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Immunoinformatics Approach-Multiple Peptides Vaccine Design from Glycoprotein E of Herpes Simplex Virus-3

Sahar Obi Abd Albagi[1*], Safaa Hag Ahmed[2], Thana Eljozoli Mohamme[3], Esameldeen Ahmed Adam[1] and Mohammed A Hassan[4]

[1]*Department of Microbiology, Africa City of Technology, Khartoum, Sudan*

[2]*Department of Physics, University of Al- Neelain, Sudan*

[3]*Department of Microbiology, Faculty of medical laboratory, The National Ribat University, Khartoum, Sudan*

[4]*Department of Biotechnology, Africa City of Technology, Khartoum, Sudan*

[*]**Corresponding author:** Sahar Obi Abd Albagi, Department of Microbiology, Africa City of Technology, Khartoum, Sudan, Tel: +249903772594; E-mail: saharalabady@gmail.com

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Abstract

Background: Herpes simplex virus (HSV) is a common human pathogen, causing infections of orofacial mucosal surfaces (HSV-1) and genital mucosal surfaces (HSV-2). Productive infection results in the formation of vesicular lesions in the mucosal epithelia, followed by spread of the virus to sensory neurons and establishment of a latent infection that may remain for the life of the host.

Material and method: All sequences of glycoprotein E [Human herpes virus 3] were obtained from NCBI and these sequences were subjected to IEDB predicted tools, including B cell and T cell examination, with B cell having multiple tests such as epitopes prediction, surface accessibility and antigenicity prediction; T cell included MHC I and MHC II predicted tools. Finally we used population coverage to select a highest percent of peptides related with different alleles.

Result: We obtained some candidate peptides as vaccine derived peptides from B cell test which had a highest score in Emini surface accessibility ("DEDKLDTNSVYEPYYHSDHAESSWVNRGESSRKAYDHNSPYIWPRNDYDGF") of 21.807, and "LKFVDTPESL" with score 1.061 for Kolaskar and Tongaonkar antigenicity test, in another hand we got a highest affinity of peptides that interacted with major coverage of different alleles in MHC I ("KAYDHNSPY") and in MHC II ("MWNYHSHVF").

Conclusion: The efficiency and safety degree in predicted candidate epitopes by computational examination methods are required to be estimated through studies of animal model, to check whether they are able to induce a good defending immune response or not with previous mentioned properties, and we considered this study as first promising peptide based vaccine of [Human herpes virus 3] glycoprotein E in comparison to the previous studies.

Keywords: Glycoprotein E; B-cell epitopes; Herpes virus 3; B-cell binders

Introduction

Herpes simplex virus (HSV) is a common human pathogen, causing infections of orofacial mucosal surfaces (HSV-1) and genital mucosal surfaces (HSV-2). Productive infection results in the formation of vesicular lesions in the mucosal epithelia, followed by spread of the virus to sensory neurons and establishment of a latent infection that may remain for the life of the host [1]. Nearly one half-billion people worldwide are infected with herpes simplex virus type 2 (HSV-2) and another one-quarter billion have genital infection caused by herpes simplex virus type 1 (HSV-1) [2,3]. The disease manifestations vary from asymptomatic genital infection to severe, recurrent ulcerative genital disease [4-6]. Genital herpes poses major risks to newborns delivered through an infected birth canal with an estimated 14,000 annual cases globally and a mortality of 60% if untreated [3,7]. HSV-2 genital infection carries a three-fold increased risk for acquisition and transmission of HIV [8]. The common cold sores caused by HSV-1 and the genital herpes lesions caused by HSV-2 are not life-threatening conditions, but serious pathology can result from infections of the cornea (keratitis) or central nervous system (encephalitis), and infection of newborns or immunocompromised individuals can result in severe disseminated disease [9], and Varicella-zoster virus (VZV) or human herpes virus 3 (HHV-3) is 1 of 9 human herpes viruses [10]. VZV is a human pathogen that spreads to children as varicella or chicken pox and reemerges later in life as zoster or shingles [11,12]. The virus is well adapted to its human host and infects most people in a given community [13]. The VZV genome is also the smallest among the human herpes viruses; it encodes 71 open reading frames, 3 of which are duplicated [14]. Of note, VZV lacks the herpes simplex virus 1 (HSV-1) ICP34.5 neuro virulence gene [15].

HSV is a member of a family of viruses whose genomes consist of a single large double-stranded DNA molecule [16], and consists of four components: [17] an electron-dense core containing viral DNA [18]; an icosadeltahedral capsid [19], an amorphous, at times eccentric layer of proteins, designated tegument, which surrounds the capsid; and an envelope [20]. The capsid consists of 162 capsomeres and is surrounded by the tightly adhering tegument, the envelope surrounds the capsid-tegument structure and consists of at least 10 glycosylated

and several non-glycosylated viral proteins, lipids, and polyamines [21].

The aim of the study is to predict effective epitope-based vaccine against human herpes virus-3 glycoprotein E Development in immune genetics will enhance apprehension of the impact of genetic factors on the inter individual and inter population variations in immune responses to vaccines that could be helpful for progress new vaccine strategies [22]. *In-silico*/reverse vaccinology had replaced conventional culture-based vaccine because it reduces the cost required for laboratory investigation of pathogen, also speeds up the time needed to achieve the results [23,24]. Therefore, using immunoinformatics approaches to predict this new kind of vaccine could be magnificently additive in the way forward of preventing varicella or chicken pox. Normally, the investigation of the binding affinity of antigenic peptides to the MHC molecules is the main goal when predicting epitopes. Using such tools and information leads to the development of new vaccines [25,26]. While these approaches permit the optimization of a vaccine for a specific population, the problem can also be reformulated to design a 'universal vaccine': a vaccine that provides maximum coverage on the whole worlds' population [27,28].

