


A Review on Computational Tools and Databases for the Development of Vaccines Against Infectious Diseases

Enfeksiyon Hastalıklarına Karşı Geliştirilen Aşıların Geliştirilmesinde Kullanılan Gereç ve Veri Tabanlarının Derlemesi

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Abstract

The emergence and successful implementation of bioinformatics and computational technology in the different area of molecular biology has a positive impact on the scientists and researchers. Fast accessibility of computer and internet resources generated new possibilities to help the biological scientific community with the best of the previous knowledge to expand the possibilities in the area of immunology and vaccine designing. Many databases and tools with huge molecular level information are freely available to utilize in the outgoing research work. Thus, the article provides information about online resources, database and tools which could be helpful in vaccine designing.

Keywords: Bioinformatics, immunology, database, vaccine designing, MHC, epitope

Öz

Biyobilişim ve hesaplama teknolojilerinin moleküler biyolojinin farklı alanlarında yeni gelişen ve başarılı uygulamaları bu konuda yapılan çalışmalara ve araştırmacılara olumlu katkıda bulunmuştur. Bilgisayarlara ve internet kaynaklarına hızlı bir şekilde ulaşabiliyor olmak biyoloji bilmi topluluğuna var olan bilgiyi genişletme ve bağışıklık bilimi ve aşı geliştirme konusundaki olanakları geliştirmiştir. Devasa moleküler düzey bilgi ve bir çok veritabanı bilimsel çalışmalara destek sağlayabilecek şekilde herkesin kullanımına sunulmaktadır. Bu makale, aşı tasarımında yararlı olabilecek çevrimiçi kaynaklar, veri tabanı ve benzeri olanakların derlemesini içermektedir.

Anahtar Kelimeler: Biyobilişim, bağışıklık bilimi, veri tabanı, aşı tasarımı, MHC, epitop

Introduction

The revolutionary role of vaccine designing in saving the mankind has been great. Although, the bacteria and viruses are the common part and unavoidable species in the human world, but still the vaccine designing has its own significance in saving mankind from deadly evils.

The discovery of vaccines has eradicated several important diseases, which resulted in the reduction in healthcare cost. The vaccines, which are in use now were found a century ago. The use of science to modify and control vaccine design is helping medical and scientific researchers to stay one step ahead of most of the deadly scenarios. The swine and bird flu were a big scare over the last few years, but vaccinations are now available if the public wishes to use them.

The only problem is that the vaccine design often cost large amounts of money and is not always readily available for everyone. Vaccine design for the HIV virus and deadly retroviruses are being constantly tested in laboratories for the safety of the population from these diseases.^[1]

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Without it the ever increasing chance of a pandemic of super viruses would linger over us constantly. First the world encountered the black plague, smallpox and other deadly diseases and now today we have been subjected to the Bird Flu plus another strain known as the H1N1 Flu. After the discovery of antibiotics, bacteria were put into control, however the virus was still unstoppable.

The viral infections can be stopped with the help of vaccination. Medical staff in Queensland, Australia have found a vaccine which may prevent the spread of the potentially lethal H1N1 Flu.^[2] Vaccine design is about creating a drug that either stimulates the immunity to fight the virus or a vaccine that is capable of fighting the virus itself.

The second outcome would be greatly desired, so that the immunity can focus on doing other jobs such as protecting itself and therefore also not drain the body of so much energy. The destruction of the immunity will eventuate in death, which is a viral infection such as Acquired Immune Deficiency Syndrome (AIDS) which specifically affects the immune system.^[3]

During the early days the vaccine designing was done by pen and paper, recording complex algorithms and notes to document the result of the study. Recent advancement and involvement of computers in vaccine design has made the process faster (Figure 1).

The calculation of the active immunization results can be done faster with the help of computers. Bioinformatics proves as strong tool for computer based vaccine designing. The computational methods have helped to understand the and explore the hidden reality of immunology and vaccine design.

Several Bioinformatics tools and database are discussed in the article.

Bioinformatics Tools for Vaccine Designing

Vaccine Investigation and Online Information Network (VIOLIN)

The designing of VIOLIN is an important source of vaccine information which will help the researchers in basic and clinical sciences with curated data and bioinformatics tools. VIOLIN is a web-based central resource. The research data derived from vaccine studies on humans, and lab animals are available in VIOLIN. The VIOLIN data available in an XML-based data exchange format can be downloaded by the users.^[4]

MtbVeb

According to Dhanda et al. the MtbVeb a web based platform can be used for designing vaccines against existing and emerging strains of *Mycobacterium*

