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Prediction of MHC Class Binding Peptide and High Affinity TAP Binders to Design Synthetic Peptide Vaccine of Long Neurotoxin 3 from *Naja Naja*

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Abstract

Naja naja is a highly poisonous snake species of cobra in Elapidae family and is commonly found in middle Asia. Long neurotoxin 3 from *Naja naja* binds to the nicotinic acetylcholine receptors in the postsynaptic membrane, preventing the binding of acetylcholine and blocks excitation of muscles. Antigenic peptides are complex biomolecules that have unique chemical and physical properties resulting of their amino acid composition. In this study, we have predicted the binding affinity of Long neurotoxin 3 from *Naja naja* having 71 amino acids, which shows 63 nonamers. Peptide fragments of the neurotoxin can be used to select nonamers for use in synthetic peptide vaccine design and to increase the understanding of roles of the immune system in neurotoxin studies. Antigenic peptides of Long neurotoxin 3 from *Naja naja* are most suitable for synthetic peptide vaccine development because with Small segment' 15-PNGHVCYTKT-24, 26-CDAFCSIRG-34, 36-RVDLGCAATCPTVKTGVDIQCCSTD-60 called the antigenic epitopes is sufficient for eliciting the desired immune response. In this research, we predict of MHC class I and II binding peptide because MHC molecules are cell surface proteins which take active part in immune response, antigenicity, Solvent accessibility, polar and nonpolar residue that are likely exposed on the surface of proteins that are potentially antigenic that allows to design synthetic peptide vaccine.

Keywords: Long neurotoxin 3; *Naja naja*; Antigenic peptides; MHC-Binders; TapPred; PSSM; SVM; Nonamers

Introduction

Naja naja is one of the most venomous snake species occurs in wild forest and in cultivated areas [1,2]. The genus *Naja* consists of currently 26 species of cobra of which 11 inhabit Asia and 15 occur in Africa [3,4]. *Naja naja*'s venom mainly contains a powerful post-synaptic neurotoxin [5]. Long neurotoxin 3 binds to muscular and neuronal nicotinic acetylcholine receptors and Produces peripheral paralysis by blocking neuromuscular transmission at the postsynaptic site [6-8]. Antigenic peptides from *Naja naja* are most suitable to design synthetic peptide vaccine because a small segment can generate sufficient immune response. Major histocompatibility complex (MHC) molecules are cell surface proteins that binds to the peptides derived from host or antigenic proteins and present them at the cell surface for recognition by T-cells [9,10]. T cell recognition is a fundamental mechanism of immune system by which the host identifies and responds to foreign antigens [11,12]. There are two types of MHC molecule and are extremely polymorphic [13]. MHC class I molecules present peptides from intracellular proteins that are targeted by proteasome, cleaved them into short peptides of 8-11 amino acids in length. These peptides are bound by the transmembrane peptide transporter (TAP) and translocate them from cytoplasm to endoplasmic reticulum, where they are bound by MHC molecule. The second and the C-terminal position of the peptide are the most important for binding [14,15] and the amino acids at each position contribute a certain binding energy [16]. Whereas, MHC class II molecule present peptides derived from endocytosed extracellular proteins. Identification of MHC-binding peptides and T-cell epitopes helps improve our understanding of specificity of immune responses [17-20].

Methodology

Database searching

The antigenic protein sequence of Long neurotoxin 3 from *Naja naja* was retrieved from UniProtKB/Swiss-Prot, www.ncbi.nlm.nih.gov [21].

Prediction of antigenicity

Prediction of antigenicity program predicts those segments from neurotoxin protein that are likely to be antigenic by eliciting an antibody response. In this research work antigenic epitopes of Long neurotoxin 3 from *Naja naja* are determined by using the Hopp and Woods, Welling, Parker, Bepipred, Kolaskar and Tongaonkar antigenicity methods [22-26].

Prediction of MHC binding peptide

The major histocompatibility complex (MHC) peptide binding of Long neurotoxin 3 from *Naja naja* is predicted using neural networks trained on C terminals of known epitopes. Rankpep predicts peptide binders to MHC-I ligands whose C-terminal end is likely to be the result of proteosomal cleavage using Position Specific Scoring Matrices (PSSMs). Support Vector Machine (SVM) based method for prediction of promiscuous MHC class II binding peptides from protein sequence; SVM has been trained on the binary input of single amino acid sequence [27-36].

