

In Silico Analysis of a Proposed New Generation Multiepitopic Vaccine Against HIV: Can we Facilitate Immune System Challenges?

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Received: March 16, 2020; **Published:** March 25, 2020

Abstract

Development of new vaccines against infectious disease is permanent challenge in hygiene organization of every country. AIDS is one of the most dispersed infectious disease word wild. High prevalence of HIV may be because of the low ability of WHO in treatment of this disease. It seem vaccination can be a powerful strategy in this case. However several generation of vaccines introduced in past decade, development of the new effective vaccines is necessary. In this study, we introduced a new strategy in design and development of next generation of vaccines against HIV or other infectious diseases with hard treatment process. Employment of molecular adjuvants can help as a bypass in effective immune response. In this study we applied gp120 protein of HIV joined with CD4 in combined with different linkers. Epitope mapping of our construct confirmed high antigenic properties and effective recognition by B-cell and T-cell receptors.

Key words: HIV; AIDS; Vaccine; Epitope mapping

Introduction

The HIV is one of the major implications for public health worldwide [1]. After 30 years passed from HIV discovery as the cause of AIDS [2, 3], there are more than 36.7 million people affected by HIV. Moreover, there are about 90% of the infected population living in developing countries [4]. Behalf on unavailability of antiretroviral drugs in these countries, development of new effective HIV-1 vaccine generation would be necessary for the elimination of the AIDS pandemic. Unfortunately, there is no fully effective HIV vaccine till present time [8]. Normally, humoral immunity is the first challenge for vaccine-induced immunity against some infectious diseases, such as AIDS. Many researches have deal with humoral anti-HIV immunity [11]. The extraordinary worldwide genomic and phenotypic variance of HIV-1 is one of the greatest obstacles in

development of effective vaccines [14]. Some researchers have showed coincident emergence of CTL responses against virus during acute infection synchronous with the control of primary viremia [21-23]. One of the Viral targeting T lymphocyte responses limitations is the mutagenesis in T cell specific epitopes of virus for evading from cellular immunity [24-26]. It seem the most important limitation in achievement to an effective vaccine with cellular immune responses is non-protectively administration of them against HIV-1 infection and the virus rapidly establishes latent titer [27, 28]. Moreover, it is unclear whether T-cell specific vaccine will be able to function rapidly enough within the first few days in order to induce immunity against acute HIV-1 infection[10]. In this study, in order to overcome these limitations, we are designed a fusion protein containing a human CD4 protein as co-receptor of HIV-1 and

Citation: Atefeh Amiri, Ali Mohammad Ahadi, Hoda Ayat. (2020). In Silico Analysis of a Proposed New Generation Multiepitopic Vaccine Against HIV: Can we Facilitate Immune System Challenges? *Journal of Biotechnology and Immunology* 2(1).

HIV-1 envelope glycoprotein. This strategy can help immune system for firing of an effective response against HIV. Application of referable software in our in silico study can ensure this approach.

Material and Methods

Data collection and linker design and modeling

The 3D structure of human CD4 protein (PDB entry 1WIP) and HIV-1 gp120 glycoprotein (PDB entry 2nzx) were extracted from RCSB database [29]. According to Ryoichi Arai study at 2001 [30], six helical linkers were arranged and designed. The chosen linkers were developed to achievement an appropriate conformational and dynamical structure. The Servers and the software that are used in this study are listed in Table 1. The PHYRE2 server [31] and YASARA software [32] were employed for prediction of 3D structure of linkers. Our proposed fusion proteins were containing three different compartment with different source. We used the Chimera 1.8 software [33] to joining the CD4 to every linker and joining this complex to gp120 glycoprotein in the next step. Physical and chemical properties of the models were analyzed with ProtParam server [34].