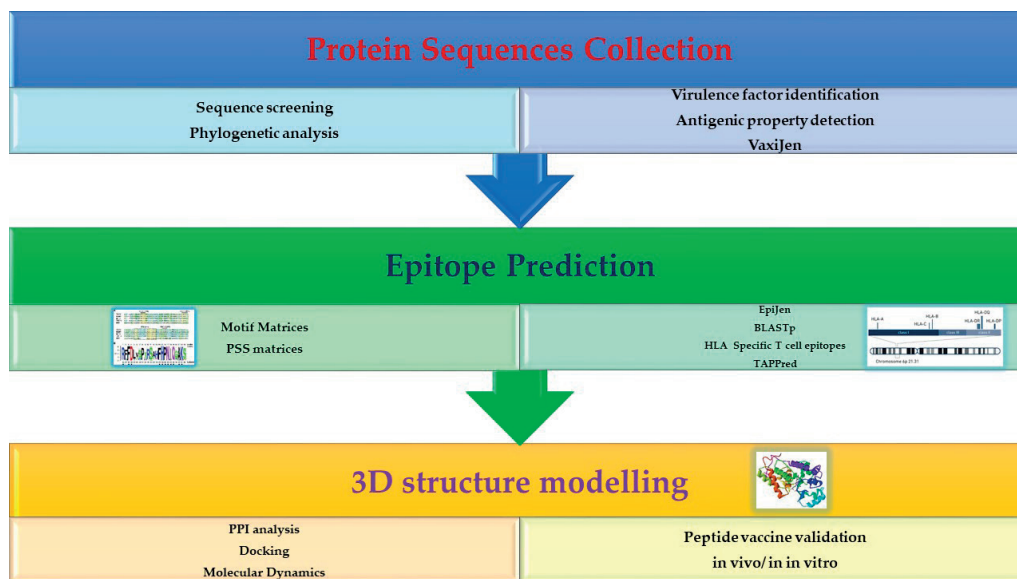


Figure 1. Flowchart showing steps in the in silico vaccine designing

Table 1. List of bioinformatics tools for vaccine designing

S.No	Name of Tools	Website details	Functions
1.	VIOLIN	http://www.violinet.org/	Vaccine data analysis, vaccine target prediction
2.	MtbVeb	http://crdd.osdd.net/raghava/mtbveb/	vaccines against M.tb
3.	DyNAVacS	http://miracle.igib.res.in/dynavac/	designing of DNA vaccines
4.	Epigraph	https://www.hiv.lanl.gov/content/sequence/EPIGRAPH/epigraph.html	vaccine or reagent design
5.	EpiToolKit 2.0	http://www.epitoolkit.de/	Epitope and vaccine design
6.	VaxiJen	http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html	alignment-independent prediction of protective antigens
7.	Mosaic Vaccine Designer	https://www.hiv.lanl.gov/content/sequence/MOSAIC/	design and assess vaccine candidate protein sequences
8.	IgBLAST	https://www.ncbi.nlm.nih.gov/igblast/	perform analysis for immunoglobulin and T cell receptor sequences

tuberculosis. The vaccines against MtbVeb can be developed by using all three methods (strain, antigen and epitope based vaccines).^[5]

DyNAVacS: an integrative tool for optimized DNA vaccine design

The rapid and effortless design of DNA vaccines can be developed through DyNAVacS: an integrative tool for optimized DNA vaccine design. The vaccine design flow is stepwise. The Apache HTTP server is used by this web version. The interface was written in HTML and utilizes the Common Gateway Interface scripts written in PERL for functionality DyNAVacS does not require much information from the user. This tool consists of user friendly programs. This software is available free of cost.^[6]

Epigraph

The role of Epigraph as a tool was introduced by Theiler et al. The Epigraph sequences are developed with this tool. The base of the sequence is on an input population of diverse sequences.^[7]

EpiToolKit

Schubert et al. described EpiToolKit is a virtual workbench for immunological questions with a focus on vaccine design. The range of immunoinformatics including MHC genotyping, epitope and neo-epitope prediction, epitope selection for vaccine design, and epitope assembly are present in this kit.^[8]

Vaxigen

Vaxign (Vaccine Design) is an antibody target prediction and investigation technique in light of the standard of reverse vaccinology.^[9]

Mosaic Vaccine Designer

Thurmond et al. explained that the generation of candidate vaccine protein cocktails can be done by the Mosaic Vaccine Designer. A small set of proteins could be included in a vaccine cocktail of potential T-cell epitopes in a large diverse set of proteins.^[10]

IgBLAST tool

An analysis of immunoglobulin variable domain sequences can be done by IgBLAST. The tool was developed at NCBI. It uses a BLAST search algorithm reported by Ye et al.^[11]

Immunology Database

The immunological information is available in many databases which are as follows:

AntiJen

AntiJen is a database framework concentrated on the coordination of kinetic, thermodynamic, cellular and molecular information related to immunology and vaccinology. The database contains more than 31,000 entries.^[12]

AntigenDB

AntigenDB database have collection of data related to the sequence, structure, origin, etc. of an antigen

Table 2. List of Immunology database

S. No.	Database Name	Website details	Available information
1.	AntiJen	http://www.ddg-pharmfac.net/antijen/AntiJen/antijenhomepage.htm	containing quantitative binding data for peptides binding to MHC Ligand, TCR-MHC Complexes, T Cell Epitope, TAP, B Cell Epitope molecules and immunological Protein-Protein interactions.
2.	AntigenDB	http://crdd.osdd.net/raghava/antigendb/	experimentally-validated antigens
3.	McPAS-TCR	http://friedmanlab.weizmann.ac.il/McPAS-TCR/	catalogue of T cell receptor (TCR) sequences in Human and Mice
4.	IMGT Database	http://www.imgt.org/IMGTindex/databases.php	immunoglobulins (IG) or antibodies, T cell receptors (TR), major histocompatibility (MH) of human and other vertebrate species, and in the immunoglobulin superfamily (IgSF), MH superfamily (MhSF) and related proteins of the immune system (RPI) of vertebrates and invertebrates
5.	IPD-ESTDAB	https://www.ebi.ac.uk/cgi-bin/ipd/estdab/print_cell.cgi?ESTDAB-001	polymorphic genes in the immune system, cell bank of immunologically characterized melanoma cell lines
6.	IPD-HPA	https://www.ebi.ac.uk/ipd/hpa/	human platelet antigens (HPA)
7.	MHCBN 4.0	http://crdd.osdd.net/raghava/mhcbn/	Major Histocompatibility Complex (MHC) Binding, Non-binding peptides and T-cell epitopes
8.	MPID-T2	http://biolinfo.org/mpid-t2/	Sequence-structure-function information on T cell receptor/peptide/MHC interactions.
9.	MUGEN	http://bioit.fleming.gr/mugen/mde.jsp	contain genetic and phenotypic data of relevance to the mouse as a model organism and immunological processes
10.	VBASE2	http://www.vbase2.org/	contains immunoglobulin germ-line V genes
11.	Glydin'	http://glycoproteome.expasy.org/epitopes/	Visualization of Epitope Network
12.	Epitome	https://www.rostlab.org/services/epitome/	antigen/antibody complex structures, a detailed description of the residues that are involved in the interactions, and their sequence/structure environments
13.	SAbDab	http://opig.stats.ox.ac.uk/webapps/sabdab-sabpred/Welcme.php	Antibodies structural information
14.	STCRDab	http://opig.stats.ox.ac.uk/webapps/stcrdab/	T Cell Receptor Structural Information

also with information about B and T-cell epitopes, MHC binding, function, gene-expression and post translational modifications.^[13]

