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Role of artificial intelligence in peptide vaccine design against RNA viruses

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ABSTRACT

RNA viruses have high rate of replication and mutation that help them adapt and change according to their environmental conditions. Many viral mutants are the cause of various severe and lethal diseases. Vaccines, on the other hand have the capacity to protect us from infectious diseases by eliciting antibody or cell-mediated immune responses that are pathogen-specific. While there are a few reviews pertaining to the use of artificial intelligence (AI) for SARS-COV-2 vaccine development, none focus on peptide vaccination for RNA viruses and the important role played by AI in it. Peptide vaccine which is slowly coming to be recognized as a safe and effective vaccination strategy has the capacity to overcome the mutant escape problem which is also being currently faced by SARS-COV-2 vaccines in circulation.Here we review the present scenario of peptide vaccines which are developed using mathematical and computational statistics methods to prevent the spread of disease caused by RNA viruses. We also focus on the importance and current stage of AI and mathematical evolutionary modeling using machine learning tools in the establishment of these new peptide vaccines for the control of viral disease.

1. Introduction

RNA viruses use the host's cellular mechanism for their rapid growth and mass-scale transmission and are responsible for the spread of many serious and lethal diseases in humans and many other animal species [1,2]. It has been difficult to develop vaccines for many RNA viruses due to the high mutation rate in replication such as Dengue virus (2.64×10^{-5}), Influenza H3N2 (1.35×10^{-5}), and HIV-1 (4×10^{-5}) [3–6]. DNA sequencing techniques have produced extensive data on the genetic diversity of these viruses. The integration and analysis of these large data sets provide valuable information which, when combined with mathematical and computational statistic methods, can become a powerful tool in predicting future vaccine candidates [7]. In the present scenario of the COVID 19 pandemic, the therapeutic approaches based on computational biology and machine-learning algorithms provide faster and better outcomes in vaccine development and other therapeutics such as drug repurposing, plasma therapy, and drug discovery [8–12]. Machine-learning tools help to predict components that generate an immune response in humans against RNA viruses. These tools enable researchers to understand the virus and its structure, tracks the virus's genetic mutations over time, information that will determine any vaccine's value in the years to come [13]. Different bioinformatics tools have been established to identify potential immunogenic regions in viral antigenic protein sequences that helped in generation of peptide vaccine some of which are now licensed and in use while many are in the pipeline [14].

The surge in coronavirus 2 (SARS-CoV-2)variants of concern (VOC) in the ongoing pandemic i.e AlphaB.1.1.7, BetaB.1.351, GammaP.1, Delta B.1.617.2, Kappa*B.1.617.1 is a major international public health concern as these altered genomes has led to an increase in the viral transmissibility, virulence, and ability to evade host response. The vaccines introduced are based on introducing the spike protein either in **mRNA**, Adenovirus vectors, recombinant protein form using the early isolates or as the inactivated whole virus as the Indian vaccine BBV152. Studies suggest that BNT162b2 (***mRNA)*** vaccines were able to neutralize Alpha and Gamma variants but less significantly against Betavariant [15–17]. mRNA-1273 (***mRNA)*** was able to neutralize the Alpha variant but to a lower extent against the Beta variant [15,18,19]. Ad26.COV2.S (Adenovirus vector based)was shown to have low efficacies to the Beta (64%), the Gamma (61%) and the Alpha (72%) [20]. ChAdOx1 nCoV-19 (Oxford) was 74.6% efficacious against Alpha and 10.4% against Beta [21,22]. BBV152 (Bharat Biotech International Limited) vaccinated human serum is able to neutralize the Alpha variant [23].The phase 3 clinical trial data fact sheet of Novavax (recombinant

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protein) shows its vaccine to have 90.4% overall efficacy as well as 93.2% efficacy against VOC(https://ir.novavax.com).Peptide vaccination could be a possible strategy which could protect against VOC. Hence this review brings forward the advancement in the process of peptide vaccine design due to AI along with the advantages and drawbacks.

2. Peptide vaccine for RNA virus: how far have they come?

The rapid evolution of RNA viruses makes it difficult to develop robust vaccine candidates.