Prediction of antigenic peptides by cascade SVM based TAPPred method

In the present study, we predict cascade SVM based several TAP binders which was based on the sequence and the features of amino acids [37]. We found the MHCI binding regions (Table 1), the binding affinity of Long neurotoxin 3 from *Naja naja*.

Peptide Rank	Start Position	Sequence	Score	Predicted Affinity
1	58	STDDCDPFP	8.636	High
2	41	CAATCPTVK	8.618	High
3	30	CSIRGKRVD	8.586	High
4	38	DLGCAATCP	8.549	High
5	61	DCDPFPTRK	8.499	High
6	20	CYTKTWCDA	8.487	High
7	50	TGVDIQCCS	8.385	High
8	57	CSTDDCDPF	8.151	High
9	7	PDITSKDCP	8.071	High
10	40	GCAATCPTV	8.01	High
11	32	IRGKRVDLG	7.958	High
12	36	RVDLGCAAT	7.814	High
13	47	TVKTGVDIQ	7.576	High
14	46	PTVKTGVDI	7.561	High
15	22	TKTWCDAFC	7.38	High
16	48	VKTGVDIQC	7.319	High
17	51	GVDIQCCST	7.318	High
18	60	DDCDPFPTR	7.183	High
19	55	QCCSTDDCD	7.139	High
20	33	RGKRVDLGC	6.855	High
21	44	TCPTVKTGV	6.789	High
22	15	PNGHVCYTK	6.764	High
23	63	DPFPTRKRP	6.707	High
24	16	NGHVCYTKT	6.535	High
25	17	GHVCYTKTW	6.355	High
26	29	FCSIRGKRV	6.308	High
27	11	SKDCPNGHV	6.13	High

Table 1: Cascade SVM based High affinity TAP Binders of Long neurotoxin 3 from *Naja naja.*

Solvent accessible regions

We also predict solvent accessible regions of proteins having highest probability that a given protein region lies on the surface of a protein Surface Accessibility, backbone or chain flexibility by Emani et al., [38] and Karplus and Schulz [39]. By using different scale we predict the hydrophobic and hydrophilic characteristics of amino acids that are rich in charged and polar residues i.e. Sweet et al., Kyte and Doolittle, Abraham and Leo, Bull and Breese, Guy, Miyazawa, et al., Roseman, Wolfenden et al., Wilson et al., Cowan, Chothia [40-48].

Results and Discussion

Long neurotoxin 3 from *Naja naja* contain a long residue with 71 amino acids.

IRCFITPDITSKDCPNGHVCYTKTWCDGFCSRRGERVDLGCAA TCPTVKTGVDIQCCSTDDCDPFPTRKRP

Prediction of antigenic peptides

In this study, we found the antigenic determinants by finding the area of greatest local hydrophilicity. The Hopp-Woods scale Hydrophilicity Prediction Result Data found high in position 10-12, 34-37, 64-67 (1.011), 60-61 (1.129) in a protein, assuming that the antigenic determinants would be exposed on the surface of the protein and thus would be located in hydrophilic regions (Figure 1).

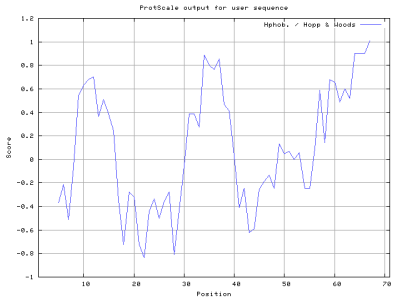

Figure 1: Hydrophobicity plot of Hopp and Woods [22] of Long neurotoxin 3 from *Naja naja.*

Welling antigenicity plot gives value as the log of the quotient between percentage in a sample of known antigenic regions and percentage in average proteins and Prediction Result Data found high in position 20-21 (0.440) (Figure 2).