McPAS-TCR

McPAS-TCR is a manually curated catalogue of T cell receptor (TCR) sequences that were found in T cells associated with various pathological conditions in humans and in mice.^[14] The database is available for download.

IMGT Database

IMGT[®], the International ImMunoGeneTics[®] data system. <http://www.imgt.org>, is the worldwide reference

in immunogenetics and immunoinformatics, made in 1989 by Marie-Paule Lefranc. Comprises of sequence databases, genome database, structure database, and monoclonal antibodies.^[15] <http://imgt3d.igh.cnrs.fr/>

IPD-ESTDAB

The European Searchable Tumor Line Database (ESTDAB) Database and Cell Bank give an access to the scientific communities to scan online query for HLA, immunologically described tumor cells as a feature of the European Commission Fifth Framework Infrastructures Program.^[16]

IPD-HPA

The database gives a unified collection of the information which characterizes the human platelet antigens (HPA). All antibodies against human platelet antigens are engaged with neonatal alloimmune thrombocytopenia, post-transfusion purpura and recalcitrance to irregular contributor platelets.^[17]

MHCBN 4.0

The MHCBN is a curated database comprising of data about Major Histocompatibility Complex (MHC) Binding, Non-restricting peptides and T-cell epitopes.^[18] Database furnishes data about peptides connecting with TAP (Transporter related with antigen handling) and MHC connected immune system diseases.

MPID-T2

The MHC-Peptide Interaction Database-TR version 2 (MPID-T2) is another database for sequence-structure-functional data on T cell receptor/peptide/MHC interactions. It contains all known structures of TR/pMHC and pMHC complexes.^[19]

MUGEN Mouse Database (MMdb)

Aidinis et al. detailed a completely accessible database of murine models of immune processes and immunological ailments.^[20]

VBAS2

VBASE2 is an integrative database of germ-line variable genes from the immunoglobulin loci of human and mouse. All gene sequences are accessed from the EMBL.^[21]

Glydin'

GlyDyn' is an investigation system to explore the connections between epitopes based on monosaccharide composition.^[22] The server gives a graphical representation of the Epitope Network.

<http://glycoproteome.expasy.org/epitopes/>

Epitome

Epitome is a database of the known antigenic residues and the antibodies that interact with them also provide complete of residues involved in the interaction and their sequence/structure environments.^[23]

SAbDab

The Structural antibody database is an online asset containing all the openly accessible. It contains antibody structures clarified and introduced in a reliable way. The information contains exploratory data of antibody-antigen binding affinity.^[24]

STCRDab

The Structural T-cell Receptor Database (STCRDab) is an online asset that consequently gathers and accessible TCR structural information from the Protein Data Bank.^[25]

Databases of MHC Binding Peptides

List of MHC binding peptides database is described below:

SYFPEITHI

SYFPEITHI is a database including more than 7000 peptide sequences known to tie class I and class II MHC biomolecules. It contains a gathering of MHC class I and class II ligands and peptide motifs of humans and different species, for example, primates, dairy cattle, chicken, and mouse. All motifs as of now accessible will be available as individual entries. Looks for MHC alleles, MHC themes, normal ligands, T-cell epitopes, source proteins/organisms and references are available.^[26]

MHCPEP

MHCPEP is a curated database including more than 4000 peptide sequences known to interact with MHC molecules. Sections are assembled from reported experimental evidences.

Every data contains the source protein and is completely referenced.^[27] The present organization of the database permits test string coordinating inquiries. The database can be gotten to through the Internet utilizing gopher.

EPIMHC

EPIMHC is a database of MHC-binding peptides and T cell epitopes that are seen in genuine proteins. As of now, the database contains 4867 different peptide sequences from different sources, including 84 tumor-related antigens. The database is available through a web server that has been intended to encourage inquire about in computational vaccinology.^[28]

Table 3.: List of MHC binding peptides database

S.No.	Database Name	Website details	Available information
1.	SYFPEITHI	http://www.syfpeithi.de/	peptide sequences known to bind class I and class II MHC molecules
2.	MHCPEP	http://wehih.wehi.edu.au/mhcpep	4000 peptide sequences known to bind MHC molecules
3.	EPIMHC	http://immunax.dfci.harvard.edu/bioinformatics/epimhc/	Sequences of MHC-binding peptides and T cell epitopes
4.	MHCBN 4.0	http://crdd.osdd.net/raghava/mhcbn/	peptide sequences
5.	IPD-IMGT/HLA	https://www.ebi.ac.uk/ipd/imgt/hla/	Sequences of Human MHC
6.	dbMHC	https://www.ncbi.nlm.nih.gov/gv/mhc/main.fcgi?cmd=init	clinical data related to MHC
7.	HIV Molecular Immunology database	https://www.hiv.lanl.gov/content/immunology/	HIV-1 cytotoxic and helper T-cell epitopes and antibody binding sites
8.	JenPep	http://www.jenner.ac.uk/JenPep	quantitative data on peptide binding MHCs, TAP and annotated list of T-cell epitopes.
9.	FIMM	http://sdmc.krdl.org.sg:8080/fimm	protein antigens, MHC molecules, MHC-associated peptides and relevant disease associations
10.	IEDB	http://www.iedb.org/	Experimental data characterizing antibody and T cell epitopes studied in humans, non-human primates, and other animal species. Epitopes involved in infectious disease, allergy, autoimmunity, and transplant are included
11.	HPtaa	http://www.bioinfo.org.cn/hptaa/	Human Potential Tumor Associated Antigen database (HPtaa) with pTAAs identified by in silico computing