Vaccine development deals with the four major attributes of viral evolution: diversity, virulence, dynamics, and fitness [24]. Each one of these parameters has been exposed to enormous studies but still remains a problem to predict robust vaccine candidates, probably due to complexity of each attributes and the intrinsic randomness of the evolutionary process [24]. The earlier vaccines were either made by killed viruses that are relatively safe but sometimes ineffective, or by live, attenuated viruses that constitute safety risks [25]. Recently developed vaccines target only immunogenic components of a virus including specific viral protein domains or peptides [14] and are believed to be safe and effective [26]. The progress and increased use of Next-Generation Sequencing (NGS) helped create a large database of the viral genomic sequences for identifying putative vaccine targets, thus enabling a rationalized peptide vaccine design [27].

Viral peptide vaccines are composed of one or more viral antigenic sites that, when administered, elicit protective immunity against the targeted viral pathogen. The design of a peptide vaccine includes initially the identification of immuno-dominant domains of epitopes that can induce protective immune response in terms of humoral or cell mediated immunity against a specific viral antigen [28]. Peptide vaccines can create immunity against multiple strains of a specific virus due to the presence of multiple non-contiguous immunodominant conserved epitopes of different genotypes/serotypes/immunotypes of the virus. While peptide vaccines could restrict notably the chances for allergenic and/or reactogenic complications, they need carriers and adjuvants to increase the low efficacy of oligopeptides [29,30]. Peptide vaccine manufacturing is safe and cost effective in comparison to conventional vaccines.

Unlike replication-incompetent or live and attenuated viral vaccines, peptide vaccines include those epitopes of the virus genome that could develop high levels of both B cell and T cell responses against the virus [31,32]. Various B and T cell epitope prediction tools developed using machine learning (ML) algorithms are in use for identification of the right epitope(s) or peptide(s) that can activate a good amount of T cells is the next challenge to confer protective immunity [33]. Various tools used in vaccine design are listed in Table 1.

For development of B-Cell responses, Virus like Particles (VLP) or nanoparticles are linked to the selected peptide so that the presentation of ordered, multivalent epitopes can efficiently cross-link B cell receptors (BCRs), required for improved antibody response [34]. Antibodies can target the specific epitopes in conformation dependent or independent manners (Linear epitopes) [35]. Protein or peptide engineering is used to mimic the “structural epitope” or conformation dependent larger epitopes [36,37]. “Mimetope” selection is when a collection of peptides is selected based on their ability to bind to the antibody by phage display or other display methods [38,39]. For development of T Cell responses, peptide epitope is fused to the major histocompatibility complex (MHC) using a polypeptide linker to recognize particular T cell receptors(TCRs) on cells or sometimes a universal helper T cell epitope which stimulates the antibody response is fused to the peptide or protein sequences [28,29]. Examples of immunodominance peptide vaccines are HIV-1, influenza and dengue viruses where the most conserved epitopes on the virus genomes that are also sites of susceptibility for virus neutralization have been used as the respective vaccine candidates [36,37]. In some cases, the epitope structure in the antigen-antibody complex is important for the activity of the antibody [40], the presentation of peptide vaccines in a relevant manner becomes very crucial for vaccine design [41]. For development of a peptide vaccine for respiratory syncytial virus (RSV), the epitope for protective antibody (motavizumab) targeting the F protein was determined by computational methods [25].

The identification, selection, and construction of candidate epitope (s) or peptide vaccine antigen(s) is followed by chemical synthesis of antigenic peptides [14]. The optimal length for peptide-MHC affinity should be approximately 18–20 amino acids as it has been observed that the relationship between peptide length and MHC class II affinity has

Table 1
The bioinformatics prediction tools used in vaccine designing.

Tools for B-cell epitope prediction	Tools for T-helper epitope prediction	Tools for prediction of MHC Class I binders	Tools for prediction MHC Class II binders	Tools for prediction of endogenous antigen processing	Tools for prediction of Allergenicity of peptides	Tools for prediction of Antigenicity
ABCpred	IFNepitope	ProPred1	Propred	CTLPred	AllerHunter	SVMTriP,
Bcepred	IL4pred	NetMHCcons	Consensus	NetTepi	Algpred	VaxiJen,
BepiPred		nHLAPred	EpiDOCK	FRED	Toxinpred	ANTIGENpro
SVMTriP		MMBPred	EpiTOP	TAPPred	PREAL	
COBEpro		NetCTLpan	MHC2Pred	TAPhunter	Hemolytik	
EPMLR		RANKPEP	HLA DR4Pred	TAPreg	AHTPDB	
Pep-3DSearch			MULTIPRED2	Pcleavage	AllergenFP	
IgPred			MARIA	NetChop	Allertop	
Lbtope						
BEpro						
CBTOPE						
CEP						
PEASE						
DiscoTope						
Epitopia						
SEPPA						
BEST						
EPCES						
BEPro (PEPITO)						
EpiSearch						
MimoPro						
MIMOX						
Pep-3D-Search						
PepSurf						
ElliPro						