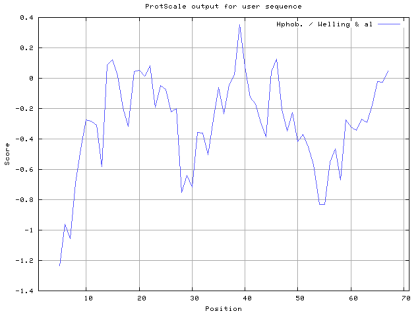

Figure 2: Hydrophobicity plot of Welling et al. [23] of Long neurotoxin 3 from *Naja naja*. Result Data found high in position 37-39(0.38).

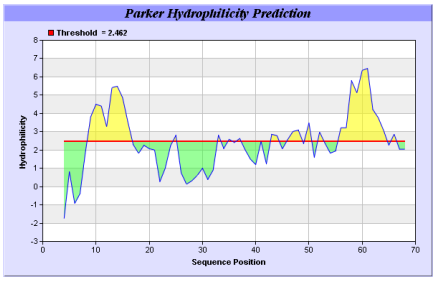

Figure 3: Hydrophobicity plot of HPLC / Parker et al. [24] of Long neurotoxin 3 from *Naja naja.*

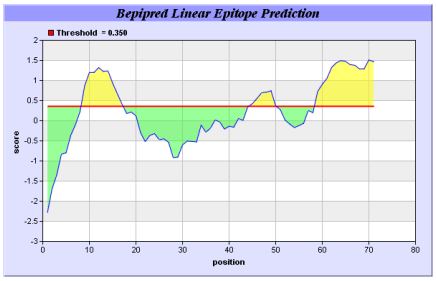

Figure 4: Bepipred Linear Epitope Prediction plot showing antibody recognized B-cell epitopes of Long neurotoxin 3 from *Naja naja* Result found that 9-ITSKDCPNG-17 and 45-CPTVKT-50.

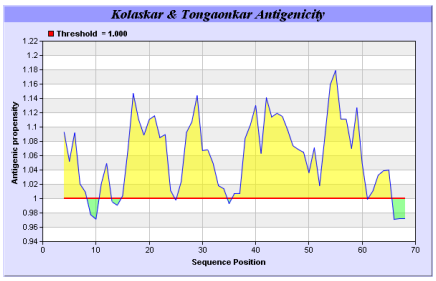

Figure 5: Kolaskar and Tongaonkar antigenicity plot for the Long neurotoxin 3 from *Naja naja* Predicted peptides result found i.e. 15-PNGHVCYTKT-24, 26-CDAFCSIRG-34 and 36-RVDLGCAATCPTVKTGVDIQCCSTD-60 [26].

We also study Hydrophobicity plot of HPLC/Parker Hydrophilicity Prediction Result Data found 7-PDITSKDDITSKDC-14, 10-TSKDCPNSKDCPNG-17, 55-QCCSTDD-61, 56-CCSTDDC-62 (5.129), 57-CSTDDCD-63 (6.357), 58-STDDCDP-64 (6.457) maximum (Figure 3), BepiPred predicts the location of linear B-cell epitopes Result found that 9-ITSKDCPNG-17, 45-CPTVKT-50 (Figure 4) (Table 2), Kolaskar and Tongaonkar antigenicity methods (Figure 5) Predicted peptides result found i.e. 15-PNGHVCYTKT-24, 26-CDAFCSIRG-34, 36-RVDLGCAATCPTVKTGVDIQCCSTD-60 (Table 3) and the predicted antigenic fragments can bind to MHC molecule is the first bottlenecks in vaccine design.

No.	Start Position	End Position	Peptide	Peptide Length
1	9	17	ITSKDCPNG	9
2	45	50	CPTVKT	6

Table 2: Predicted Antigenic epitopes of Long neurotoxin 3 from *Naja naja.*

No.	Start Position	End Position	Peptide	Peptide Length
1	15	24	PNGHVCYTKT	10
2	26	34	CDAFCSIRG	9
3	36	60	RVDLGCAATCPTVK TGVDIQCCSTD	25

Table 3: Predicted Antigenic epitopes of Long neurotoxin 3 from *Naja naja.*

Solvent accessible regions

We also predict solvent accessible regions in proteins; different measurement was performed for the prediction of antigenic activity, surface region of peptides.