Materials and Methods

In-silico studies

A complete total sequences 130 of glycoprotein E [Human herpes virus 3] were obtained from NCBI in FASTA format in March 2016 , all sequences were identified from NCBI separately in Table 1. These sequences of Glycoprotein E were subjected to software of multiple sequence alignments by using CLUSTALW tool of BIOEDIT sequence alignment editor (version 7.0.9.1) in order to detect conserved regions between sequences (Figure 1). Then an applied analysis epitopes prediction test was done using different tools in immune epitope data base IEDP software.

Gene bank protein accession number	Date of collection	Country
CAA25034.1	1983	Netherland*
CAL40870.1	2006	US
AAF61669.1	2000	N/A
AIT53004.1	2014	Guinea Bissau
AIT53077.1	2014	Guinea Bissau
AIT53150.1	2014	Guinea Bissau
AIT53223.1	2014	Guinea Bissau
AIT53296.1	2014	Guinea Bissau
AIT53369.1	2014	Guinea Bissau
AIT53442.1	2014	Guinea Bissau
AIT53515.1	2014	Guinea Bissau
AIT53588.1	2014	Guinea Bissau
AIT53661.1	2014	Guinea Bissau
AIT53734.1	2014	Guinea Bissau
AIT53807.1	2014	Guinea Bissau
AIT53880.1	2014	Guinea Bissau
AIT53953.1	2014	Guinea Bissau
AIT54026.1	2014	Guinea Bissau
AIT54099.1	2014	Guinea Bissau
AIT54172.1	2014	Guinea Bissau
AIT54245.1	2014	Guinea Bissau
AIT54318.1	2014	Guinea Bissau
AIT54391.1	2014	Guinea Bissau
AIT54464.1	2014	Guinea Bissau

AIT54537.1	2014	Guinea Bissau
AIT54610.1	2014	Guinea Bissau
AKG56137.1	2015	UK*
AKG56210.1	2015	UK
AKG56283.1	2015	UK
AKG56356.1	2015	UK
AKG56429.1	2015	UK
AKG56502.1	2015	UK
AKG56575.1	2015	UK
AKG56648.1	2015	UK
AKG56721.1	2015	UK
AKG56794.1	2015	UK
AKG56867.1	2015	UK
AKG56940.1	2015	UK
AKG57013.1	2015	UK
AKG57086.1	2015	UK
AKG57159.1	2015	UK
AKG57232.1	2015	UK
AKG57305.1	2015	UK
AKG57378.1	2015	UK
AKG57451.1	2015	UK
AKG57524.1	2015	UK
AKG57597.1	2015	UK
AKG57670.1	2015	UK
AKG57741.1	2015	UK
AKG57814.1	2015	UK
AKG57887.1	2015	UK
AKG57960.1	2015	UK
AKG58031.1	2015	UK
AKG58106.1	2015	UK
AKG58179.1	2015	UK
AKG58252.1	2015	UK
AKG58325.1	2015	UK
AKG58398.1	2015	UK
AKG58471.1	2015	UK
AKG58544.1	2015	UK

AKG58617.1	2015	UK
AKG58690.1	2015	UK
AKG58763.1	2015	UK
AAY57677.1	2008	Japan
AAY57748.1	2008	Japan
AAK01047.1	2000	USA/Japan/Iceland
AAG48520.1	2000	USA/Japan/Iceland
AAP32865.1	2003	Thailand/Iceland/US
AAP32861.1	2003	Thailand/Iceland/US
AAP32856.1	2003	Thailand/Iceland/US
AAP32851.1	2003	Thailand/Iceland/US
AAP32846.1	2003	Thailand/Iceland/US
AAP32841.1	2003	Thailand/Iceland/US
AAP32836.1	2003	Thailand/Iceland/US
AAP32831.1	2003	Thailand/Iceland/US
AGC94542.1	2015	Mexico
AGM33090.1	2013	China (Unpublished)
P09259.1	1983	Netherland
Q9J3M8.1	2000	Japan/US
AAT07825.1	2000	Japan/US/Netherland
AAT07749.1	2004	US/Canada/Netherland
AFJ68569.1	2012	US (Unpublished)
AEW89484.1	2012	Germany
AEW89340.1	2012	Germany
AEW89268.1	2012	Germany
AEW89196.1	2012	Germany
AEW89124.1	2012	Germany
AEW89052.1	2012	Germany
AEW88980.1	2012	Germany
AEW88908.1	2012	Germany
AEW88836.1	2012	Germany
AEW88764.1	2012	Germany
AEW88692.1	2012	Germany
AEW88620.1	2012	Germany
AEW88548.1	2012	Germany
AEW88476.1	2012	Germany

AEW88404.1	2012	Germany
AEW88332.1	2012	Germany
AEW88260.1	2012	Germany
AEW88188.1	2012	Germany
AEW88116.1	2012	Germany
AEW88044.1	2012	Germany
CAA27951.1	1986	Netherland
AGL51024.1	2010	N/A
AFO85645.1	2012	US
AFO85572.1	2012	US
ABF22298.1	2006	US/Netherland/Canada/Japan
ABF22225.1	2006	US/Netherland/Canada/Japan
ABF22152.1	2006	US/Netherland/Canada/Japan
ABF22079.1	2006	US/Netherland/Canada/Japan
ABF22006.1	2006	US/Netherland/Canada/Japan
ABF21933.1	2006	US/Netherland/Canada/Japan
ABF21860.1	2006	US/Netherland/Canada/Japan
ABF21787.1	2006	US/Netherland/Canada/Japan
ABF21714.1	2006	US/Netherland/Canada/Japan
ABF21641.1	2006	US/Netherland/Canada/Japan
ABF21568.1	2006	US/Netherland/Canada/Japan
CAI44910.1	2004	N/A
AAK19250.1	2001	Thailand/Iceland/US
AAK19955.1	2001	Thailand/Iceland/US
AAK19963.1	2001	Thailand/Iceland/US
AAK19972.1	2001	Thailand/Iceland/US
AAK19946.1	2001	Thailand/Iceland/US
AAK01056.1	2000	N/A
AAG32558.1	2000	N/A
AON76680.1	2016	UK
AON76607.1	2016	UK
AON76534.1	2016	UK

Table 1: Countries and accession numbers of retrieved sequences from NCBI; *Ref sequence, remaining data as extra file, N.A*: not available.

