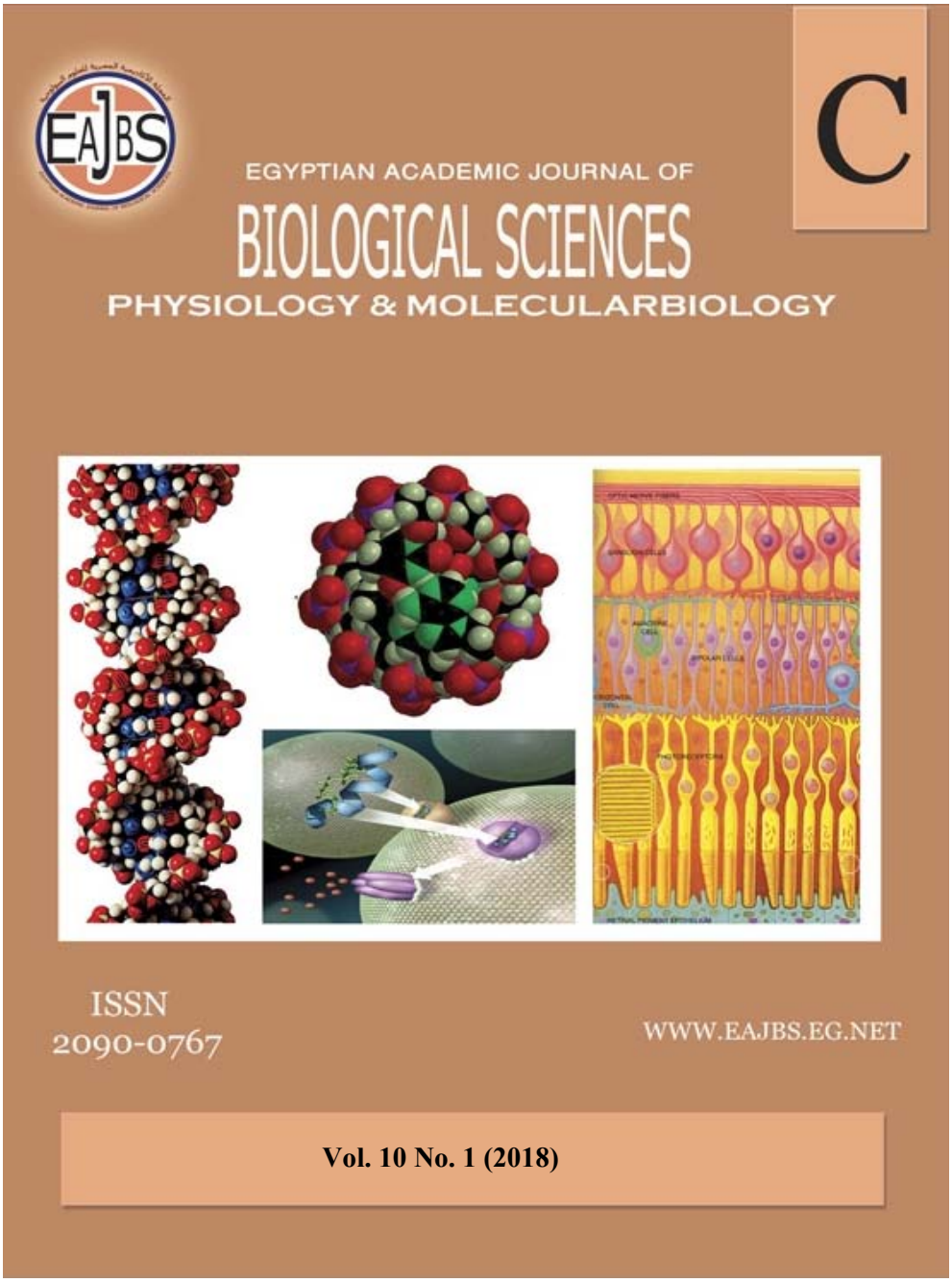

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In silico Prediction of Epitope Based Vaccine Candidates against Powassan Virus Infection

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ABSTRACT

Powassan virus (POWV) is responsible for encephalitis and severe neurological sequelae globally. Peptide target based designing offers a promising therapeutic invention for the eradication of viral infection. Immunoinformatics serves as a powerful tool to screen and select antigenic peptide sequences as potential epitopes for binding affinity with HLA alleles. In the present study, a computational pipeline was developed for the identification of B-cell and T-cell epitopes for suitable vaccine candidates. Further, immunogenicity and physico-chemical prediction studies enable the discrimination between antigens and non-antigens. Considering the population setting globally, population coverage analysis was also performed for the identification of possible binding alleles (MHC class-I and MHC class-II*) of T-cell epitopes.* This computational prediction analysis will enhance our understanding of B-cell/T-cell immune response and assist in selecting the antigenic peptide(s) for the formulation of antigen based diagnostic kit or peptide based subunit vaccine design against POWV.