MHCBN 4.0

MHCBN is a database containing more than 25,857 peptide sequences (1053 TAP restricting peptides). It is a physically curated database where sections are gathered and aggregated from distributed research articles and existing immunological open databases. MHCBN has various online systems for the investigation and access of data like mapping of antigenic locales, formation of the allele particular dataset, BLAST analysis, and different ailments related with MHC alleles reported by Lata et al.^[18]

IPD-IMGT/HLA Database

The IPD-IMGT/HLA database gives a master database to sequences of the human major histocompatibility complex (MHC) Furthermore incorporates the sequences named by WHO Nomenclature Committee to elements of the HLA framework.^[29] The IPD-IMGT/HLA database is the part of ImMunoGeneTics venture (IMGT).

dbMHC

The dbMHC database gives an open, publicly accessible stage to DNA and clinical information identified related to the human Major

Histocompatibility Complex (MHC). The MHC database might have been outlined on provide a stage the place the HLA scientific group could submit, edit, view, MHC information. At present comprises of sequence alignment Viewer for HLA Furthermore, related genes, an MHC microsatellite database, sequence understanding region for Sequencing based Typing (SBT), also a Primer/Probe database.^[30]

HIV Molecular Immunology database

The HIV Molecular Immunology Database is an annotated, searchable gathering from claiming HIV-1 cytotoxic also aide T-cell epitopes and antibody binding sites.^[31] <http://www.hiv.lanl.gov/>

JenPep

JenPep is a databases supporting those developing group of immunoinformaticians.

It holds quantitative information once peptide binding to major histocompatibility Complexes (MHCs), Transmembrane peptide transporter (TAP), and additionally an annotated information about T-cell epitopes.^[32,33]

FIMM

FIMM holds information related to functional molecular immunology, centering cellular immunology. It holds completely referenced information on protein antigens, MHC molecules, MHC-associated peptides. FIMM use tools to retrieve information in the form of lists.^[34]

Immune epitope database (IEDB) 3.0

IEDB is a free database, financed by an agreement from the National Institute of Allergy and Infectious Diseases. It offers simple searching for trial information characterizing antibody and T cell epitopes studied in humans, non-human primates, and other animal species. Epitopes included in irresistible disease, allergy, and autoimmunity, furthermore transplant would have included. Those IEDB Additionally hosts software to aid in those prediction about B cell and T cell epitopes.^[35] <http://www.niaid.nih.gov>

HPtaa Database

Human Potential Tumor Associated Antigen database (HPtaa) has currently 3518 possibility focuses information, which may be uninhibitedly accessible for academic clients. It effectively screened 41 from claiming 82 referred to the Cancer-Testis antigens, 6 from claiming 18 separate antigens, 2 from claiming 2 oncofetal antigen, and 7 about 12 FDA sanction disease markers that bring gene ID, along these lines thus database will be a great stage to ID number for tumor/cancer target genes.^[36]

MHC Binding Peptide and Epitope Prediction

Many freely available tools are available to find out the MHC binding peptide and Epitopes. Most of them are discussed below:

Table 4. MHC binding peptide and epitope prediction tools

S.No.	Name of tools	Websites details	Functions
1.	SVMHC	https://abi.inf.uni-tuebingen.de/Services/SVMHC/index_html	prediction of MHC-binding peptides
2.	MHCPred	http://www.ddg-pharmfac.net/mhcpred/MHCPred/	Predict binding affinity of MHC
3.	FRED 2	http://fred-2.github.io/	Epitope prediction
4.	ProPred	http://crdd.osdd.net/raghava/propred/	predict MHC class II binding regions
5.	Bcipep	http://crdd.osdd.net/raghava/bcipep/	B cell epitopes
6.	MAPPP	http://www.mpiib-berlin.mpg.de/MAPPP/	predict the potential antigenic epitopes presented on the cell surface by major histocompatibility complex class I (MHC I) molecules to CD8 positive T lymphocytes
7.	SYFPEITHI	http://www.syfpeithi.de/bin/MHCServer.dll/EpitopePrediction.htm	Predict the ligation strength to a defined MHC I or II type for a sequence of amino acids
8.	POPI	http://iclab.life.nctu.edu.tw/POPI/	for predicting immunogenicity of binding peptides of MHC class I and II
9.	BIMAS	https://www.bimas.cit.nih.gov/molbio/hla_bind/	HLA peptide binding prediction
10.	NetCTL 1.2 Server	http://www.cbs.dtu.dk/services/NetCTL/	predicts CTL epitopes in protein sequences
11.	NetMHC 4.0 Server	http://www.cbs.dtu.dk/services/NetMHC/	Prediction of peptide-MHC class I binding
12.	CTLPred	http://crdd.osdd.net/raghava/ctlpred/	prediction of CTL epitopes
13.	ProPred-I	http://crdd.osdd.net/raghava/propred/	identifying the MHC Class-I binding regions in antigens
14.	SMM	http://cagt.bu.edu/page/SMM_about	predict HLA-A2 binding peptides
15.	SVMTrip	http://sysbio.unl.edu/SVMTriP/prediction.php	predict antigenic epitopes
16.	BCPREDS	http://ailab.ist.psu.edu/bcpred/	predict B cell epitope
17.	ABCPred	http://crdd.osdd.net/raghava/abcpred/	predict B cell epitope(s) in an antigen sequence
18.	BepiPred-2.0	http://www.cbs.dtu.dk/services/BepiPred/	predict potential B-cell epitopes
19.	TEPredict	http://tepredict.sourceforge.net/	Software for T cell epitope prediction
20.	PEPVAC	http://imed.med.ucm.es/PEPVAC/	Tool for multi epitope vaccine, genome wide predictions of promiscuous MHC I-restricted epitopes
21.	Rankpep	http://imed.med.ucm.es/Tools/rankpep.html	prediction of binding peptides to Class I and Class II MHC molecules