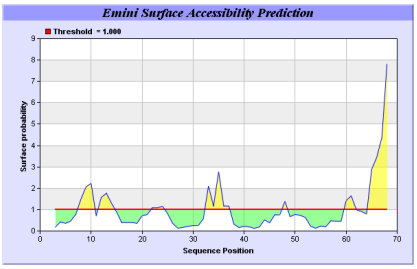

Figure 6: Emini Surface Accessibility Prediction plot of Long neurotoxin 3 from *Naja naja* predicts the highest probability i.e. found 31-SIRGKRIRGKRVRGKRVD-38, 64PFPTRKFPTRKRPTRKRP-71(7.808) (maximum).

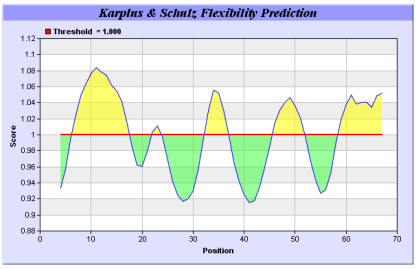

Figure 7: *Karplus and Schulz Flexibility Prediction of* Long neurotoxin 3 from *Naja naja* High score is found i.e. found 7-PDITSKD-13(1.077), 8-DITSKDC-14 (1.084) (maximum), 9-ITSKDCP-15 (1.078).

Emini et al. [37], (Figure 6) predicts the highest probability i.e. found 31-SIRGKRIRGKRVRGKRVD - 38, 64PFPTRKFPTRKRPTRKRP - 71 (7.808) (maximum), that a given protein region lies on the surface of a protein and are used to identify antigenic determinants on the surface of proteins.

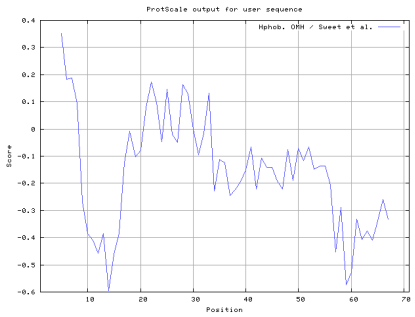

Figure 8: Hydrophobicity plot of Sweet et al. [39] of Long neurotoxin 3 from *Naja naja.*

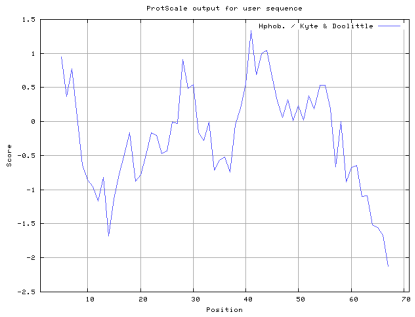

Figure 9: Kyte and Doolittle [40] hydrophobicity plot of Long neurotoxin 3 from *Naja naja.*

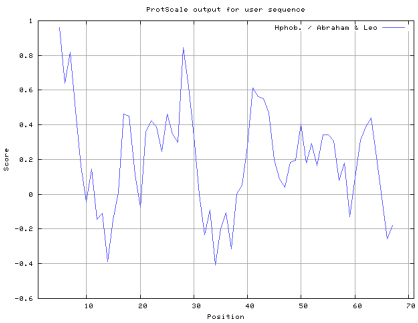

Figure 10: Abraham and Leo [41] hydrophobicity plot of Long neurotoxin 3 from *Naja naja.*

Karplus and Schulz (Figure 7) High score is found i.e. found 7-PDITSKD-13 (1.077), 8-DITSKDC-14 (1.084) (maximum), 9-ITSKDCP-15 (1.078). Predict backbone or chain flexibility on the basis of the known temperature B factors of the a-carbons.