The name of sever/soft-ware	Application	link Address	Ref.
RCSB	Protein Data Bank	http://www.rcsb.org/pdb/home/home.do	[29]
PHYRE2	Protein fold recognition server	www.sbg.bio.ic.ac.uk/phyre2/	[31]
YASARA	molecular-graphics, modeling and -simulation program	http://www.yasara.org/	[32]
Chimera	an extensible visualization system	https://www.cgl.ucsf.edu/chimera/	[33]
ProtParam	computation of various physical and chemical parameters of proteins	http://web.expasy.org/prot-param/	[34]
BCPREDS	B-cell epitope prediction server	http://ailab.ist.psu.edu/bcpred/	[35]
ABCpred	predict B cell epitope(s)	http://www.imtech.res.in/raghava/abcpred	[36]
Bcepred	Prediction of linear B-cell epitopes	http://www.imtech.res.in/raghava/bcepred/	[37]

Ellipro	Antibody epitope prediction	http://tools.immuneepitope.org/tools/ElliPro/iedb_input	[38]
CTLPred	prediction of CTL epitopes	http://www.imtech.res.in/raghava/ctlpred/	[39]
NetCTL	predicts CTL epitopes	http://www.cbs.dtu.dk/services/NetCTL/	[40]
EpiJen	T cell epitope prediction	www.ddg-pharm-fac.net/epijen/	[41]
TAPPred	T cell epitope prediction	http://www.imtech.res.in/raghava/tappred	[42]

Table 1: The list of server and software utilized in this study.

Prediction of B-cell epitopes

In order to the prediction of B-cell-specific epitopes, primary sequences of the proposed fusion proteins were submitted to 4 servers included; BCPREDS [35], ABCpred [36], Bcepred [37] and Ellipro [38]. In addition, Ellipro [38] server was utilized to predict conformational epitopes indictable by B lymphocytes.

Prediction of T-cell epitopes

T-cell-specific epitopes were identified by submission of primary sequences of the proposed fusion proteins, to CTLPred [39], EpiJen [41], TAPPred [42] and NetCTL [40] servers.

Results

Primary and 3D structure of linkers designed for joining of fusion protein compartments are listed in table 2. As it is shown in 3D structure of every linker, the number of proline amino acid residues can affect the structure effectively. Constructs are named "A" to "F" in this study based on the type of their linker. By utilizing of six linkers, six models were obtained respectively (figure 1).

A summary of physical and chemical properties of our proposed fusion proteins extracted from ProtParam server is presented in the table 3. Result showed that all of the presented models are hydrophobic. The Aliphatic index of the models show that all of them have a good thermostability. As it is shown in table 4, the main structure of fusion proteins consist of β -sheet and coil.

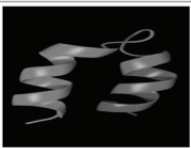

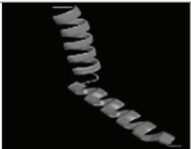

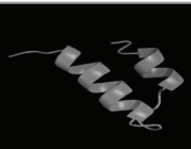
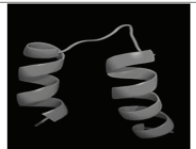
Linker name	linker A	linker B
Sequence	KEAAAKEAAAKEAAKALPPEAEAAKEAAA	AEAAAKEAAAKEAAKALPPEAEAAKEAA AKEAA
3D structure		
Linker name	linker C	linker D
Sequence	KEAAAKEAAAKEAAKALPPEAEAAKEAAK EAAAKE	KEAAAKEAAAKEAAKALPPPPEAEAAKEAAA
3D structure		
Linker name	linker E	linker F
Sequence	KEAAAKEAAAKEAAKALPPPPEAEAAKEAA A	AAAKEAAAKEAAKALPPPPEAEAAKEAAA
3D structure		

Table 2: The linkers designed in this study, sequence and 3D structures.

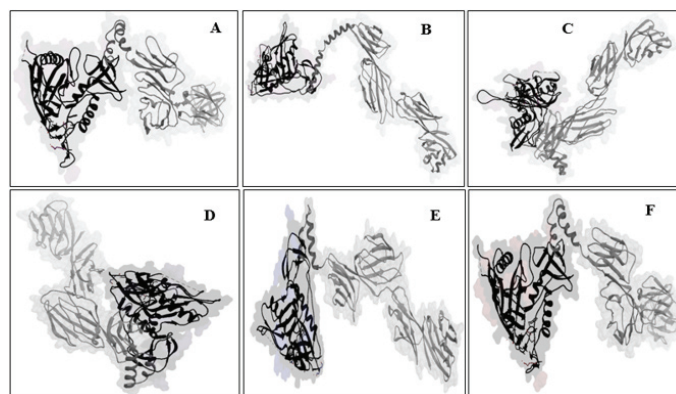


Figure 1: 3D structure of fusion proteins. CD4 part colored by light gray, the linker colored by gray and gp120 colored by black. Name of every model is based on that linker is applied for every construct. Linker must act as a spacer between two macromolecule.