SVMHC

A server for prediction about MHC-binding peptide recognition of MHC-binding peptides will be a requirement for the designing of T-cell based peptide antibodies. SVMHC server is useful to find out the both MHC class I and class II binding peptide through computational methods. This server might use to identify the binder protein sequence which could be useful in the detection of SNPs within MHC binding peptides.^[37]

MHCPred

MHCPred uses the extra computational approach to predict the binding affinity of MHC class I and II molecules and also Transporter associated with Processing (TAP). Allele QSAR models were generated using partial least squares (PLS) reported by Guan et al.^[38]

FRED 2

FRED 2 is a platform in order to detect the T-cell epitope and vaccine design. It provides reliable and effortless entry to the fine immunoinformatics strategies followed by computational approach.^[39]

ProPred

The server is useful in the identification of MHC Class-II binding regions in an antigen sequence, using quantitative matrices developed from published literature by Sturniolo et al.^[40] Also the server will support and help in the finding of binding regions that are helpful in identification of vaccine candidates.^[41]

Bcipep

Bcipep is a great collection of information collected from different resources like literature and other freely available information related to experimentally determined linear B-cell epitopes.^[42]

MAPPP (MHC-I Antigenic Peptide Processing Prediction)

MAPPP is an online available tool which can predict the possible antigenic epitopes existing on the cell surface by MHC I molecules to CD8 positive T lymphocytes. It also predicts the proteasomal cleavage site with peptide binding to MHC I molecules.^[43]

SYFFPEITHI

The database has also a facility to identify the ligation potency to an available MHC I or II type of a sequence of amino acids.^[26]

POPI (Prediction of Peptide Immunogenicity) prediction system

POPI is a Support Vector Machine (SVM) based prediction server using revealing physicochemical properties for predicting immunogenicity of binding peptides of MHC class I and II.^[44]

BIMAS (Bioinformatics and Molecular Analysis Section)

BIMAS tool predict 8-mer, 9-mer, or 10-mer peptides depend on a predicted half-time of dissociation to HLA class I molecules.^[45]

NetCTL 1.2 Server

NetCTL predicts CTL epitopes in protein sequences reported by Larsen et al.^[46] for the possible identification of large-scale rationale of methods for cytotoxic T-lymphocyte epitope.

NetMHC 4.0

The server predicts the peptide-MHC class I binding using artificial neural networks (ANNs) first time reported by Andreatta and Nielsen et al.^[47]

CTLPred

CTLPred is a tool for accurate prediction of CTL epitopes essential in the process of vaccine design.^[48]

ProPred-I

The ProPred-I is an online platform for detecting the MHC Class-I binding regions in antigens sequence. It works with the execution of matrices for 47 MHC Class-I alleles, proteasomal and immunoproteasomal models. It also provides facility to the researchers in the detection of promiscuous regions.^[49]

SMM

A SMM method based software for the possible identification of HLA-A2 binding peptides.^[50]

SVMTrip

The online server helps in the detection of protein surface regions with the intention of the predictable by antibodies (antigenic epitopes) can provide support in the design of vaccine machinery and immuno-diagnostic reagents.^[51]

BCPREDS

B-cell epitope is an online prediction platform to provide the scientific community to select among three prediction methods: (i) execution of AAP method ^[52]; (ii) BCPred ^[53]; (iii) FBCPred ^[54]. Obtained output could be in different user-friendly formats reported by several researchers. ^[52,53]

ABCPred

The main purpose of ABCpred server is to identify possible B cell epitope (s) in an antigen sequence, using artificial neural network. ^[55]

BepiPred-2.0

Sequential B-Cell Epitope Predictor BepiPred predicts potential B-cell epitopes. Also, it can be downloaded on a personal computer for academic and research purpose. ^[56]

TEpredict

TEpredict is a tool for the T-Cell epitope detection also used to predict T cell epitopes reported by Antonets and Maksyutov. ^[57]

PEPVAC

PEPVAC is a tool followed by computational methods helps in the designing and development of multi-epitope vaccines targeting the pathogenic organisms based on the analysis of genome wide detection of promiscuous MHCII-restricted epitopes. ^[58,59]

Rankpep

A server designed to predict possible peptide binders to MHCII and MHCII molecules from protein sequence alignments after implementing Position Specific Scoring Matrices (PSSMs). It also helps in the detection of C-terminal end MHCII ligands for the usefulness of proteasomal cleavage. ^[60-62]

Commercial Software and Tools

There would additionally commercial software and tools are accessible for the epitope prediction.

DNASTAR's Epitope Prediction Software

DNASTAR's Lasergene Structural Biology Suite have different software and tools like Protean 3D function, which provide epitope prediction in order to detect B-cell epitopes based on protein sequence data with visualization software.

<https://www.dnastar.com/t-products-dnastar-lasergene-structural-biology.aspx>

EpiQuest

EpiQuest is an exceptional software package for the investigation of linear protein sequence for the prediction of B-cell, T-cell epitopes.

<http://www.apturn-bio.com/software>

OptimumAntigen™ Design Tool

OptimumAntigen™ Design Tool is a complete suite for the peptide detection, identification for the experimental assay(s).