important consequences for the binding and functioning of antigenic peptides as vaccines [42–45].Hence, peptides of 20–30 amino acids length, which are highly immunogenic and capable of triggering a protective immune response, are synthesized in vitro [14]. The peptides are subsequently conjugated to carrier molecules or adjuvants, as needed. Immunoprofiling of the resultant constructs is carried-out in vitro as well as in appropriate animal models for ascertainment of efficacy and safety, followed by pre-clinical and clinical trials.A few critical bottlenecks for peptide vaccines are (1) only a single peptide epitope can be presented as vaccine candidate, (2) vaccines that are able to evade immune system as the exogenously administered peptide will not necessarily follow the same pathway of processing as the native pathogen [46], (3) a peptide may be unable to generate a prolonged immune response, (4) lack of efficacy may be the result of degradation and conformational instability [46],(5) the improper programming of clinical trials, which includes protocol design, execution, and successive trial planning [47], and (6) safety issues related to the use of adjuvants and particulate peptide vaccine delivery systems [14].

Peptides being short, the epitopes in these vaccines tend to be small, linear and non-conformational. However, the antibodies produced in response to a peptide vaccine targeting B cell epitopes (which are mostly conformational in nature) may offer only restricted protection against natural infection [24]. In order to overcome these shortcomings, support vector machine (SVM) based models have been developed for prediction of antigen presenting cell (A-cell) epitopes that could be used to formulate vaccine adjuvants, which is likely to have the potential to provide protection against viruses and other pathogens [48]. To cover the criteria of population coverage, a subunit vaccine with a set of peptides is incorporated, which can encode a three-dimensional epitope to stimulate neutralizing antibody production by B cells thus improving its efficacy and population coverage [49]. The translation of somatic mutations into neoantigens in the development of neoantigen vaccines by the use of ML helps to overcome the time limitation in the development of potential vaccines for cancer patients thus allowing better selection of therapeutically efficient antitumor immunity [50,51]. To speed up the process of vaccine designing, rapid prediction of potential vaccine candidates (PVCs) reverse vaccinology (genome to vaccine) is helpful (Fig. 1). This utilizes bioinformatics tools to design vaccines based on the genetic sequences of the organism [52]. Multi epitope based peptide (MEBP) vaccine candidates have been designed recently using this Immunoinformatics approach for RNA viruses such as zika, nipah and SARS-COV-2 [53–55] by studying immunogenetics and immunology data using bioinformatics.

Promising results for peptide vaccine development have been obtained with the following viruses: Influenza virus [56], hepatitis B virus [57], respiratory syncytial virus [58,59], bovine leukemia virus [60,61], feline immunodeficiency virus [62,63] and hepatitis C virus [64]. Lately, many predictions of peptide vaccine candidates for RNA viruses have been made due to progress in bioinformatics, for e.g.: corona virus [65–68], rotavirus [69–71], foot-and-mouth disease [72,73], Hepatitis C [74–76], influenza [77,78]. These are predicted using bioinformatics tools, which are based on statistics, AI and ML application to the known data sets in immunology [79]. Improvised therapeutic strategies with the help of ML applications in structure prediction, docking, molecular dynamics simulation are being used for the development of a peptide vaccine for covid-19 [8]. Peptide vaccines for human immune-deficiency virus (HIV) [80], hepatitis-C virus (HCV) [81], malaria [82], foot-and-mouth disease [83], swine fever [84], influenza [49], anthrax [85], human papilloma virus (HPV) [86], therapeutic anti-cancer vaccines [87–91] for pancreatic cancer, melanoma, lung cancer, advanced hepatocellular carcinoma cutaneous T cell lymphoma and B Cell chronic lymphocytic leukemia are under development.