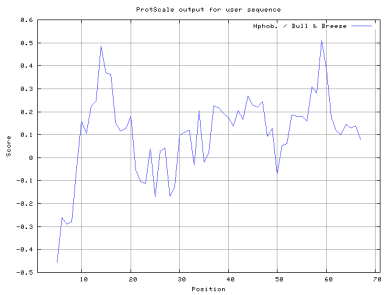

Figure 11: Bull and Breese [42] use surface tension to measure hydrophobicity and also uses negative values to describe the hydrophobicity of Long neurotoxin 3 from *Naja naja.*

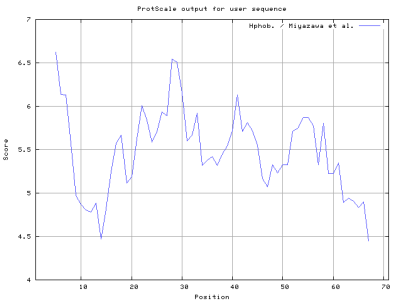

Figure 12: Hydrophobicity plot of Miyazawa et al. [43] of Long neurotoxin 3 from *Naja naja.*

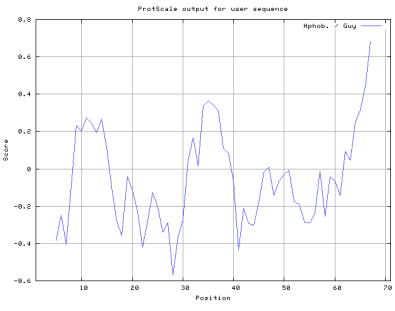

Figure 13: Hydrophobicity plot of Roseman [44] of Long neurotoxin 3 from *Naja naja.*

The hydrophobicity and hydrophilic characteristics of amino acids is determined by using different scales that are rich in charged and polar residues i.e. Sweet et al. [39] hydrophobicity prediction Result Data found high in position 5 (0.352), 21-23, Kyte and Doolittle result high in position 40-42 (1.333), 43-44, Abraham and Leo result high in position 5-7 (0.961), 28-30, Bull and Breese result high in position 12-16,57-60 (0.510), Guy result high in position 10-12, 34-37, 65-67 (0.682), Miyazawa result high in position 5-7 (6.620), 16-2122-27,28-30, 39-42, 52-56, Roseman result high in position 43-44 (0.232), 17-18, 42-43, Wolfenden result high in position 43-44, Wilson et 17-18, 22-23, 27-30 (3.211), Cowan 5-7 (0.727), 28-30, 41-43, Chothia 5-7, 28-30, 40-44 (0.388 (Figures 8-18).

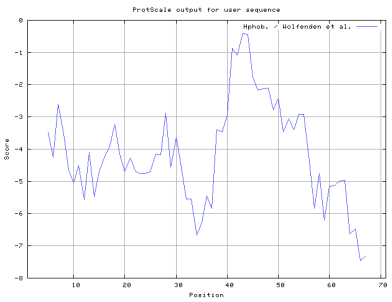

Figure 14: Hydrophobicity plot of Wolfenden et al. [45] of Long neurotoxin 3 from *Naja naja.*

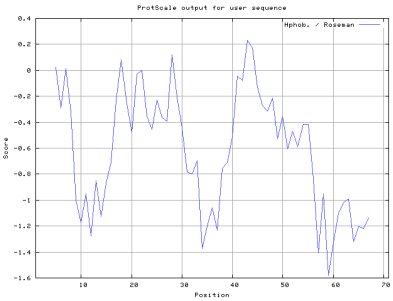

Figure 15: Hydrophobicity plot of Roseman MA [44] of Long neurotoxin 3 from *Naja naja.*

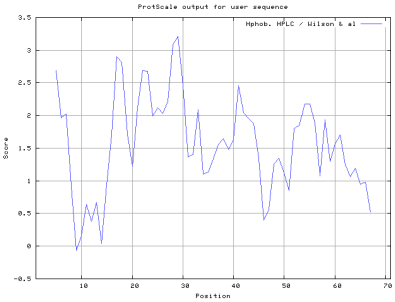

Figure 16: Hydrophobicity/HPLC plot of Wilson et al. [46] of Long neurotoxin 3 from *Naja naja.*