<https://www.genscript.com/antigen-design.html>

TEPITOPE

The software allows users to predict promiscuous peptide ligands for the HLA binding also predicts the T cell epitopes. ^[63]

Proteasomal Cleavage Site Prediction Tools

List of software and tools for the prediction of proteasomal cleavage sites discussed below:

Table 5. List of commercial software and tools

S.No.	Software name	Website details	Functions
1.	DNASTAR's Epitope Prediction Software	https://www.dnastar.com/t-sub-solutions-structural-biology-epitope-prediction.aspx	predict B-cell epitopes based on protein sequence data
2.	EpiQuest	http://www.apturn-bio.com/software	predict B cell, T cell epitopes
3.	OptimumAntigen™ Design Tool	https://www.genscript.com/antigen-design.html	Antigen and epitopes prediction
4.	TEPITOPE	http://www.biokdd.fudan.edu.cn/Service/TEPITOPEpan/	Predict HLA binding sites and T cell epitopes

Table 6. Proteasomal cleavage site prediction tools

S.No.	Tools name	Website details	Functions
1.	Pcleavage	http://crdd.osdd.net/raghava/pcleavage/	predict immunoproteasome cleavage sites in antigenic sequences
2.	PAProC	http://www.paproc.de/	prediction tool for cleavages by human and yeast proteasomes
3.	MAPPP	http://www.mpiib-berlin.mpg.de/MAPPP/cleavage.html	predict the 20S proteasomal cleavage sites
4.	NetChop 3.1	http://www.cbs.dtu.dk/services/NetChop/	predict cleavage sites of the human proteasome
5.	PepCleave	http://peptibase.cs.biu.ac.il/PepCleave_II/	prediction of peptides cleaved by the proteasome

Pcleavage

A tool to detect the immunoproteasome cleavage sites in antigenic sequences using a support vector machine (SVM) based prediction methods.^[64]

PAProC

PAProC is a tool for the prediction of cleavage sites by human and yeast proteasomes, supported by the experimental cleavage data. It also predicts the MHC class I molecule (MHC I) ligands and cytotoxic T-lymphocyte (CTL) epitopes.^[65]

MAPPP

MAPPP tool can predict the 20s proteasomal cleavage sites.^[44]

NetChop 3.1

The NetChop server detects the human proteasomal cleavage sites using ANNs.^[66]

Conclusion

Web design tools are working in rapid growth of the field of immunological Bioinformatics. Several online tools, software and servers have been developed and freely available through the websites and can be accessed by the research groups without any expert knowledge of bioinformatics.

Peer-review: Externally peer-reviewed.

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References

- Shapiro SZ. Clinical development of candidate HIV vaccines: different problems for different vaccines. *AIDS Res Hum Retroviruses* 2014;30:325–9. [CrossRef]
- Vandegrift KJ, Sokolow SH, Daszak P, Kilpatrick AM. Ecology of avian influenza viruses in a changing world. *Ann N Y Acad Sci* 2010;1195:113–28. [CrossRef]
- Al-Jabri AA. Mechanisms of Host Resistance Against HIV Infection and Progression to AIDS. *Sultan Qaboos Univ Med J* 2007;7:82–96.
- He Y, Racz R, Sayers S, Lin Y, Todd T, Hur J, et al. Updates on the web-based VIOLIN vaccine database and analysis system. *Nucleic Acids Res* 2014;42(Database issue):D1124–32. [CrossRef]
- Dhanda SK, Vir P, Singla D, Gupta S, Kumar S, Raghava GPS. A Web-Based Platform for Designing Vaccines against Existing and Emerging Strains of Mycobacterium tuberculosis. *PLoS ONE* 2016;11:e0153771. [CrossRef]
- Harish N, Gupta R, Agarwal P, Scaria V, Pillai B. DyNAVacS. an integrative tool for optimized DNA vaccine design. *Nucleic Acids Res* 2006;34(Web Server issue):W264–6. [CrossRef]
- Theiler J, Yoon H, Yusim K, Picker LJ, Fruh K, Korber B. Epigraph: A Vaccine Design Tool Applied to an HIV Therapeutic Vaccine and a Pan-Filovirus Vaccine. *Sci Rep* 2016;6:33987. [CrossRef]
- Schubert B, Brachvogel HP, Jürges C, Kohlbacher O. EpiToolKit –a web-based workbench for vaccine design. *Bioinformatics* 2015;31:2211–3. [CrossRef]
- He Y, Xiang Z, Mobley HL. Vaxign: the first web-based vaccine design program for reverse vaccinology and applications for vaccine development. *J Biomed Biotechnol* 2010;2010:297505. [CrossRef]
- Thurmond J, Yoon H, Kuiken C, Yusim K, Perkins S, Theiler J, et al. Web-based design and evaluation of T-cell vaccine candidates. *Bioinformatics* 2008;24:1639–40. [CrossRef]
- Ye J, Ma N, Madden TL, Ostell JM. IgBLAST. an immunoglobulin variable domain sequence analysis tool. *Nucleic Acids Res* 2013;41(Web Server issue):W34–40. [CrossRef]
- Toseland CP, Clayton DJ, McSparron H, Hemsley SL, Blythe MJ, Paine K, et al. AntiJen: a quantitative immunology database integrating functional, thermodynamic, kinetic, biophysical, and cellular data. *Immunome Res* 2005;1:4. [CrossRef]