3. Role of AI in peptide vaccine development

ML is an AI tool that has the capacity to process large amount of data and generate models for data so that similar data can fit in. This allows AI to classify the inputs and predict the outcomes. AI and mathematical evolutionary modeling using ML tools will pave the road for the development of these new peptide vaccines and the control of viral disease [7]. AI helps in identifying genomic regions that are under selective pressure, selection of vaccine strains and estimating the efficacy and efficiency of therapeutic vaccines by determining epitope hotspots and conserved regions among different strains of the virus, hence, designing universal vaccines. Progress in studying how these factors interact depends on quantitative descriptions and predictive models [92]. AI applications work best when the data set is large and clean. Ironically, most of the known data sets in immunology are very small and of low quality [93–96]. At present, AI is in the nascent stage of its use in the field of vaccines. The computational algorithms developed are trained on in vitro binding data which is insufficient and contains high noise and outliers with algorithmic constraints. To get accurate results, these tools require larger good quality data sets, which unfortunately are very limited [97,98]. In the current pandemic scenario, ML tools and computational analyses have shown its importance in keeping a real-time track of the pattern in spread of the SARSCoV-2 infection, management of the large amount of big data generated, improving diagnostic speed and accuracy, and developing candidate drugs and vaccines in a short time [99,100]. A new approach in ML applications such as SIMONs (Sequential iterative modeling overnight), an automated ML system that compares results from different clinical datasets to increase the predictive accuracy from heterogeneous biological datasets, can provide new targets for the development of the next generation of vaccines [101]. Computationally optimized broadly reactive antigens with consensus sequences, phylogenetic model-based ancestral sequence reconstruction, and immunomics to compute conserved cross-reactive T cell epitopes are some of the algorithms under development for the application of ML in vaccine development [102]. Random Forest (RF) [103], an ensemble learning tool for classification, regression and other tasks, which operate by constructing many decision trees at training time and gives an output of the class in the mode of the classes (classification) or mean/average prediction (regression) of the individual trees. SVM [104] finds a hyperplane in an N-dimensional space (N — the number of features) that distinctly classifies the data points and Recursive Feature Selection (RFE) [105], selects those features in a training dataset that are most relevant in predicting the target variable. Deep Convolutional Neural Networks (DCNN) [106] are neural networks that process data in complex ways by using sophisticated math modeling. LSTM networks [107] classify, process and make predictions based on time series data, since there can be lags of unknown duration between important events in a time series. NEC Immune Profiler (http://www.oncoimmunity.com/products/1-nec-immune-profiler.htm) integrates patent pending modules of HLA binding, processing, and antigen presentation in an integrated system. Immune Epitope Database (IEDB) (https://www.iedb.org/) has tools which assist in the prediction and analysis of epitopes. BepiPred [108] is a web server for predicting B cell epitopes from antigen sequences, which is based on a random forest algorithm trained on epitopes annotated from antibody-antigen protein structures. The state machine model can be used to compare different viral clades and detect mutations separating the clades without the need for alignment, the temporal characteristics of viral evolution can be captured and can be used to characterize the evolution within a clade and in the identification of the actively mutating regions that could lead to the emergence of a new viral clade [109]. Generative adversarial networks (GANs) detect unknown genetic mutations and classifies genes while maintaining a high performance level when facing unseen data with unknown patterns and providing explain-ability capabilities [110]. The AI-based framework DeepVacPred, skips 95% of unnecessary predictions to directly predict the potential vaccine subunit sequence without the need to use numerous in silico vaccine design tools which address only one of the several predictions at a time manually [111]. AI and ML applications have the limitation that they cannot overcome the