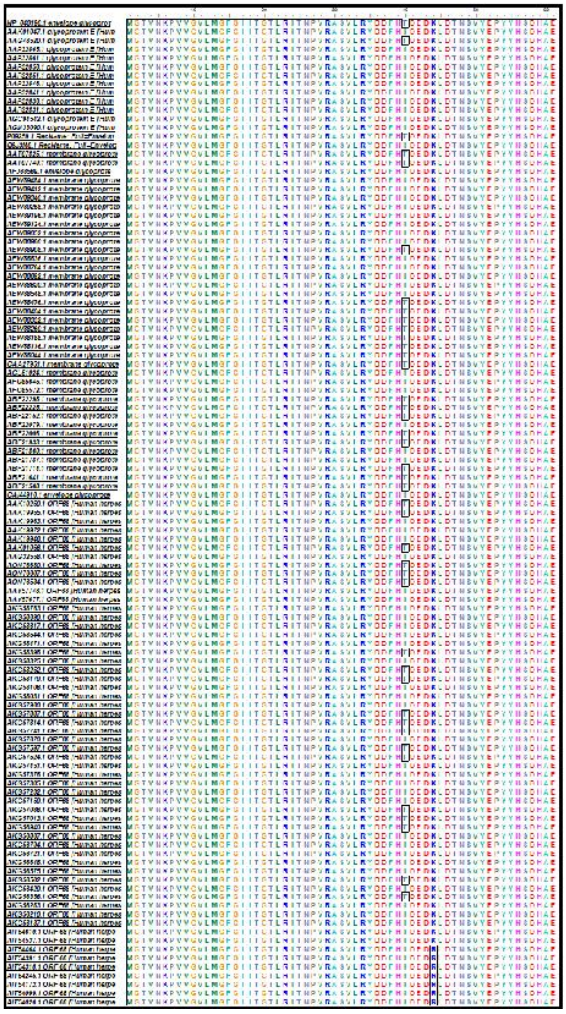

Figure 1: Partial alignment of all sequences observed as conserved peptides and non-conserved peptides covered by square, used BIOEDIT (version 7.0.9.1).

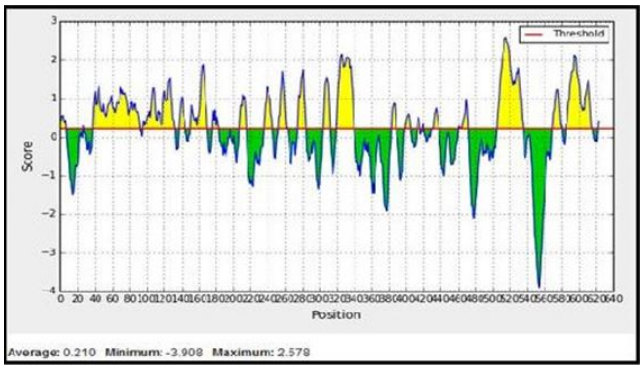

Figure 2: Bepipred linear Epitope Prediction, yellow diagram above threshold describe any predicted peptides.

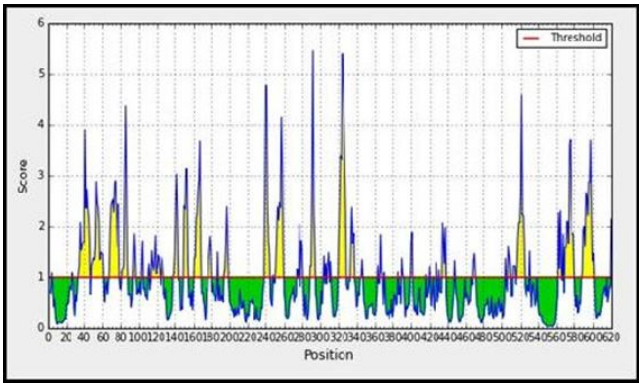

Figure 3: Emini surface accessibility of peptides prediction, the average is 1.000 the yellow part is considered as predicted peptides with maximum score and green part as unpredicted peptides (Epitopes prediction).

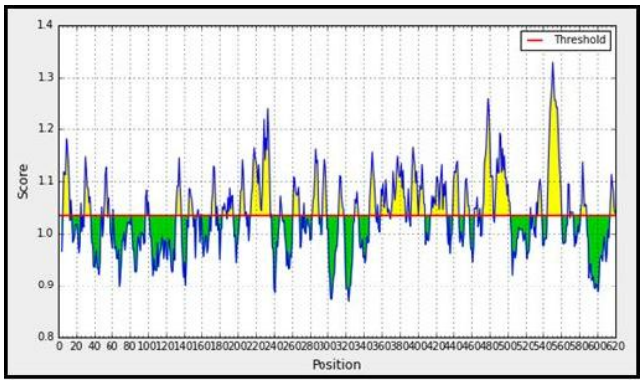

Figure 4: Kolaskar and Tongaonkar Antigenicity Result of peptides prediction, with average score of 1.034 as threshold, yellow part shows predicted peptides and green part shows unpredicted peptides.

Epitopes Prediction

Predication of B-cell epitopes

The initial test for identification by B cells is BepiPred-test which was done from immune epitope database [27] as linear prediction of B-cell epitopes after being selected from conserved region with a default threshold value of 0.210. A combination between hidden (Parker and Levitt) method and Markov model (HMM) was done to predict epitopes accurately (Figure 2-4) [27].

Surface accessibility prediction

Through prediction of Emini surface accessibility tool of IEDB [28], the surface accessibility of epitopes were predicted from the region where they were conserved and the default threshold holding value is 1.0.