13. Ansari HR, Flower DR, Raghava GP. Antigen DB: an immunoinformatics database of pathogen antigens. *Nucleic Acids Res* 2010;D847–53. [[CrossRef](#)]
14. Tickotsky N, Sagiv T, Prilusky J, Shifrut E, Friedman N. McPAS-TCR. a manually curated catalogue of pathology-associated T cell receptor sequences. *Bioinformatics* 2017;33:2924–9. [[CrossRef](#)]
15. Lefranc MP. IMGT, the international ImMunoGeneTics database. *Nucleic Acids Res* 2001;29:207–9. [[CrossRef](#)]
16. Pawelec G, Marsh SG. ESTDAB: a collection of immunologically characterised melanoma cell lines and searchable databank. *Cancer Immunol Immunother* 2006;55:623–7. [[CrossRef](#)]
17. Metcalfe P, Watkins NA, Ouwehand WH, Kaplan C, Newman P, Kekomaki R, et al. Nomenclature of Human Platelet Antigens (HPA). *Vox Sanguinis* 2003;85:240–5. [[CrossRef](#)]
18. Lata S, Bhasin M, Raghava GP. MHCBN 4.0: A database of MHC/TAP binding peptides and T-cell epitopes. *BMC Res Notes* 2009;2:61. [[CrossRef](#)]
19. Khan JM, Cheruku HR, Tong JC, Ranganathan S. MPID-T2: a database for sequence-structure-function analyses of pMHC and TR/pMHC structures. *Bioinformatics* 2011;27:1192–3. [[CrossRef](#)]
20. Aidinis V, Chandras C, Manoloukos M, Thanassopoulou A, Kranidioti K, Armaka M, et al. MUGEN mouse database; animal models of human immunological diseases. *Nucleic Acids Res* 2008;36(Database issue):D1048–54. [[CrossRef](#)]
21. Retter I, Althaus HH, Münch R, Müller W. VBASE2, an integrative V gene database. *Nucleic Acids Res* 2005;33(Database issue):D671–4. [[CrossRef](#)]
22. Alocci D, Ghraichy M, Barletta E, Gastaldello A, Mariethoz J, Lisacek F. Understanding the glycome: an interactive view of glycosylation from glycompositions to glycoepitopes. *Glycobiology* 2018;28:349–62. [[CrossRef](#)]
23. Schlessinger A, Ofra Y, Yachdav G, Rost B. Epitome: database of structure-inferred antigenic epitopes. *Nucleic Acids Res* 2006;34(Database issue):D777–80. [[CrossRef](#)]
24. Dunbar J, Krawczyk K, Leem J, Baker T, Fuchs A, Georges G, et al. SAbDab: the structural antibody database. *Nucleic Acids Research* 2014;42(Database issue):D1140–6. [[CrossRef](#)]
25. Leem J, de Oliveira SHP, Krawczyk K, Deane CM. STCRDab: the structural T-cell receptor database. *Nucleic Acids Res* 2018;46(D1):D406–12. [[CrossRef](#)]
26. Rammensee H, Bachmann J, Emmerich NP, Bachor OA, Stevanovic S. SYFPEITHI. database for MHC ligands and peptide motifs. *Immunogenetics* 1999;50:213–9. [[CrossRef](#)]
27. Brusic V, Rudy G, Harrison LC. MHCPEP. a database of MHC-binding peptides. *Nucleic Acids Res* 1994;22:3663–5. [[CrossRef](#)]
28. Reche PA, Zhang H, Glutting JP, Reinherz EL. EPIMHC. a curated database of MHC-binding peptides for customized computational vaccinology. *Bioinformatics* 2005;21:2140–1. [[CrossRef](#)]
29. Robinson J, Halliwell JA, Hayhurst JD, Flicek P, Parham P, Marsh SG. The IPD and IMGT/HLA database: allele variant databases. *Nucleic Acids Res* 2015;43(Database issue):D423–31. [[CrossRef](#)]
30. Helmborg W, Dunivin R, Feolo M. The sequencing-based typing tool of dbMHC. typing highly polymorphic gene sequences. *Nucleic Acids Res* 2004;32(Web Server issue):W173–5. [[CrossRef](#)]
31. Yusim K, Korber BTM, Brander C, Barouch D, R de Boer, Haynes BF, et al. HIV Molecular Immunology. Los Alamos National Laboratory, Theoretical Biology and Biophysics, Los Alamos, New Mexico 2016;LA-UR 17–24847.
32. Blythe MJ, Doytchinova IA, Flower DR. JenPep: a database of quantitative functional peptide data for immunology. *Bioinformatics* 2002;18:434–9. [[CrossRef](#)]
33. McSparron H, Blythe MJ, Zygouri C, Doytchinova IA, Flower DR. JenPep: A Novel Computational Information Resource for Immunobiology and Vaccinology. *J Chem Inf Comput Sci* 2003;43:1276–87. [[CrossRef](#)]
34. Schönbach C, Koh JLY, Sheng X, Wong L, Brusic V. FIMM, a database of functional molecular immunology. *Nucleic Acids Res* 2000;28:222–4. [[CrossRef](#)]
35. Vita R, Overton JA, Greenbaum JA, Ponomarenko J, Clark JD, Cantrell JR, et al. The immune epitope database (IEDB)3.0. *Nucleic Acids Res* 2014;43(D1). [[CrossRef](#)]
36. Wang X. HPTaa database-potential target genes for clinical diagnosis and immunotherapy of human carcinoma. *Nucleic Acids Res* 2006;34(90001):D607–12. [[CrossRef](#)]
37. Dönnies P, Kohlbacher O. SVMHC. a server for prediction of MHC-binding peptides. *Nucleic Acids Res* 2006;34(Web Server issue):W194–7. [[CrossRef](#)]
38. Guan P, Doytchinova IA, Zygouri C, Flower DR. MHCpred: bringing a quantitative dimension to the online prediction of MHC binding. *Appl Bioinformatics* 2003;2:63–6.
39. Schubert B, Walzer M, Brachvogel H-P, Szolek A, Mohr C, Kohlbacher O. FRED 2: an immunoinformatics framework for Python. *Bioinformatics* 2016;32:2044–6. [[CrossRef](#)]
40. Sturniolo T, Bono E, Ding J, Radrizzani L, Tuereci O, Sahin U, et al. Generation of tissue-specific and promiscuous HLA ligand databases using DNA microarrays and virtual HLA class II matrices. *Nat Biotechnol* 1999;17:555–61. [[CrossRef](#)]
41. Singh H, Raghava GPS. ProPred: prediction of HLA-DR binding sites. *Bioinformatics* 2001;17:1236–7. [[CrossRef](#)]
42. Saha S, Bhasin M, Raghava GP. Bcipep: a database of B-cell epitopes. *BMC Genomics* 2005;6:79. [[CrossRef](#)]
43. Hakenberg J, Nussbaum AK, Schild H, Rammensee HG, Kuttler C, Holzhutter HG, et al. MAPP: MHC class I antigenic peptide processing prediction. *Appl Bioinformatics* 2003, 2:155–8.
44. Tung C-W, Ho S-Y. POPI. predicting immunogenicity of MHC class I binding peptides by mining informative physicochemical properties. *Bioinformatics* 2007;23:942–9. [[CrossRef](#)]
45. Parker KC, Bednarek MA, Coligan JE. Scheme for ranking potential HLA-A2 binding peptides based on independent binding of individual peptide side-chains. *J. Immunol* 1994;152:163–75.
46. Larsen MV, Lundegaard C, Lamberth K, Buus S, Lund O, Nielsen M. Large-scale validation of methods for cytotoxic T-lymphocyte epitope prediction. *BMC Bioinformatics* 2007;8:424. [[CrossRef](#)]
47. Andreatta M, Nielsen M. Gapped sequence alignment using artificial neural networks: application to the MHC class I system. *Bioinformatics* 2016;32:511–7. [[CrossRef](#)]
48. Bhasin M, Raghava GPS. Prediction of CTL epitopes using QM, SVM and ANN techniques. *Vaccine* 2004;22:3195–204. [[CrossRef](#)]