Model	Number of amino acids	Molecular weight (kD)	Theoretical pI	Instability index	Aliphatic index	GRAVY
A	699	770.7	8.86	38.67/stable	86.05	-0.293
B	709	779.8	8.80	38.81/stable	85.68	-0.291
C	707	779	8.85	39.08/stable	85.5	0-.305
D	701	772.1	8.86	39.13/stable	85.81	-0.297
E	702	773.6	8.86	39.37/stable	85.68	-0.299
F	701	771.9	8.86	40.35/unstable	85.25	-0.300

Table 3: physical and chemical properties of the proposed fusion proteins.

Model	α -Helix (%)	β -Sheet (%)	Turn (%)	Coil (%)
A	10.6	40.3	8.9	40.2
B	13.5	39.8	8.2	38.5
C	13.8	39.9	7.6	39.6
D	12.1	40.4	7.7	39.8
E	11.4	40.2	7.7	40.7
F	11.5	40.2	8.3	40

Table 4: 2D structure of the proposed fusion proteins.

Different bioinformatics programs were used to predict the linear B-cell epitopes whose results are presented in table 5. In addition to the linear epitopes, discontinuous epitopes were predicted too, as it is shown in tables 6. For each model Elipro server predicted several conformational epitopes but we are chosen only the epitopes with 0.7 and higher score. Also, T lymphocyte specific epitopes were predicted by various programs and the results including the sequence of epitope, the PI of models and GRAVY score of them, are presented in table 7.

Motif	position (at "A" model)	Position (at "B" model)	Position (at "C" model)	Position (at "D" model)	Position (at "E" model)	Position (at "F" model)	Length	GRAVY Score	PI	Software
EVVIRS- VNFTD- NAKTI	516-531	526-541	524-239	518-533	519-534	519-534	16	0.1	6.17	1,2
EIFRPGG	674-680	684-690	682-688	676-682	677-683	677-683	7	-0.443	6.10	1,2,3
TIIFKQSS- GGD	576-586	586-596	584-594	578-588	579-589	579-589	11	-0.200	5.5	1,2,3
GKAMYAP- PISGQIRCS	639-654	649-664	647-662	641-656	642-657	642-657	16	-0.113	9.31	1,2
TWFN- STGS	612-619	622-629	620-627	614-621	615-622	615-622	8	-0.625	5.19	1,2,3
VVLVN- VTENFN- MWKND	395-410	405-420	403-418	397-412	398-413	398-413	16	-0.075	4.37	1,2,4
PIHYCA- PAGFAI	461-472	471-482	469-480	463-474	469-480	469-480	12	0.967	7.12	1,2,4
ISLWDQS- LKP- CVKLTP	420-435	430-445	428-443	422-437	464-475	464-475	16	0.087	8.20	1,2,4
NGTGPCT- NVSTVQC	481-494	491-504	489-502	483-496	484-497	484-497	12	-0.117	5.51	1,2,4
EVWGPTS	304-310	304-310	304-310	304-310	304-310	304-310	7	-0.529	4.00	2,3
CEVEDQK	84-90	84-90	84-90	84-90	84-90	84-90	7	-1.600	4.14	1,2,3,4
TLTLESP- PGSSPS- VQC	115-130	115-130	115-130	115-130	115-130	115-130	16	-.156	4.00	1,2,3,4
WQAER- ASSSK	215-224	215-224	215-224	215-224	215-224	215-224	10	-1.510	8.75	1,3,4
QIASKLR	562-568	572-578	570-576	564-570	565-571	565-571	7	-0.371	11	1,2,3,
TCTASQKK	15-22	15-22	15-22	15-22	15-22	15-22	8	-1.150	9.30	1,3,4

*Servers used for prediction are shown as number described as follows:

1) BCPred 2) ABCpred 3) Bcepred 4) Elipro.