Epitopes antigenicity sites

The antigenicity method of Kolaskar and Tongaonker was proposed to determine the sites of antigenic epitopes with a default threshold value of IEDB (Table 2).

No.	Start	End	Length	Peptides	Conserved	Emini score (1.000)	Antigenicity score (1.034)
1	1	6	6	MGTVNK	MGTVNK	0.695	0.95
2	38	91	54	FHTDEDKLDTNSVYEPYYHSDHAESSWVNRGE	DEDKLDTNSVYEPYYH	21.807	0.989
				SSRKAYDHNSPYIWPRNDYDGF	SDHAESSWVNRGESS		
					RKAYDHNSPYIWPRN		
					DYDGF		
3	96	132	37	HEHHGVYNQGRGIDSGERLMQPTQMSAQED	HEHHGVYNQGRGIDS	0.484	0.976
				LGDDTGI	GERLMQPTQMSAQE		
					DLGDDTGI		
4	137	144	8	TLNGDDRH	TLNGDDRH	1.705	0.94
5	151	170	20	QRQYGDVFKGDLNPKPQGQR	QRQYGDVFKGD	1.769	0.995
					NPKPQGQR	5.415	0.951
6	176	183	8	VEENHPFT	VEENHPFT	1.14	1.004
7	207	215	9	TCTGDAAPA	TCTGDAAPA	0.274	1.025
8	236	245	10	CAENTKEDQL	CAENTKEDQL	1.283	0.992
9	253	261	9	QGKKEADQP	QGKKEADQP	4.996	0.957
10	275	284	10	ELDPPEIEPG	ELDPPEIEPG	1.309	0.989
11	304	311	8	RGSDGTST	RGSDGTST	1.451	0.916
12	320	339	20	KGDEKTRNPTPAVTPQPRGA	KGDEKTRNPTPAVTPQ	7.185	0.968
					PRGA		
13	383	388	6	IDPTCQ	IDPTCQ	0.499	1.07
14	399	405	7	HPNAPQC	HPNAP	1.421	1.015
15	413	416	4	CTFT	CTFT	0.34	1.08
16	432	438	7	CEHADNY	CEHADNY	0.846	1.034
17	463	472	10	LKFVDTPESL	LKFVDTPESL	0.54	1.061
	505	535	31	EERGFPPTAGQPPATTKPKEITPVNPGTSPL	EERGFPP	1.897	0.953
					AGQPPATTKPKEITPV	1.314	1.008
					NPGTSPL		
18	570	580	11	RVDKSPYNQSM	RVDKSPYNQSM	3.187	0.993
19	585	616	32	LPVDDFEDSESTDTEEEFGNAIGGSHGGSSYT	GSSYT	1.081	0.994
					NAIGGSH	0.321	0.98
					DDFEDSESTDTEEEF	6.339	0.916

Table 2: Predicted peptides in Bepipred test with their Emini and Antigenicity score for each peptide.

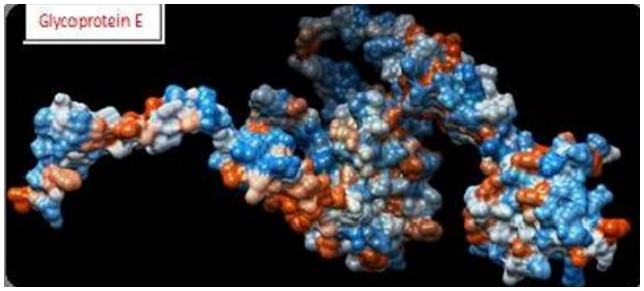

Figure 5: 3D Structure of Glycoprotein E, obtained by "Chimera 1.8" program.

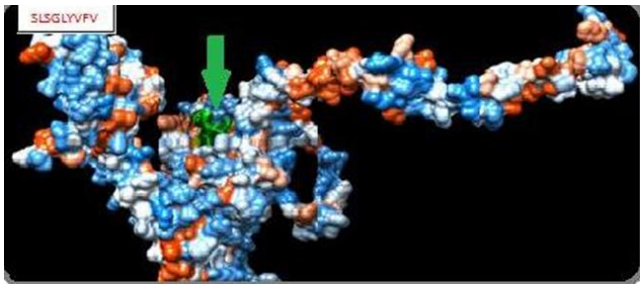

Figure 6: 3D of promising conserved peptide with highest score in population coverage in MHC I, obtained by 'Chimera 1.8' program.

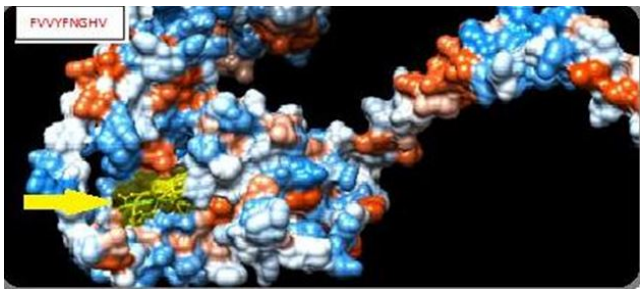

Figure 7: 3D of promising conserved peptide with highest score in population coverage in MHC II, obtained by 'Chimera 1.8' program.

MHC Epitopes Prediction

Several specific tests of IEDB were used to select predicated peptides by determining the binding of MHC class I, MHC class I under specific scoring of inhibitory concentration 50.

MHC class I epitope prediction

First step in major histocompatibility class I affinity test of prediction process has been tested on large set of different peptide MHC class I measurement affinity on the IEDB [29], this process has been done by artificial neutral network (ANN) method with specific length of nine amino acids, score of bound used ≤ 100 IC_{50} of conserved epitopes for structural protein were chosen for further analysis [30].

MHC class II binding prediction

Subsequent immunological steps to predicate targeting peptides included MHC class II test to estimate the available MHC class II in world with binding prediction tools performances. MHC II binding tool from IEDP was used by relating NN align as prediction process. Then value of prediction of ≤ 500 IC_{50} of conserved epitopes were chosen for more analysis [31].