INTRODUCTION

Among the tick borne flaviviruses, various cases of infection caused by Powassan virus (POWV) have been reported globally. It is a neuroinvasive virus transmitted by *Ixodid* tick *Hyalomma dromedarii* (McLean and Donohue, 1959) to mammalian system and consequently affects the central nervous system. The only therapy available for the infection caused by Powassan virus is supportive care (Birge and Sonnesyn, 2012), which is possibly due to the lymphocytic infiltration of perivascular neuronal tissue. This condition is generally identified as gray matter in various regions of the brain (Gholam *et al.*, 1999). The exhibition of infectivity requires a period of 1–4 weeks and diagnosed with brain imaging technologies (LaSala and Holbrook, 2010; Romero and Simonsen, 2008). The endemicity caused by Powassan virus encephalitis spread across North America, Africa, and tropical regions of South East Asia (Ebel *et al.*, 2001).

As per the previously published literature, phylogenomic-related studies reveal more than 80% similarity in phylogenetic relationship among deer tick virus (DTV) and POWV (Ebel *et al.*, 2010). Molecular epidemiology deciphers the organization of 11kb single-stranded, positive-sense RNA genome encoding seven non-structural proteins and three structural proteins: capsid (C) protein, premembrane (preM) protein, and envelope (E) glycoprotein (Hermance and Thangamani, 2017). Despite being completely sequenced, the vague knowledge regarding causing infection and survival in the host raised the quest for the development of novel vaccines. Therefore, in this study, an *in silico* approach was employed for epitope identification (Somvanshi and Seth, 2009; Singh *et al.*, 2009) and characterization, which provides a solid platform for future researchers to develop potential vaccines against Powassan virus. The identification of B-cell and T-cell epitopes (HLA class-I CD8+ T-cells and HLA class-II CD4+ T-cells) to unwire the underlying viral pathogenesis has been performed nearly a decade ago (Somvanshi and Seth, 2009; Singh *et al.*, 2009; Somvanshi *et al.*, 2008a; Somvanshi *et al.*, 2008b). In order to overcome the limitation of presence of extreme polymorphisms among maximal population setting, population coverage analysis was performed which will help in the discovery of novel vaccine against Powassan virus.

MATERIALS AND METHODS

Data-set Collection:

The complete protein sequences of Powassan virus were retrieved from the NCBI genome database (https://www.ncbi.nlm.nih.gov/genome/) in FASTA format. The retrieved sequences were further subjected to immunogenicity and epitope prediction.

Physico-Chemical Characterization:

The assessment of several physico-chemical properties of the proteins/peptides using sequences was performed by using an online server at EXPASY Bioinformatics Suite, ProtParam (Gasteiger *et al.*, 2005). The physico-chemical properties included molecular weight, amino acid composition, extinction coefficient, theoretical pI, and grand average of hydropathicity, aliphatic index, and instability index (Gasteiger *et al.*, 2005).

Immunogenicity Prediction:

The evaluation of immunogenicity of the protein sequences was performed by using VaxiJen V2.0 server (http://www.ddg-pharmfac. net/vaxijen/Vaxi-Jen/VaxiJen.html) which enables the discrimination between antigens and non-antigens by predicting protective antigens, tumor antigens, and subunit vaccines with the precision level of 70 to 89% employing the underlying Auto Cross Covariance (ACC) algorithm.

Epitope Prediction:

ABCpred server (www. imtech. res.in/abcpred) was employed for the prediction of B-cell epitopes from the primary protein sequences. This server enables B-cell epitope prediction using artificial neural network strategy using *n-1* combinations for *n* number of possible outcomes. Additionally, a combinatorial machine learning platform NetCTL 1.2 server enables the identification of T-cell epitopes (MHC class-I and MHC class-II) for Powassan virus protein sequences. The properties of the possible identified epitopes were calculated by using Peptide Property Calculator available at https://www.genscript.com.

Toxicity Assessment:

The toxicity check of the identified epitopes was performed by using Toxin Pred server (Gupta *et al.*, 2013). This server takes into account the frequency and probability of amino acids

at a particular position by generating a quantitative matrix using Support Vector Machine (SVM).