Table 5: B-Cell Linear Motif Prediction of Model A-F

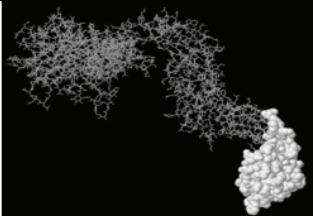
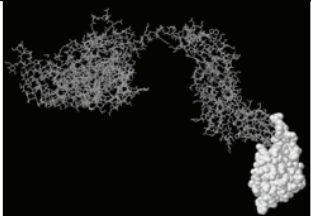
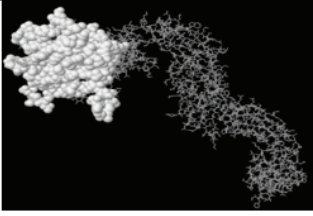
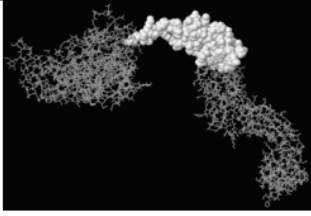
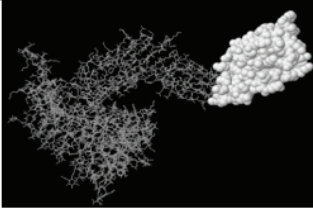
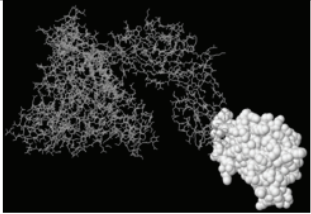
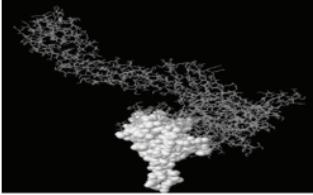
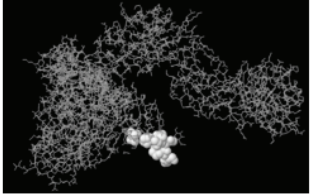
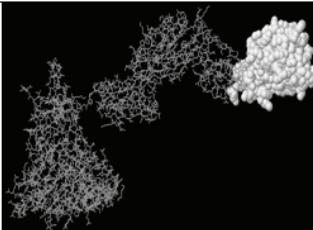
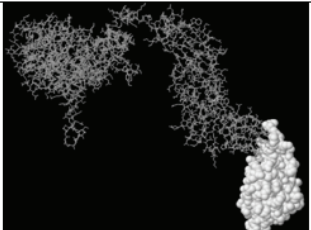
3D structure with linker "A"	Residues and score	3D structure with linker "B"	Residues and score
	0.812 B:K1- B:K166		0.803 B:K1- B:K166
	0.704 B:D424- B:R780		0.745 B:E190, B:E218, B:R219, B:A267, B:R293- B:A381
3D structure with linker "C"	Residues and score	3D structure with linker "D"	Residues and score
	0.818 B:K1- B:V168		0.825 B:K1- B:K166
	0.714 B:W415-B:E425, B:I428- B:G791		0.776 B:P437-B:A442, B:G507-B:T511, B:V743
3D structure with linker "E"	Residues and score	3D structure with linker "F"	Residues and score
	0.811 B:K1-B:F98, B:L118-B:S127, B:Q139-B:T143, B:V161-B:V168		0.812 B:K1-B:F98, B:L118-B:S127, B:Q139-B:T143, B:V161- B:V168

Table 6: Conformational B-Cell Epitopes of model "A-E" Were predicted by the Ellipro Server.

Motif	sequence	Position at "A" model	Position at "B" model	Position at "C" model	Position at "D" model	Position at "E" model	Position at "F" model	Length	GRAVY Score	PI	Software
1	DTYICEV	80-86	80-86	80-86	80-86	80-86	80-86	7	0.314	3.67	1,4
2	FQKASSI	179-185	179-185	179-185	179-185	179-185	179-185	7	0.014	8.75	1,4
*3	KKLPLHLT	251-258	251-258	251-258	251-258	251-258	251-258	7	-0.237	10.00	1,3
4	IVQLNTSVE	532-540	542-550	540-548	534-542	535-543	535-543	9	0.522	4.00	1,2
5	GSDTITLPC	618-626	628-636	626-634	620-628	621-629	621-629	9	0.344	3.80	2,4
*6	LTANS DTHL	100-108	100-108	100-108	100-108	100-108	100-108	9	-0.333	5.08	2,4
*7	ASSSKSWIT	220-229	220-229	220-229	220-229	220-229	220-229	9	-0.267	8.80	2,4
8	LLSDSGQVL	346-354	346-354	346-354	346-354	346-354	346-354	9	0.733	3.80	1,2,4
*9	AILKCNNKT	471-479	481-489	479-487	473-481	474-482	474-482	9	-0.322	9.32	2
*10	ARAKWNNTL	552-560	562-570	560-568	554-562	555-563	555-563	9	-1.067	11.00	3
11	FTDNAKTII	524-532	534-545	532-540	526-534	527-535	527-535	9	0.144	5.84	4
12	LSVSQLELQ	144-152	144-152	144-152	144-152	144-152	144-152	9	0.389	4.00	1