Population coverage

The estimation of the population coverage was based on the result of MHC. Nemours established tools to predict population coverage of T cell epitope-based analytical and vaccine-based on MHC binding with or without T cell restriction data [32]. All alleles that interact with epitopes from glycoprotein E were exposed to population coverage tool of IEDB to estimate the whole world population coverage of MHC class I, and MHC II alleles for glycoprotein E [32].

Homology modeling

The 3D structure for Glycoprotein E obtained using Raptor X structure prediction server [33] and Chimera 1.8 [34] was used to show the structure of suggested T cell epitopes that can be utilized for vaccine development as shown in Figures 5-7.

Results

Prediction of B cell epitopes

Glycoprotein E of human herpes virus 3 was tested to isolate best peptides passing specific score for the major tests in B cell *via* Bepipred linear epitope production, Emini surface accessibility and Kolaskar and Tongaonkar antigenicity tools of IEDB. Bepipred linear epitope calculation method used specific average binding score for glycoprotein E of 0.210. All values equal or above than score of default threshold were considered as potential B-cell binders [35]. Concerning Emini surface accessibility prediction, the binding score was 1.00. All values equal or greater than the default threshold were predicted to have good surface accessibility. The last test of protein used Kolaskar and Tongaonkar antigenicity prediction tool of IEDB to predict peptides with probability of being antigenic, with an average threshold value of 1.034. Any epitope of target protein with values equal or greater than the average score were considered as antigenic peptides. The values resulting after peptides tested for Glycoprotein E by the three tests are shown in Table 2. The highest result of scores was in Emini surface accessibility ("DEDKLDTNSVYEPYYHSDHAESSWVNRGESSRKAYDHNSPYIW PRNDYDGF") with score 21.807, and "LKFVDTPESL" with score 1.061 for Kolaskar and Tongaonkar antigenicity test.

Prediction of T-cell epitopes and MHC class I interaction analysis

The epitopes sequences of glycoprotein E were subjected to MHC I in binding prediction tool of IEDP and T-cell epitope was predicted to interact with different MHC class I alleles using ANN (artificial natural network) as prediction method and a length of nine amino acids [35] using the same score for each peptide interacted with MHC I. The top

three peptides which had highest affinity to interact with largest coverage of different alleles were "KAYDHNSPY" (HLA-B*35:01, HLA-B*15:01, HLA-B*15:02, HLA-*30:01), "MWNYHSHVF" with HLA-B*35:01, HLA-B*15:01, HLA-A*24:02, HLA-A*23:01 and "SSYTVYIDK" with HLA-A*11:01, HLA-A*03:01, HLA-A*68:01,HLA-A*30:01. These data found in Table 3.

Alleles	Start	End	Length	Peptides	Seq_num	IC_{50}	Rank
HLA-A*30:01	324	332	9	KTRNPTPAV	1	2.3	0.2
HLA-A*30:01	565	573	9	RVKAYRVDK	1	2.92	0.2
HLA-A*68:02	478	486	9	FVVYFNGHV	1	3.35	0.2
HLA-A*29:02	357	365	9	FSLAMHLQY	1	3.6	0.1
HLA-A*11:01	613	621	9	SSYTVYIDK	1	4.45	0.1
HLA-A*68:02	309	317	9	TSTYATFLV	1	4.49	0.2
HLA-A*68:01	415	423	9	FTSPHLAQR	1	6.82	0.1
HLA-A*68:02	3	11	9	TVNKPVVGV	1	7.08	0.2
HLA-A*68:02	24	32	9	ITNPVRASV	1	7.51	0.2
HLA-A*68:02	355	363	9	DTFSLAMHL	1	7.86	0.2
HLA-A*02:01	471	479	9	SLSGLYVFV	1	8.98	0.1
HLA-A*02:01	295	303	9	YLGVYIWNM	1	9.47	0.1

Table 3: Conserved peptides interacted with MHC I and linked alleles, also show percentile rank number and IC_{50} for each peptide.

Prediction of T helper cell epitopes and interaction with MHC class II

Via MHC class II binding prediction tools of IEDB and depending on NN align with IC_{50} of 500 was used in analysis of glycoprotein E in predicated epitopes which interacted with MHC II, the top core sequence FVVYFNGHV bind to highest number of alleles "16 alleles" (HLA-DRB1*15:01, HLA-DRB1*01:01, HLA-DRB5*01:01, HLA-DRB1*13:02, HLA- DRB1*07:01, HLA-DRB1*13:02, HLA-DRB1*04:05, HLA-DRB1*04:04, HLA-DRB3*01:01, HLA-DRB1*04:01, HLA- DRB3*01:01, HLA-DQA1*01:01/DQB1*05:01, HLA-DRB1*07:01, HLA-DPA1*02:01/DPB1*01:01, HLA-DRB1*11:01, HLA- DRB3*01:01) (Table 4).