Population Coverage Analysis:

Taken into consideration the population coverage globally, Immune Epitope Database and ANALYSIS RESOURCE (IEDB) Population Coverage tool available at http://tools.immuneepitope.org/tools/population/iedb_input was used for the identification of possible binding alleles (MHC class-I and MHC class-II*) of T-cell epitopes* (Bui *et al.*, 2006).

RESULTS AND DISCUSSIONS

The prevalence of infections caused by Powassan virus is evolving at high pace. This sudden health burden becomes a major concern for the countries having tropical cover (Black *et al.*, 2010). Despite several advancements in healthcare sector, a huge impact will be justified by the development of a vaccine against the infection of Powassan virus (Huang *et al.*, 2011).

In order to appraise the role of humoral immunity against the infection of Powassan virus, a computational pipeline was developed by considering immunogenicity prediction of viral protein and the identification of B-cell and T-cell epitopes (Saha and Raghava, 2006). The antigenic property of viral proteins has been ensured using VaxiJen V2.0 at a constant threshold of 0.4 (Table 1).

Table 1: Immunogenic and physicochemical properties of proteins of Powassan virus.

Protein	Molecular Weight	Amino Acid Composition	Instability Index	Extinction Coefficient	Aliphatic Index	GRAVY	Vaxijen Score
Anchored Core Protein C	12385.04	110	56.75	22000	80.64	-0.186	0.5251 (Probable ANTIGEN)
Core Protein C	10530.83	94	63.83	11000	77.77	-0.389	0.4034 (Probable ANTIGEN)
PreM Protein	18760.68	168	32.7	39335	86.43	-0.088	0.4699 (Probable ANTIGEN).
Matrix Protein M	8378.96	75	30.19	28990	118.27	0.408	0.2530 (Probable non-ANTIGEN)
Envelope Protein	54014.9	497	27.51	69160	82.9	-0.12	0.6884 (Probable ANTIGEN)
Non-Structural Protein NS1	39266.71	353	43.94	76150	73.12	-0.351	0.4795 (Probable ANTIGEN).
Non-Structural Protein NS2a	25209.34	230	33.77	28085	128.30	0.744	0.6463 (Probable ANTIGEN).
Non-Structural Protein NS2b	14494.87	131	44.51	30480	119.08	0.372	0.7628 (Probable ANTIGEN).
Non-Structural Protein NS3	68878.02	622	30.85	116350	77.11	-0.455	0.4792 (Probable ANTIGEN).
Non-Structural Protein NS4a	13517.22	126	39.19	21095	134.6	0.855	0.4803 (Probable ANTIGEN).
2K Protein	2271.64	23	10.97	-	152.61	1.135	1.0620 (Probable ANTIGEN).
Non-Structural Protein NS4b	27048.48	252	34.69	44585	102.66	0.279	0.5598 (Probable ANTIGEN).
Non-Structural Protein NS5	102903.33	903	32.98	225250	76.21	-0.486	0.4422 (Probable ANTIGEN).

To combat the complexity related to the pathogenesis of Powassan virus, antigenic determinant sites were identified for B-cells and T-cells using ABCpred, an epitope identification tool based on machine learning algorithmic strategy. The occurrence of both continuous and discontinuous epitopes

(Shen *et al.*, 2015; Blythe and Flower, 2005) in viral sequences ensured greater accuracy of the results obtained. The immunogenic potential of viral envelope protein in Powassan virus with a score of 0.6884 indicated its capability to use as a probable antigen. Table 2 represents the probable B-cell epitopes for POWV and their respective immunogenic potentials.

Table 2: Predicted B-cell epitopes in Powassan virus.

