology, International Immunology, Immunology Letters, Annals of Tropical Medicine and Parasitology, and American Journal of Epidemiology.

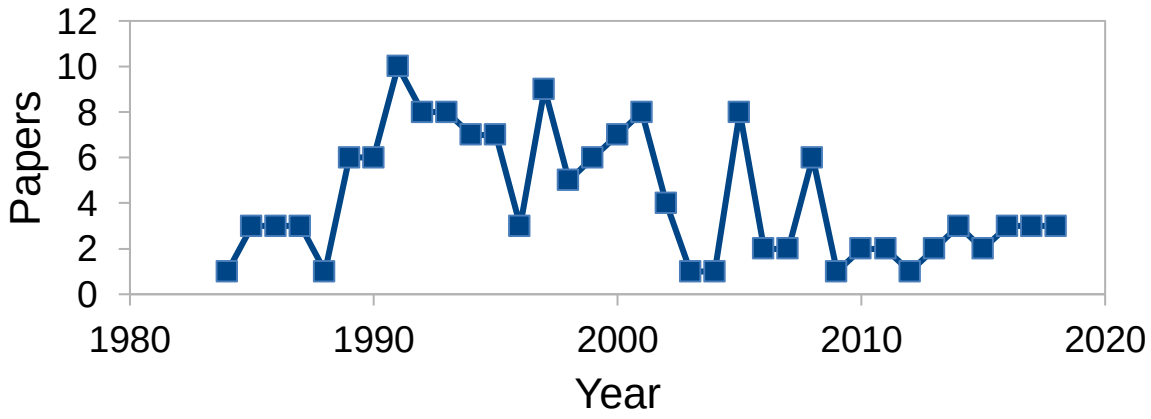

Fig. 3:Total number of publications of linear B cell epitope by *Plasmodium falciparum* in human host per year

Antigens

Figure 4 shows the antigens according to the scientific journals according to IEDB, with the condition that they appear in four or more articles in a journal. This result reveals that the majority of papers is Circumsporozoitic and later DNAJ.