Core sequence	Start	End	Alleles	Peptides sequence	IC_{50}	Rank
FLICTAKRM	556	564	HLA-DRB1*01:01	LVIFLICTAKRMRVK	4.2	0.19
	564	565	HLA-DRB1*01:01	CLVIFLICTAKRMRV	4.5	0.39
	556	564	HLA-DRB1*01:01	VIFLICTAKRMRVKA	4.8	0.62
	556	564	HLA-DRB1*01:01	LCLVIFLICTAKRMR	5	0.79
	556	564	HLA-DRB5*01:01	LVIFLICTAKRMRVK	5	0.84
WTGGLAAVV	541	549	HLA-DRB1*01:01	YAAWTGGLAAVVLLC	3.5	1.06
	541	549	HLA-DRB1*01:01	RYAAWTGGLAAVVLL	4.5	1.15
	541	549	HLA-DQA1*05:01/DQB1*03:01	LRYAAWTGGLAAVVL	5.8	0.49
	541	549	HLA-DQA1*05:01/DQB1*03:01	YAAWTGGLAAVVLLC	6.1	0.55
YRVDKSPYN	569	577	HLA-DRB3*01:01	AYRVDKSPYNQSMYY	6.2	0.21
	569	577	HLA-DRB3*01:01	MRVKAYRVDKSPYNQ	5.5	0.15
	569	577	HLA-DRB3*01:01	RMRVKAYRVDKSPYN	6.5	0.22
	569	577	HLA-DRB3*01:01	YRVDKSPYNQSMYYA	8.4	0.38
	569	577	HLA-DRB5*01:01	VKAYRVDKSPYNQSM	66.1	11.97
	569	577	HLA-DRB1*04:01	RVKAYRVDKSPYNQS	75.4	6.09
CTGDAAPAI	207	215	HLA-DQA1*05:01/DQB1*03:01	LTCTGDAAPAIQHIC	13.5	2.25
	208	216	HLA-DRB1*01:01	PSLTCTGDAAPAIQH	128.3	33.79
	208	216	HLA-DRB1*01:01	LTCTGDAAPAIQHIC	140.7	35.19

	208	216	HLA-DRB3*01:01	TCTGDAAPAIQHICL	155.7	5.89
	209	217	HLA-DQA1*01:02/DQB1*06:02	LTCTGDAAPAIQHIC	236.8	16.1
TFTSPHLAQ	414	422	HLA-DRB1*11:01	NSGCTFTSPHLAQRV	237.3	22.12
	413	421	HLA-DRB1*07:01	NSGCTFTSPHLAQRV	242.3	23.61
	413	421	HLA-DPA1*01/DPB1*04:01	GCTFTSPHLAQRVAS	251.7	9.86
	420	428	HLA-DRB1*07:01	TFTSPHLAQRVASTV	254.2	24.2
	413	421	HLA-DPA1*01/DPB1*04:01	SGCTFTSPHLAQRVA	263.6	10.14
	412	420	HLA-DRB1*15:01	GCTFTSPHLAQRVAS	267	20.43

Table 4: Conserved core peptides and their peptides interacted with MHC II and linked alleles, also show percentile rank number and IC_{50} for each peptide (Remaining data in extra file).

Examination of population coverage

Epitopes of MHC I and MHC II were analyzed to detect the accurate affinity for each predicted peptides with their interacted alleles, and it was used to determine the actual percent of the world coverage. The aim from Population coverage test was to observe all epitopes of the world coverage binds to MHC I alleles and MHC II alleles also to join MHC 1 and MHC 11 as well as a selection of the best promising epitope for each test [36].

The best epitope with the highest coverage for MHC I was "SLSGLYVFV" with the coverage percent "42.53%", and the coverage of population set for whole epitopes was 97.74%, for MHC II the best one epitope was "FVVYFNGHV" with highest coverage percent "68.32%" and the coverage of population set was 81.65% (Table 5, Figure 8,9).

Note: Same alleles were not available and therefore not included in the calculation.

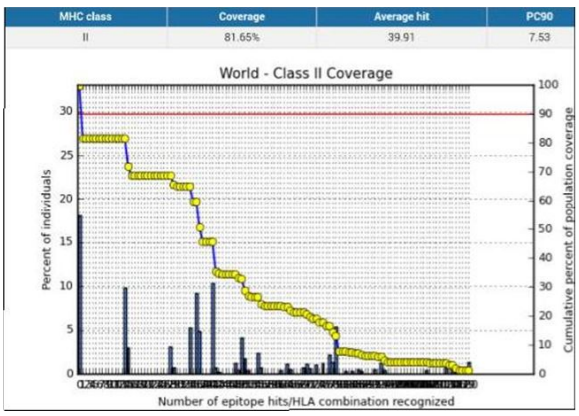

Figure 8: Result of MHC class one score with explanation diagram of population coverage of the world. PC90* minimum number of epitope hits/combination recognized in by 90% of population.

MHC I Peptides	The coverage	MHC II Peptides	The coverage
SLSGLYVFV	42.53%	FVVYFNGHV	68.32%
HMWNYHSHV	40.60%	ILHDGGTTL	61.50%
YLGVYIWNM	39.08%	RMRVKAYRV	61.09%
VLLCLVIFL	39.08%	IVVNTSTLF	59.76%
Epitope set	97.74%		81.65%

Table 5: Summarizing the high score population coverage in MHC I and MHC II with their epitopes set percent.

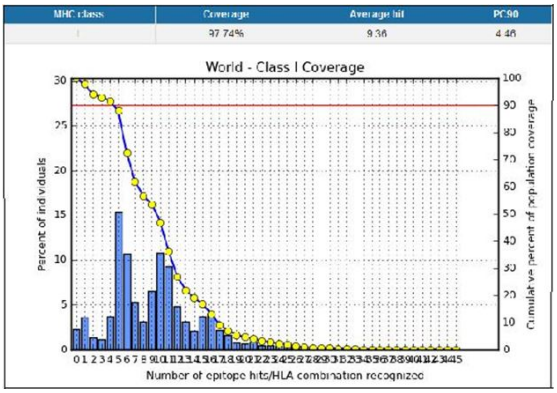

Figure 9: Result of MHC class two score with explanation diagram of population coverage of the world. PC90* minimum number of epitope hits/combination recognized in by 90% of population.

Discussion

The purpose of this study was to obtain candidate peptide-based vaccine for [Herpes simplex virus 3] glycoprotein E, the study selected Herpes virus based on a surprising number of spreading this disease among people and we specified this selecting by studies of the virulence factors and determined "Glycoprotein E" as good immunogenic part designed for targeting and fasting stimulation to immune response. So we used immunoinformatics examinations accordingly to previously proposed idea to achieve the best response with little vaccine dose using candidate peptide-based vaccine. Many studies used immunoinformatics tools as vaccine designated tools to

several viruses, such as Zika virus, Ebola, human papilloma virus, merkel cell polyoma virus and Duvenhage Rabies Virus. So firstly we must be achieve the FASTA format of "Glycoprotein E" with identified number "NP_040190.1" from NCBI data base followed by the initial antibody epitope prediction of B cell examination by Bepipred linear Epitope predication method to predict the location of B-cell using a combination of a hidden Markov model and propensity scale method. The result with scores above threshold "0.210" was considered to be part of an epitope [36-40].