Protein	Predicted B-Cell Epitopes
Anchored Core Protein C	MTTSKGKGGGPPRRKLKVTANKSRPATSPMPK TGTARPP LRQ RRRSGV
Core Protein C	MTTSKGKGGGPPRRKLKVTANKSRPATSPMPK TGTARPP LRQ
PreM Protein	IHRDRE ASGRDAASQVRVQ GEWCEDS IDQEEEPVD GRCGRQAGSRGKRSVVIPTHAQKDMVGR AWLKGDNIRDHVTR
Matrix Protein M	PTHAQKDMVGR AWLKGDNIRDHVTR
Envelope Protein	L DFVTGTQGTTR TITAEGKPSID FQESPAETRE NTKVEARCPTTGPATLPEEHQA KRDQSDRGWGN CEEAKKAVGHVYDST VEPHTGDYLAANETNSNRKSAQFTV YGDV A GIDV DSSKDHLPSAWQV PWKHKDNQDWNS VEFGPPHAV
Non-Structural Protein NS1	GCAIDPERMEI SEWYDGYAYHPESPDTLAQ GVVPQ STAPE GEAN DKTDPADYRGGTPMVLKKTGKESKVSWKSW WSVPDSPRR DGVGECPLYR GEASKECDTGVMGAAVKNGKAIHT SM FRNDTGT CTWPASHTIDNDGV LAGPRSKYNRIPGYSEQVRGPWDQTPLR DHCPGTSVRIDSHCDKRGASVRSTTESGKI LPPVTFRSGTD PVHSQGG
Non-Structural Protein NS2a	DNGALLSEGGVPG RPGSV G M AMEDR IYNGQKER LGGSGSG
Non-Structural Protein NS2b	SLSE H AGVVEWNPELVNEGGEVSLK DAM VEREE

Non-Structural Protein NS4a	GGV NETPGSRAMKMAERDAPEA DYGTM
2K Protein	SGEDN
Non-Structural Protein NS4b	YLEQTKTDI RREDQGGMVWD NIDIQPARSW SVAAGTQAMRDLGGGTPFFG LVGATPTSL GLEAELTQR NPMVDGEIINPIPDGDPKPALY AAAMTEAGAV LRPEEESWWT
Non-Structural Protein NS5	GGAEGSTLGDI NSCT GVMETNRDQAR ETNMG RGYATL GCGRGGWSYYAASRPSV TIGGKGHEAPRL IGESSPDPEKEGARS KARNPDAA PYRPEV FSRNSTHEMY AVTGN GETRGPIQVPEIDLGTG EDKVKPRDVAER REQYSESWHEDKEHPYRTWQYWGSYRTPATGSAAS WNAREDVTRMAMTDTTAFG VFKEKVDTKAQEPQPGTR NAALGAWSDEQNKWSSAKEAVEDPEFW DEERSRHL

Additionally, a positive correlation between physiochemical properties (antigenicity and surface amino acid residues) of viral sequences and B-cell antigenic determining sites was observed. Combining amino acid anchoring pair composition (APC) and support vector machine (SVM) methods to obtain an area under curve of 0.847 was set as default parameter with respect to the occurrence of both continuous and discontinuous B-cell epitopes (Kori *et al.*, 2015).

Physico-chemical characterization enables computation of instability index, extinction coefficient, GRAVY, aliphatic index, and theoretical pI of protein sequences of Powassan virus. As per the results, envelope protein and 2K protein showed least instability index; hence they were found more stable under *in vitro* conditions. The total amino acid composition (mainly rate of cystine residue formation) reflected the molar concentration of protein which in turn assists in determining the strength by which protein absorbs the light at a given wavelength per molar concentration. The thermostability of the protein sequences was revealed by the estimation of volume occupied by the aliphatic side chains in a protein (aliphatic index). The solubility of protein sequences was determined by computing the hydropath values ranging from -2 to +2 for most of the proteins, with the positively rated proteins being more hydrophobic (Table 1). Anchored protein C showed highest hydropathicity index and antigenicity score of 0.5251.

Further, the identification of T-cell epitopes (MHC class-I and MHC class-II) assists in the development of potential vaccines for the treatment of infection caused by Powassan virus (Table 3).

Table 3: Predicted T-cell epitopes (MHC class-I and MHC class-II) in Powassan virus.