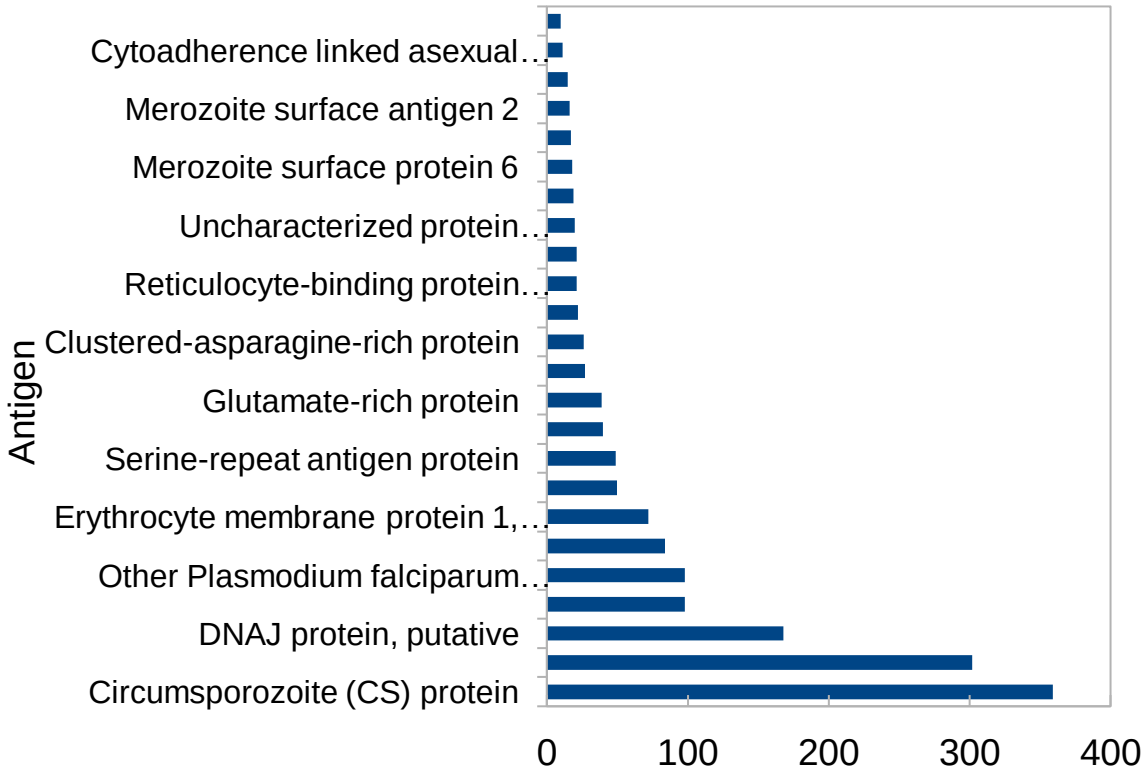

Fig. 5: Antigens present in the publications registered in IEDB

Consensus linear B-cell epitope and Similarity Index

There are 985 epitopes in the 146 scientific journals and they are grouped by antigens in Table 1. For example, 101 kDa malaria antigen has 6 linear B-cell epitope in the IEDB corresponding to *Plasmodium falciparum* (human host). These six epitopes are all shown with the IEDB ID in the second column of Table 1. However, when there is a large number of epitopes the list is truncated, *i.e.*, membrane protein 1 with 137 epitopes.

The first and second column of Table 1 corresponds to name and ID antigen, respectively. The third column indicates the consensus epitope according to the highest value of the Similarity Index (X means any amino acid). For this reason, the epitopes that are not considered in the consensus are crossed out in column 2.

For example, liver stage antigens there are twelve linear B cell epitopes. The consensus formed by the epitope ID: 7763, 7818, 9449, 11799, 24930, 43702 is D- [E / L] -D- [E / L] –G-I-E-K- [E / S] - [L / S] – E-X-D-L-S-E with a Similarity Index equal to 4,21. However, when considering the epitopes ID: 2172, 13913, 13914, 34828 the consensus is E-Q-Q-S-D-L-E-Q-E-R-L-A-K-E-K-L-Q with an index higher than 9, and the first consensus is discarded. Unfortunately, the consensus epitope of antigens formed with more than 47 epitopes could not be obtained as it was in the case of erythrocyte membrane protein 1, Merozoite surface protein 1, Merozoite surface protein 1 precursor, and ring-infested erythrocyte surface antigen.

Table 1: Antigen, Epitope ID, consensus and Similarity Index of linear B cell epitope in *Plasmodium falciparum* (human host)

Antigen	Epitope ID	Consensus epitopes (X means any amino acid)	Similarity Index
101 kDa malaria antigen	3367,13460,44251,70437,74430	N-X-S-X-N-K-K-K-K-[K/N]-N	4,54
antigen 332, Ag332=Pf332 gene clone G1	62347,62348,11652,~~11927~~,13834,26178,27395,29409,34197,40575,58251,58957,60424,~~62354~~,~~63344~~,~~63345~~,70536,70537	E-E-G-S-V-T-E	5,14
antigen CARP	2803,9419,~~10581~~,13470,14891,28938,34935,42148,~~43198~~,44153,44634,~~44740~~,45082,~~45197~~,45198,~~45291~~,45823,46432,46479,46664,51737,58759,59062,63723,70076,74131	N-S-N-N	1,5
apical membrane antigen-1	2163,11356,21373,27620,74433	E-X-I-S-H-X-X-K	4,38
Circumsporozoite protein	14317,18741,20224,25768,42196,43117,74323,12200,~~13438~~,24137,26865,32761,~~32769~~,32770,43242,43247,43249,~~43255~~,43256,48618,~~49325~~,756433,~~768466~~,768504,~~768505~~,~~768568~~	N-P-D-P-N-A-N-P	2,38
Circumsporozoite protein precursor	9424,~~9692~~,~~9694~~,15056,20166,26870,32573,36912,43233,43240,~~43246~~,~~43248~~,~~43250~~,~~43337~~,~~45110~~,~~46354~~,~~47747~~,~~48600~~,~~49324~~,62344,~~73090~~,~~982~~	N-A-N-P-N-A-N-P-N-A-N-P-N-A-N	1,87