All successful predicted epitopes were examined in Emini surface accessibility scale "1.00" based on formulae to calculate the surface factional probability. The third examination done was Kolaskar and Tongaonkar antigenicity scale "1.034" which belong to physicochemical properties of amino acids remaining and their occurring frequencies in epitopes developed to antigenic determinant on protein, for that reason we considered any peptides scored both tests have candidate properties peptide can be selected as excellent stimulation in immune reaction determined by B-cells. So we found a number of peptides having a highest score including "DEDKLDTNSVYEPYYHSDHAESSWVNRGESSRKAYDHNSPYIWP RNDYDGF" with score 21.807 and "LKFVDTPESL" with score 1.061 in surface accessibility and antigenicity tests consequently, but these peptides don't achieve exact score for both tests.

One of the importances in methods in IEDB-analysis resource that exists as complementary steps to B-cell was MHC binding prediction tools for T-cell epitopes, these tools based on used IC_{50} values was predicted for any peptides binding to target molecules of MHC. Firstly, we tested our peptides to know if any amino acids sequence has ability in specific binding to MHC class one molecules and we found multi-peptides in target sequence with different alleles binding to each on candidate peptides. The subsequence step was examined by specific binding to MHC class two molecules, this tool was available with different methods to predict epitopes, and from these methods we selected NN-align approach. These services were also developed to predict multiple alleles independent of CD4-T cell immunogenicity on the population.

The T cell epitope results recognized one specific immunogenic peptide of Glycoprotein E (471-479) and (478-486) that were able to stimulate cellular immunity since they were predicted to bind to 2 and 16 different HLA alleles (HLA- A*02:01, HLA-A*02:06), (HLA-DRB1*15:01, HLA-DRB1*01:01, HLA-DRB5*01:01, HLA-DRB1*13:02, HLA-DRB1*07:01,HLA-DRB1*13:02, HLA-DRB1*04:05, HLA-DRB1*04:04, HLA-DRB3*01:01, HLA-DRB1*04:01, HLA-DRB3*01:01, HLA- DQA1*01:01/ DQB1*05:01, HLA-DRB1*07:01, HLA-DPA1*02:01/ DPB1*01:01, HLA-DRB1*11:01, HLA-DRB3*01:01) consequently.

All epitopes predicted were tested using population coverage tool of IEDB to given measured percentage of people in whole world who have potential to developed immune response as vaccine contains this epitope (Table 5).

Peptide results in our population coverage mentioned availability or coverage the linked alleles with it result to induced specific immunity more reporting in different population with percentage of each peptide to select a highest score. We considered four peptides as top promising immunogenic which prevents any type of hyper-immunogenic responses at the same time, and these peptides can be safely used to at all population even for an immunocompromised patient. Due to these properties of slight reaction and quick cellular immunity response with limited sensitivity reaction, no problem was reported with people who have a weak immune system. Our greatest outcome for MHC I, MHC II classes create it best epitope which can be used for vaccine design as it has the ability to stimulate T cell immune reaction.

Conclusion

The efficiency and degree of safety in predicted candidate epitopes by used computational examination methods are required to be estimated through studies of animal model, to check whether they were able to induce a good defending immune response or not with previous mentioned properties. There are 130 sequences of glycoprotein E available in the database at that time; so these numbers of sequences are considered good to be evaluated increasing significance of the induced immunity result. The succeeding projected peptides are commended as "multiple peptides vaccine design" against HSV3; "SLSGLYVFV" and "FVVYFNGHV". This vaccine will cover good population coverage and fewer side effects among life attenuated vaccine and we could see potential induced result of "DEDKLDTNSVYEPYYHSDHAESSWVNRGESSRKAYDHNSPYIWP RNDYDGF" and "LKFVDTPESL" in B-cell predicted examination.

References

1. Taylor TJ, Brockman MA, McNamee EE, Knipe DM (2002) Herpes simplex virus: Front Biosci 7: d752-d764.
2. Looker KJ, Magaret AS, Turner KM, Vickerman P, Gottlieb SL, et al. (2015) Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One 10: e114989.
3. Looker KJ, Magaret AS, May MT, Turner KM, Vickerman P, et al. (2017) First estimates of the global and regional incidence of neonatal herpes infection. Lancet Glob Health 5: e300-e309.
4. Wald A, Zeh J, Selke S, Ashley RL, Corey L, et al. (1995) Virologic characteristics of subclinical and symptomatic genital herpes infections. The New England journal of medicine 333: 770-775.
5. https://doi.org/10.1056/NEJM199509213331205 PMID: 7643884.
6. Tronstein E, Johnston C, Huang ML, Selke S, Magaret A, et al. (2011) Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. Jama 305: 1441-1449.
7. Corey L, Adams HG, Brown ZA, Holmes KK (1983) Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med 98: 958-972.
8. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, et al. (1997) The acquisition of herpes simplex virus during pregnancy. N Engl J Med 337: 509-515.
9. Wald A, Link K (2002) Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons. a meta- analysis. J Infect Dis 185: 45-52.
10. Jarosinski KW, Carpenter JE, Buckingham EM, Jackson W, Knudtson K, et al. (2018), May. Cellular Stress Response to Varicella-Zoster Virus Infection of Human Skin Includes Highly Elevated Interleukin-6 Expression. In Open Forum Infectious Diseases 5: 118.
11. Weller TH, Varicella, herpes zoster (1983) Changing concepts of the natural history, control, and importance of a notso-benign virus. N Engl J Med 309: 1434-1440.
12. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, et al. (2015) Varicella zoster virus infection. Nat Rev Dis Primers 1: 15016.
13. Hope-Simpson RE (1965) The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med 58: 9-20.
14. Davison AJ, Scott JE (1986) The complete DNA sequence of varicella-zoster virus. J Gen Virol 67: 1759-1816.