Prediction of MHC binding peptide

We found binding of peptides to a number of different alleles using Position Specific Scoring Matrix. Long neurotoxin 3 from *Naja naja* sequence is 71 residues long, having 63 nonamers. MHC molecules are cell surface proteins, which actively participate in host immune reactions and involvement of MHC-I and MHC-II in response to almost all antigens. We have predicted MHC-I peptide binders of Long neurotoxin 3 from *Naja naja* was tested with on a set of 4 different alleles i.e. H2-Db (mouse) 8mer with the consensus sequence QNWNCCTI that yields the maximum score i.e. 52.494, H2-Db (mouse) 9mer with the consensus sequence FCIHNCDYM that yields the maximum score i.e. 50.365, H2-Db (mouse) 10mer with the consensus sequence SGYYNFFWCL that yields the maximum score i.e. 58.858, H2-Db (mouse) 11mer with the consensus sequence CGVYNFYYCCY that yields the maximum score i.e. 79.495 (Tables 4-7), and MHC-II peptide binders for I_Ab.p with the consensus sequence YYAPWCNNA that yields the maximum score i.e. 35.632, I_Ad.p with the consensus sequence QMVHAAHAE that yields the maximum score i.e. 53.145 for MHC II allele was tasted.

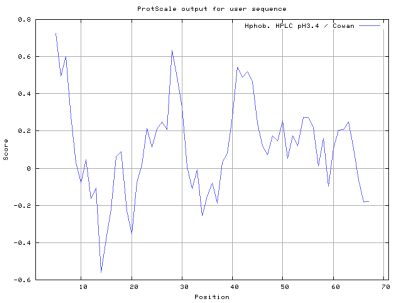

Figure 17: Hydrophobicity/HPLC pH 3.4/ plot of Cowan [47] of Long neurotoxin 3 from *Naja naja.*

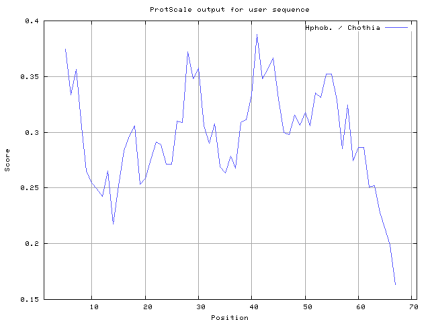

Figure 18: Hydrophobicity plot of Chothia [48] of Long neurotoxin 3 from *Naja naja.*

MHC-I Allele	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
8mer_H2_Db	41	DLG	CAATCPTV	KTG	746.89	21.518	40.99 %
8mer_H2_Db	61	STD	DCDPFPTR	KRP	932.03	4.607	8.78 %
8mer_H2_Db	58	QCC	STDDCDPF	PTR	880.89	1.654	3.15 %
8mer_H2_Db	2	I	RCFITPDI	TSK	946.14	0.021	0.04 %

Table 4: Promiscuous MHC ligands, having C-terminal ends are proteosomal cleavage sites, the binding potential (score) of antigenic peptide to the MHC-1 Allele i.e. 8mer_H2_Db.

MHC-I Allele	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.

9mer_H2_Db.	12	ITS	KDCPNGHVC	YTK	954.08	7.581	15.05 %
9mer_H2_Db.	57	IQC	CSTDDCDPF	PTR	984.03	7.131	14.16 %
9mer_H2_Db.	13	TSK	DCPNGHVCY	TKT	989.09	5.283	10.49 %
9mer_H2_Db.	40	VDL	GCAATCPTV	KTG	803.94	2.756	5.47 %

Table 5: Promiscuous MHC ligands, having C-terminal ends are proteosomal cleavage sites the binding potential (score) of antigenic peptide to the MHC-1 Allele i.e. 9mer_H2_Db.

MHC-I Allele	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
10mer_H2Db	12	ITS	KDCPNGHVCY	TKT	1117.26	7.127	12.11 %
10mer_H2Db	60	CST	DDCDPFPTRK	RP	1175.29	7.065	12.00 %
10mer_H2Db	39	RVD	LGCAATCPTV	KTG	917.1	1.576	2.68 %

Table 6: Promiscuous MHC ligands, having C-terminal ends are proteosomal cleavage sites the binding potential (score) of antigenic peptide to the MHC-1 Allele i.e. 10mer_H2_Db.

MHC-I Allele	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
11mer_H2Db	11	DIT	SKDCPNGHVCY	TKT	1204.34	14.334	18.03 %
11mer_H2Db	22	VCY	TKTWCDGFCSR	RGE	1262.45	-3.336	-4.20 %

Table 7: Promiscuous MHC ligands, having C-terminal ends are proteosomal cleavage sites the binding potential (score) of antigenic peptide to the MHC-1 Allele i.e. 11mer_H2_Db.