	15,742507,756260,756261,756262,756263,756264,756359,756363,756411,756412		
cytoadherence linked asexual protein (CLAG)	1925,4266,16090,16272,20683,22950,31638,38442,45162,73279,75645	F-I-D-K-E	2,6
Erythrocyte membrane protein 1	8594,11043,18536,32472,34948,49140,72351,107935,141606,141609,141618,141625,141632,141635,141659,141696,141732,141762,141781,141785,181540,181544,181551,181556,181559,181564,181568,181569,181573, … (list is truncated)	It could not be obtained	
Erythrocyte membrane protein, putative	122259,122308,122325,122331,122338,122393,122456,122460,122481,122578,466413	L-T-S-[K/S]-D-E-E-D-I-I-K-H-N-E-D-V-R-E-E-I-E-E	5,63
glutamate-richprotein	8942,10106,12059,12464,12465,12531,13688,13689,28742,31224,31225,33045,36840,45563,48635,464223,466615,466616,466929,466930,466931,467355,467462,469456,472326	E-D-D-K-N-E-K-V-E-H-E-I-V-E-V-E-E-I-L-P-E	0,81
heat shock 70 kDaprotein	7498,7971,11185,21381,30289,32113,32114,32596,39597,58859,68252,74095,74097	[K/Y]-[E/K]-A-K-S-S-L-E-[D/E]-T-C-I-K-[E/I/T/V]-K-[L/N/T]	1,43
high molecular weight rhoptry protein-2	463952,463953,464250,464291,467437,468427,472211,472212	T-Y-L-T-E-P-I-L-T-E	6,90
Hypothetical protein PFB0145c	12436,25526,25599,26453,26918,27699,35142,37797,38274,44271,58709,67995	I-N-[K/L]-L-N-[K/N/Q]-[E/G]-K-K-K-L-K-K-K-I-E-E-L-N-K-E-I-E-K-L	4,28
Liver stage antigen (12)	2172,7763,7818,9449,11799,13913,13914,24930,26817,34828,40042,43702	E-Q-Q-S-D-L-E-Q-ER-L-A-K-E-K-L-Q	9,64
Major merozoite surface antigen	22570,58841,71353,95818,125170	S-X-X-S-V-A-S-X-A-[E/S]-V-A-S	5,75
Major surface antigen p190	8351,11589,18758,20039,30477,58196,58266,61053,64002,67650,71536	V-A-K-[E/G/P]-[S/V]-[P/S]-A	3,85
Merozoite surface antigen 2	13500,41662,55038,59922,62779,237695,237801,237804,237880,237961	P-Q-N-T-S-D-S-Q-K-E-C-T	6,83
Merozoite surface antigen 2 precursor	1110,32454,32886,63534,66884,237625,237859,237860,237875,237941,237942,237979	[A/S/T]-[E/K/N]-[S/V]-P-T-E-Q-Q-E-P-[N/S/T]-N-[K/S/V]-P-[A/T]-E-Q	3,88
Merozoite surface protein 1	4815,18759,20013,20042,22333,22809,22815,30479,35235,38186,44354,44355,52324,56142,56956,58058,58059,59932,62054,62055,64003,66238,67762,71533, … (list is truncated)	It could not be obtained	
Merozoite surface protein 1 precursor	2777,4417,6149,7639,8349,8350,11252,11439,11590,12289,18517,18761,18859,20012,20014,2		