15. Orvedahl A, Alexander D, Tallóczy Z (2007) HSV-1 ICP34.5 confers neurovirulence by targeting the Beclin 1 autophagy protein. Cell Host Microbe 1: 23-35.
16. Wildy P, Herpes (1973) history and classification. In: Kaplan AS, ed. The viruses. New York: Academic Press 1-25.
17. Roizman B. Herpesviridae. In: Fields BN, Knipe DM, Howley PM, eds. Fields virology. Philadelphia: Lippincott-Raven 1996: 2221-2230.
18. Roizman B, Sears AE (1996) Herpes simplex viruses and their replication. In: Fields BN, Knipe DM, Howley PM, eds. Fields virology. Philadelphia: Lippincott-Raven 2231-2295.
19. Ward PL, Roizman B (1994) Herpes simplex genes: the blueprint of a successful human pathogen. Trends Genet 10: 267-74.
20. Chou J, Kern ER, Whitley RJ, Roizman B (1990) Mapping of herpes simplex virus-1 neurovirulence to 34.5, a gene nonessential for growth in culture. Science 250: 1262-1266.
21. Whitley RJ, Kimberlin DW, Roizman B (1998) Herpes simplex viruses. Clinical Infectious Diseases 26: 541-553.
22. Lemaire D, Barbosa T, Rihet P (2012) Coping with genetic diversity: the contribution of pathogen and human genomics to modern vaccinology. Braz J Med Biol Res 45: 376-385.
23. Patronov A, Doytchinova I (2013) T-cell epitope vaccine design by immunoinformatics. Open Biol 3: 120139.
24. Tomar N, De RK (2010) Immunoinformatics: an integrated scenario. Immunology 113: 153-168.
25. Toussaint NC, Maman Y, Kohlbacher O, Louzoun Y (2011) Universal peptide vaccines - optimal peptide vaccine design based on viral sequence conservation. Vaccine 29: 8745-8753.
26. Mohammed AA, ALnaby AM, Sabeel SM, AbdElmarouf FM, Dirar AI, et al. (2018). Epitope-based peptide vaccine against Fructose-bisphosphatealdolase (FBA) of Madurella mycetomatis using immunoinformatics approaches. bioRxiv 352625.
27. Larsen JE, Lund O, Nielsen M (2006) Improved method for predicting linear B-cell epitopes. Immunome Res 2: 2.
28. Emini EA, Hughes JV, Perlow DS, Boger J (1985) Induction of hepatitis A virus-neutralizing antibody by a virus-specific synthetic peptide. J Virol 55: 836-839.
29. Andreatta M, Nielsen M (2015) Gapped sequence alignment using artificial neural networks: application to the MHC class I system. Bioinformatics 32: 511-517.
30. Nielsen M, Lundegaard C, Worning P, Lauemøller SL, Lamberth K, et al. (2003) Reliable prediction of T-cell epitopes using neural networks with novel sequence representations. Protein Science 12: 1007.
31. Wang P, Sidney J, Dow C, Mothe B, Sette A, et al. (2008) A systematic assessment of MHC class II peptide binding predictions and evaluation of a consensus approach. PLoS Comput Biol 4: e1000048.
32. Bui HH, Sidney J, Dinh K, Southwood S, Newman MJ, et al. (2006) Predicting population coverage of T-cellepitope-based diagnostics and vaccines. BMC bioinformatics 7: 153.
33. Kallberg M, Wang H, Wang S, Peng J, Wang Z, et al. (2012) Template-based protein structure modeling using the RaptorX web server. Nature protocols 7: 1511-1522.
34. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, et al. (2004) UCSF Chimera-a visualization system for exploratory research and analysis. J comput chem 25: 1605-1612.
35. Elgenaid SNEM, Al-Hajj EM, Ibrahim AA, Essa MEA, Abu-haraz AH, et al. (2018) Prediction of Multiple Peptide Based Vaccine from E1, E2 and Capsid Proteins of Rubella Virus: An In-Silico Approach. Immunome Res 14: 146.
36. Albagi SOA, Ahmed OH, Gumaa MA, Abd_elrahman KA, Abu-Haraz AH, et al. (2017) Immunoinformatics-PeptideDriven Vaccine and In silico Modeling for Duvenhage Rabies Virus Glycoprotein G. J Clin Cell Immunol 8: 517.
37. Abu-haraz AH, Abd-elrahman KA, Ibrahim MS, Hussien WH, Mohammed MS, et al. (2017) Multi Epitope Peptide Vaccine Prediction against Sudan Ebola Virus Using Immuno-Informatics Approaches. Adv Tech Biol Med 5: 2379-1764.
38. Badawi MM, Osman MM, Alla AAF, Ahmedani AM, hamed Abdalla M, et al. (2016) Highly conserved epitopes of Zika envelope glycoprotein may act as a novel peptide vaccine with high coverage: immunoinformatics approach. Am J Biomed Res 4: 46-60.
39. O. S. Awad-Elkareem MAE, Mohamed HA, Hassan HAE, Abu-haraz AH (2017) Prediction and Conservancy Analysis of Multiepitope Based Peptide Vaccine Against Merkel Cell Polyomavirus: An Immunoinformatics Approach. Immunome Res 13: 143.
40. Solares AM, Baladron I, Ramos T, Valenzuela C, Borbon Z, et al. (2011) Safety and immunogenicity of a human papillomavirus peptide vaccine (CIGB-228) in women with high-grade cervical intraepithelial neoplasia: first-in-human, proof-of-concept trial. ISRN obstetrics and gynecology.