Alleles highlighted in red represent predicted binders (Tables 8 and 9). Here RANKPEP report PSSM-specific binding threshold and is obtained by scoring all the antigenic peptide sequences included in the alignment from which a profile is derived, and is defined as the score value that includes 85% of the peptides within the set. Peptides whose score is above the binding threshold that are highlighted here and peptides produced by the cleavage prediction model are also highlighted here. We also use a cascade SVM based TAPPred method which found 27 High affinity TAP Transporter peptide regions which represents predicted TAP binders residues which occur at N and C termini from Long neurotoxin 3 from *Naja naja* (Table 1). TAP is an important transporter that transports antigenic peptides from cytosol to ER. TAP binds and translocate selective antigenic peptides for binding to specific MHC molecules. The efficiency of TAP-mediated translocation of antigenic peptides is directly proportional to its TAP binding affinity. Thus, by understanding the nature of peptides, that bind to TAP with high affinity, is important steps in endogenous antigen processing. In this study, we found the MHCI and MHCII binding regions. T cell immune responses are derived by antigenic epitopes hence their identification is important for design synthetic peptide vaccine. Therefore, the prediction of peptide binding to MHCI molecules by appropriate processing of antigen peptides occurs by their binding to the relevant MHC molecules. Because, the C-terminus of MHCI-restricted epitopes results from cleavage by the proteasome and thus, proteasome specificity is important for determining T-cell epitopes. Consequently, RANKPEP focus on the prediction of conserved epitopes. C-terminus of MHCI-restricted peptides is generated by the proteasome, and thus RANKPEP also determines whether the C-terminus of the predicted MHCI-peptide binders is the result of proteasomal cleavage and these sequences are highlighted in the output results.

MHC-II Allele	POS.	N	SEQUENCE	C	MW(Da)	SCORE	%OPT.
MHC-II I_Ab	25	TKT	WCDAFCSIR	GKR	1059.27	17.73	49.76 %
MHC-II I_Ab	40	VDL	GCAATCPTV	KTG	803.94	14.967	42.00 %
MHC-II I_Ab	21	HVC	YTKTWCDAF	CSI	1093.25	12.459	34.97 %
MHC-II I_Ab	41	DLG	CAATCPTVK	TGV	875.06	10.95	30.73 %
MHC-II I_Ab	29	CDA	FCSIRGKRV	DLG	1047.29	10.823	30.37 %
MHC-II I_Ab	38	KRV	DLGCAATCP	TVK	831.96	10.5	29.47 %
MHC-II I_Ab	4	IRC	FITPDITSK	DCP	1003.16	10.03	28.15 %

Table 8: Prediction of MHCII ligands all rows highlighted represent predicted binders to the MHC-II Allele i.e. MHC-II I_Ab.

MHC-II Allele	POS.	N	SEQUENCE	C	MW(Da)	SCORE	% OPT.
MHC-II I_Ad	39	RVD	LGCAATCPT	VKT	817.97	7.417	13.96 %
MHC-II I_Ad	39	RVD	LGCAATCPT	VKT	817.97	7.417	13.96 %

Table 9: Prediction of MHCII ligands all rows highlighted represent predicted binders to the MHC-II Allele i.e. MHC-II I Ad.

Prediction Result Data found 7-PDITSKDDITSKDC-14, 10-TSKDCPNSKDCPNG-17, 55 QCCSTDD-61, 56-CCSTDDC-62 (5.129), 57-CSTDDCD-63 (6.357) and 58-STDDCDP 64 (6.457) (maximum).

Conclusion

From the above result and discussion it is concluded that the ability of RANKPEP to predict MHC binding peptides, and thereby potential T-cell epitopes, Antigenic peptides should be located in solvent accessible regions and contain both hydrophobic and hydrophilic residues. High peaks in the surface accessibility plot predict regions that have a higher chance of producing antibodies that can bind to native protein. This means the increase in affinity of MHC binding peptides may result in enhancement of immunogenicity of Long neurotoxin 3 of *Naja naja* and are helpful in the designing of synthetic

peptide vaccine. This approach can help reduce the time and cost of experimentation for determining functional properties and helps to minimize the number of validation experiments.

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