49. Singh H, Raghava GP. ProPred1: prediction of promiscuous MHC Class-I binding sites. *Bioinformatics* 2003;19:1009–14. [[CrossRef](#)]
50. Peters B, Tong W, Sidney J, Sette A, Weng Z. Examining the independent binding assumption for binding of peptide epitopes to MHC-I molecules. *Bioinformatics* 2003;19:1765–72. [[CrossRef](#)]
51. Yao B, Zhang L, Liang S, Zhang C. SVMTriP. A method to predict antigenic epitopes using support vector machine to integrate tripeptide similarity and propensity. *PLoS ONE* 2012;7:e45152. [[CrossRef](#)]
52. Chen J, Liu H, Yang J, Chou K. Prediction of linear B-cell epitopes using amino acid pair antigenicity scale. *Amino Acids* 2007;33:423–8. [[CrossRef](#)]
53. El-Manzalawy Y, Dobbs D, Honavar V. Predicting linear B-cell epitopes using string kernels. *J Mol Recognit* 2008;21:243–55. [[CrossRef](#)]
54. El-Manzalawy Y, Dobbs D, Honavar V. Predicting flexible length linear B-cell epitopes 7th International Conference on Computational Systems Bioinformatics. Stanford, CA: 2008. pp.121–31.
55. Saha S, Raghava GPS. Prediction of Continuous B-cell Epitopes in an Antigen Using Recurrent Neural Network. *Proteins* 2006;65:40–8. [[CrossRef](#)]
56. Larsen JEP, Lund O, Nielsen M. Improved method for predicting linear B-cell epitopes. *Immunome Res* 2006;2:2. [[CrossRef](#)]
57. Antonets DV, Maksyutov AZ. TEpredict: Software for T-Cell epitope prediction. *Mol Biol (Mosk)* 2010;44:119.
58. Reche PA, Reinherz EL. PEPVAC. a web server for multi-epitope vaccine development based on the prediction of supertypic MHC ligands. *Nucleic Acids Res* 2005;33(Web Server issue):W138–142. [[CrossRef](#)]
59. Reche PA, Reinherz EL. Definition of MHC supertypes through clustering of MHC peptide-binding repertoires. *Methods Mol Biol* 2007;409:163–73. [[CrossRef](#)]
60. Reche PA, Glutting JP, Reinherz EL. Prediction of MHC Class I Binding Peptides Using Profile Motifs. *Hum Immunol* 2002;63:701–9. [[CrossRef](#)]
61. Reche PA, Glutting JP, Zhang H, Reinherz EL. Enhancement to the RANKPEP resource for the prediction of peptide binding to MHC molecules using profiles. *Immunogenetics* 2004;56:405–19. [[CrossRef](#)]
62. Reche PA, Reinherz EL. Prediction of peptide-MHC binding using profiles. *Methods Mol Biol* 2007;409:185–200. [[CrossRef](#)]
63. Bian H, Hammer J. Discovery of promiscuous HLA-II-restricted T cell epitopes with TEPITOPE. *Methods* 2004;34:468–75. [[CrossRef](#)]
64. Bhasin M, Raghava GP. Pcleavage: an SVM based method for prediction of constitutive proteasome and immunoproteasome cleavage sites in antigenic sequences. *Nucleic Acids Res* 2005;33(Web Server issue):W202–7. [[CrossRef](#)]
65. Nussbaum AK, Kuttler C, Haderer KP, Rammensee HG, Schild H. PProC: A prediction algorithm for proteasomal cleavages available on the WWW. *Immunogenetics* 2001;53:87–94. [[CrossRef](#)]
66. Nielsen M, Lundegaard C, Lund O, Keşmir C. The role of the proteasome in generating cytotoxic T cell epitopes: Insights obtained from improved predictions of proteasomal cleavage. *Immunogenetics* 2005;57:33–41. [[CrossRef](#)]