Proteins	T-Cell Epitopes	Number of MHC Class-I Binding Alleles	T-Cell Epitopes	Number of MHC Class-I Binding Alleles
Anchored Core Protein C	YIWLSSVGA VD EPTIRD FVGADNNMV YAKLADEDA	22 34 11 19	CGRGGWSYYAASRP ITSNYNIMV	21 09
Core Protein C	YQPVPNLAI YESGKNTIA WVGADNNDR	02 11 28	VCGRGGWRI FYFDGPVKV ITEQKAKDA YRGLYTRMS YGRKASSPG	30 15 18 07 16
PreM Protein	LSLLLSPVQ LSIIRTLSL	22 31	VQEEENED IIRTLSLLL VKLDFGRLS LPPLNSEPE	19 27 31 14
Matrix Protein M	YAACSPCCA VHYEFSVYG IERITNTPL	31 02 15	KEGVAYAA LDLLEKNDI WKGNCRHCR YGREIERIT	11 26 28 19
Envelope Protein	GKEPTI LRLFVTATA	11 09 23	IGKEPTIRD LCPECRETT LSILCPECR	16 18 21
Non-Structural Protein NS1	WDRAKACAG	25	YRYLNSLAT FGAINNITL MVDNTRNTN	16 26 30
Non-Structural Protein NS2a	YTPLGGPGV YTFEIAEPT YRDLSSIDT FFGGLGIST YRGCKAAGT VAPEPAPPT IIPLDSLGT	16 32 08 58 15 24 19	FSFGGLGISI LQDVPGVSS VASVDAPVV	22 17 05
Non-Structural Protein NS2b	EQVRG PGVSS	11 09	KGH GGGPPRRKLKVT	17 11
Non-Structural Protein NS4a	TGDYLAANETN SNRKSAQ	17	MAMTDTTAF	13
2K Protein	GHEAPR NM	16 17	GALLSE KGKGGG	19 20
Non-Structural Protein NS4b	AGPRS TANKSRP	14 11	ECPLY	17
Non-Structural Protein NS5	GVV	18	TLPEEHQA	19

The identification of T-cell receptors on antigen presenting cells (APC) responding towards the class-I and class-II molecules was performed using NetCTL 1.2 server at default parameters of 0.5, 0.89, and 0.94, for sensitivity, specificity, and accuracy (Peters and Sette, 2005; Tenzers *et al.*, 2005). For MHC class-I alleles, IEDB database using SMM align method was employed by considering potential sites having IC_{50} value < 300 nM. In addition, the antigenicity prediction of the screened epitopes was done by VaxiJen (Doytchinova and Flower, 2007). Table 3 represents the highest number of MHC class-I binding alleles are related to anchored core protein C (4) and non-structural NS2A (7) sequences. Further, the antigenic assessment identified "YRGCKAAG" epitope with highest VaxiJen score of 2.09. In order to

increase the confidence level of the prediction of MHC class-II alleles, IC_{50} value of 300 nM was used as threshold, as there is a direct relationship between SMM-align prediction scores and log-transformed IC_{50} binding affinity (Kori *et al.*, 2015). Multiple binding of epitopes with various alleles enables the identification of T-cell epitopes responding towards MHC class-II. T-cell epitopes "CGRGGWSYYAASRP" and "ITSNYNIMV" of anchored core protein C showed highest VaxiJen score of 0.98 and 0.96, respectively. The toxicity assessment enabled the identification of toxic potential of the identified epitopes. The applicability of the potential vaccine at global level was assessed by performing population coverage analysis ranging between 16.84- 96.38% (Table 4 and Figure 1).

Table 4: Population coverage analysis (%) of MHC class-I and MHC class-II.

S. No.	MHC Class-I				MHC Class-II		
1	**Population**	**Coverage**	**Average hit**	**PC90**	**Coverage**	**Average hit**	**PC90**
2	East Asia	89.12%	2.7	1.09	94.87%	2.35	0.35
3	North East Asia	81.38%	1.78	1.11	88.18%	2.13	0.88
4	South Asia	73.55%	1.05	1.09	97.83%	1.32	1.76
5	Southeast Asia	96.38%	1.14	0.79	95.17%	1.11	0.44
6	Europe	73.88%	2.35	1.23	99.08%	2.24	1.23
7	Southwest Asia	97.83%	1.22	0.35	76.72%	1.46	0.35
8	East Africa	71.89%	0.86	0.88	84.22%	2.13	1.47
9	West Africa	59.29%	1.15	1.76	43.05%	1.12	2.65
10	North Africa	29.09%	1.09	0.44	76.72%	2.99	1.09
11	South Africa	76.72%	1.12	0.79	81.38%	1.65	1.48
12	Central Africa	84.22%	2.99	1.23	73.55%	1.47	1.23
13	North America	43.05%	2.13	0.35	96.38%	1.22	0.88
14	Central America	89.67%	1.32	1.47	73.88%	0.86	1.76
15	South America	16.84%	1.11	2.65	76.72%	1.15	0.44
16	West Indies	66.39%	2.24	1.09	84.22%	1.09	0.88
17	Oceania	92.4%	1.46	1.48	76.72%	1.12	1.76
	Average	**71.35**	**1.606875**	**1.1125**	**82.41**	**1.588125**	**1.165625**