*Antigenic motif were identified by various server. Servers used for prediction are shown as number described as follows:

1) CTLpred 2) EpiJene 3) Tapped 4) NetCTL. Hydrophilic motifs are marked with an asterisk.

Table 7: T cell Motif Prediction of Model A-F

Discussion

We are presented in this article, a new insight applicable in design of more effective vaccines against HIV. HIV was detected in 2.1 million people in 2015 and 1.1 million affected individuals were died by it [4]. Nowadays, very active antiviral reagent that targets replication of virions are available [5-7] but HIV-1 has not been removed from populations [8]. An HIV-1 vaccine must be can either to prevent infection and to reduce viral titer and progression of disease. A powerful vaccine would completely inhibit infection and provide stable immunity against HIV-1. In spite of different challenges, this degree of protection is not even achieved[10]. In these situations, improvement of vaccination strategies is necessary. Our study focuses on this weak point.

In several study, it is used used monomeric HIV-1 Env gp120 protein to induce specific humoral immune responses against viral envelop protein [12, 13]. If we consider high diversity of HIV-1, we will therefore need an effective immunogenic vaccine to promote immune system responses against different variants of HIV. We have considered this properties in our proposed vaccine. We analyzed immunogenicity of proposed fusion peptide in front of TCR and BCR. Our results are supported by other study that have been reported cross-reactive humoral and cellular immune responses against conserved regions of the virus [10].

There is a high variance in the first structure of immunogenic proteins of HIV. For example, Env protein of virus has up to 35% difference in amino acid sequence in variants [14, 15]. On the other hand, N-glycosylation of Env glycoprotein can hide some epitopes from immune system recognition result in decreasing of efficient humoral immunity [16, 17].

We proposed an effective method for designing of new vaccines that can facilitate action of Antigen presentation cells (APC). In our plan, a proline amino acid residue linker, joint gp120 protein to CD4 receptor in a "U" shaped manner. We are believing this construct can present gp120 beside of CD4 to the effector cells such as B and Ts cells. Table 1-4 and figure-1 shows conformational shape and some properties of our proposed construct. These data confirm a stable shape of final construct with highly stable secondary structures (table-4). In addition table 3 show a basic PI for all of models and instability index lower than 40 for A-E models that means optimal stability of these constructs. On the other hand, aliphatic index and GRAVY confirmed two parameters necessary for action of a molecule as an effective immunogenic particle.

Our proposed gp120-linker-CD4 construct can be supported by some reported biophysical studies. It was explained in some researches that highly immunogenic variable motives elicit type-specific antibodies that may redirect humoral responses away from conserved regions. In addition, critical changes in order to appearance of conserved motives happens after the binding of Env to its cellular receptor CD4 that result in an extensive conformational change [18]. We analyzed immunogenic parameters of new constructs by utilizing of different well known software and servers.

B-Cell Linear motives in the models A-F, showed a GRAVY score equal with .961 in minimum and maximum equal with -1.561 that confirm a good condition for an immune response (table 5). Conformational B-cell epitopes identified by Ellipro software. All of proposed models have an Ellipro score more than 0.7 that is indication of high immunogenic properties (table 6). T-cell specific epitopes are showed in table 7. GRAVY score of some motives in range of TCR detection that means we can expect an effective immune cellular response.

In summary, we introduced in this paper an new strategy can help to immune system in order to direct detection of vaccine protein independently of interaction between antigen and CD4 receptor. Bioinformatics analyses of proposal protein confirmed it as an effective candidate vaccine against HIV. However construction of this fusion protein by using of recombinant DNA technology and animal challenges experiments will help us for a better view.

Acknowledgments: We thanks Shahrekord University for its financial supports.

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