	2828,22841,30095,30476,30478,30480,30896,31214,32970,33715, … (list is truncated)	It could not be obtained	
Merozoite surface protein 2	780,21881,46258,142387,~~142414~~,142435,~~237708~~	K-T-D-G-X-K-G-E-E-S-E	6,63
Merozoite surface protein 3	2167,~~11792~~,23729,42057,44750,47302,47303,73683,119616	M-L-S-H-L-Y-V-S-S-K-D-K-E-N-I-S-K-E-N-D	5,25
Merozoite surface protein 6	11591,27084,~~38285~~,49034,57650,150372,~~150472~~	I-[L/V]-G-X-W-E-F-[G/K]-[G/N]-G-[A/I]-P	4,33
Merozoite surface protein-1	101715,101759,101871,101907,~~101925~~,~~101997~~,102082,125168,125169,8044,8738,10611,12781,12782,17492,28630,35438,36587,41286	S-Q-H-Q-C-V-K-K-Q	1,66
p101/acidic basic repeat antigen	463650,463651,467193,~~468962~~,469233,469234,472109,474217	P-E-P-T-V-T-N-E-E	10,00
PfEMP1	181590,~~181722~~,181787,181818,181823	L-S-A-T-D-V-X-L-E-K-I-A	4,91
precursor for the major merozoite surface antigens	101526,101528,101622,101623,101677,101756,101848,101855,101920,101955,101971,102090,102131,13528,101466,101494,101506,101507,101508,101513, … (list is truncated)	It could not be obtained	
Ring-infected erythrocyte surface antigen precursor	886,~~7766~~,~~11823~~,19004,~~27463~~,~~27675~~,29294,30474,32109,~~35817~~,43134,49801,59446,66932,67562,68166,73584	V-A-E-E-[H/Y]-V-E	2,85
ring-infested erythrocyte surface antigen	885,5761,8024,8730,9390,10164,11222,11813,11815,11816,11819,11820,11821,11822,11824,12518,12805,12888,27462,27674,30315,30473,32108,33177,33936, … (list is truncated)	It could not be obtained	
schizontegress antigen-1	644539,647826,647940,650560,652461	N-D-X-A-I-Q-X-D-F-X-L-L-D-N	2,14
serine-repeat antigen protein	24874,32628,227031,227066,227109,227134,227145,227153,227174,227178,227216,227228,227236,227262,227268,227270,227294,227308,227318,227345, … (list is truncated)	E-I-K-K-N-V-P-L-T	0,44
VAR2CSA	141608,141610,141612,141613,141616,141617,141627,141633,141645,141657,141658,141660,141663,141674,141676,141678,141681,141684,141686,141687, … (list is truncated)	N-E-K-A	1,0

Conclusion

The present study allows the investigator to know the state of art of the linear B cells epitope in *Plasmodium falciparum* (human host) according to the information available in the Immune Epitope Database (IEDB). In this way, we can know the type of samples and the antigens that are more frequent in this type of study, as well as the journals and years of publication. We deduce that 83% of the samples that have been analyzed come from Africa where the highest numbers of malaria cases are found.

On the other hand, the small number of scientific publications on this subject is surprising despite the fact that malaria is a very old problem and it was in

1992 when the largest numbers of papers on the subject were published. Subsequently, the numbers of publications decrease with time until it becomes constant over time. This trend may reflect that the prediction and validation of B cell epitopes in *Plasmodium falciparum* is not a subject of current scientific research but rather that the scientific community may be using the epitopes already published in the scientific literature. This last observation could explain the tendency to use Circumsporozoite protein in B cell epitopes as well as DNAJ protein, unlike other antigens, as shown in Table 1.

Finally, the consensus epitopes of linear B cells epitopes were determined using the Similarity Index defined in the present paper in order to be able to compare a consensus with each other.In fact, the Similarity Index of PfEMP1 was 10,00 which means that said consensus presents no variability of the epitopes, however the consensus obtained from the serine-repeat antigen protein whose index was 0,44. That is a great variability according to the data in IEDB. The conclusion of this work is that the predictions must be validated with experimental results and thus be able to combat malaria caused by *Plasmodium falciparum*.

Acknowledgment

I would like to acknowledge Dr. Karl E Lonngren for his unconditional help. He is a person dedicated to science and his contributions help improve this work.

Source of Support: Nil
Conflict of Interest: Nil

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