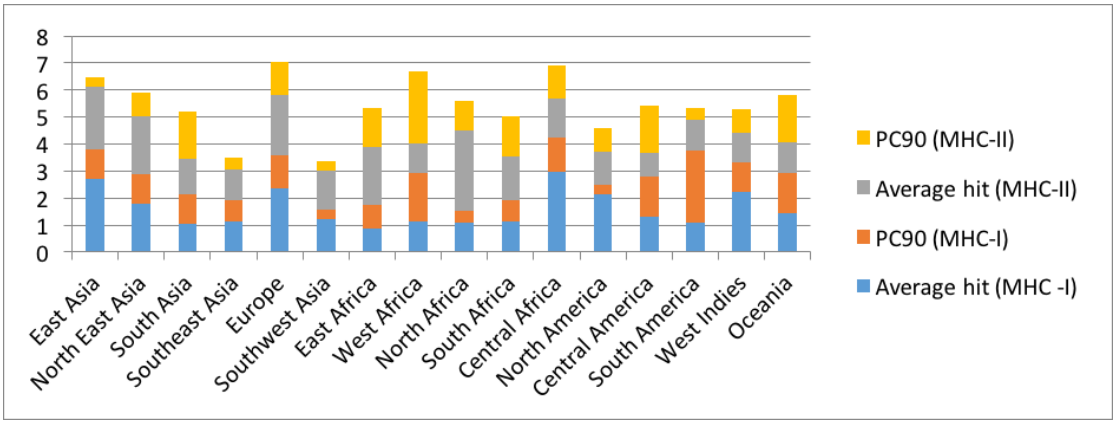

Fig. 1: Represents the average hit and PC90 analysis for MHC class-I and MHC class-II, respectively. (**blue** = average hit for MHC class-I, **orange** = PC90 for MHC class-I, **grey** = average hit for MHC class-II, and **yellow** = PC90 for MHC class-II)

Overall, the current results imply the use of the identified and characterized epitopes in vaccine discovery in the future. Further analysis of anchored protein C epitopes for vaccine discovery purpose is warranted because of positive correlation between the physicochemical properties (GRAVY) and B-cell /T-cell epitopes' VaxiJen scores.

CONCLUSIONS

The current study deals with the application of bioinformatics tools for providing the deep insight into the underlying antigenicity related to Powassan virus infection. The prediction of epitopes (for B-cell and T-cell MHC Class-I & MHC Class-II) and their respective toxic potentials will provide the solid background leading to the development of potential vaccine against Powassan virus infection in the near future.

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Conflict of Interest:

The author reports no conflict of interest.

Financial statement:

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ARABIC SUMMARY

استخدام المحاكاة بالحاسوب للتنبؤ باللقاح المضاد لمولدات الأجسام المضادة ضد العدوى بفيروس بواسون

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١- وحدة الابحاث والدراسات العلمية- كلية التمريض-جامعة جازان-الرمز البريدي ٤٥١٤٢- ص. ب٢٩١٤، المملكة العربية السعودية.

من المعروف عالمياً أن "فيروس بواسون" والذي ينتقل عن طريق حشرة القراد يعد مسئولاً عن مضاعفات الالتهابات الدماغية وكذلك المضاعفات العصبية الحادة. وتعد الببتيدات المصممة اختراعاً علاجياً مشجعاً للتخلص من تلك الإصابة الفيروسية. وتمثل المناعة المعلوماتية أداة قوية لعمل مسح يليه انتقاء لسلاسل من مولدات المضادات الببتيدية لكي تلعب دور مستقبلات الأجسام المضادة المناعية لاختبار قابلية اندماجها مع مولدات المضادات لكرات الدم البيضاء.

في الدراسة الحالية تم تطوير نموذج محاكاة حسابي لتعريف مستقبلات الأجسام المضادة المناعية في خلايا B وخلايا T المناعية لتحديد اللقاح المناسب. كذلك تم عمل دراسات تنبؤ مناعية وفيزيائية كيميائية لتمكن من التمييز بين ما هو مولدات الأجسام المضادة وغير مولدات الأجسام المضادة. إذا نظرنا للتعداد العالمي للسكان ، فقد تم عمل مسح سكاني للتعرف على احتمال الاندماج بين مستقبلات الأجسام المضادة من الصنف الأول أو الثاني من المتوافقات النسيجية . إن نموذج التوقيع بالتحليل الحسابي سوف يطور فهمنا لكيفية استجابة الخلايا المناعية من النوع B والنوع T كذلك سوف يساعد في اختيار مولدات المضادات المناعية الببتيدية من أجل عمل طقم تشخيص لمولدات المضادات أو لقاح فرعي من الببتيدات ضد فيروس بواسون