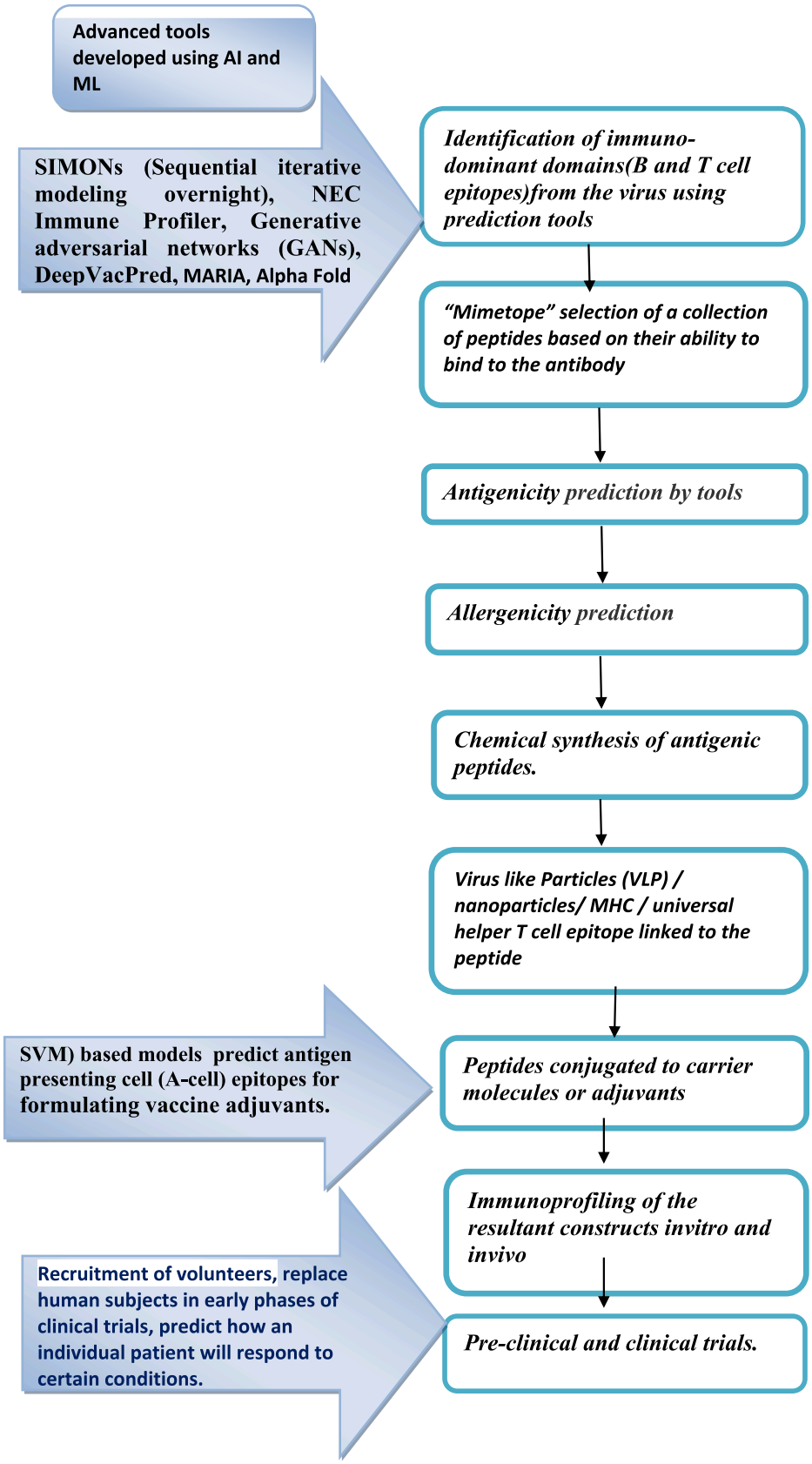

Fig. 1. Schematic of key steps involved in peptide vaccine development and the application of AI in various stages.

time-consuming but most critical aspect of a successful vaccine development, the animal model studies and human clinical trials [13].

One of the important molecular interactions for vaccine design and prediction algorithms is the ability to determine whether a peptide can be presented by the MHC molecules. This algorithm is developed using raw data from mass spectrometry (MS) techniques [112]. It can be trained by the current data on human immune-peptidome and predict whether a given peptide can be presented by MHC-I molecules. Data acquired from in vitro studies provide information on peptide-MHC affinity. At present, the MHC-I binding predictors have been found to be very efficient and have a wide allelic coverage with a prediction accuracy of 90–95% [113–115]. Epitope prediction for MHC-II molecules is even more challenging due to the differences in peptide length. AI based algorithms are good at predicting MHC-II epitopes based on the amino acid sequence and for designing vaccines that target the MHC-II immunopeptidome [116,117]. Since these models are based on in vitro experimental data, they are limited in predicting in vivo interactions with the same accuracy. The MHC-II binding prediction accuracy is low in comparison to that for MHC- I binding peptide prediction. The performance of the current prediction tools for assessing binding stability is dependent on the MHC allele association. The poor prediction is due to the low quality training data or the difficulty of modeling the allele. In a recent study on SARS-CoV2, improved performance of the prediction tool PrdX 1.0 on allele HLA-A*02:01 of the SARS-CoV2 was obtained using in-house generated stability data [118]. Recently, scientists have listed a number of targets or epitopes on the corona virus responsible for immune response using the neural-network algorithms NetMHCpan-4.0, MARIA and DiscoTope [13]. NetMHCpan-4.0 is a new framework for the training of prediction methods for MHC–peptide presentation prediction integrating information from two data sources (mass spectrometry eluted ligand and peptide binding affinity) [119] and DiscoTope server predicts discontinuous B cell epitopes from the three dimensional structures of proteins. Peptide presentation by MHC and accurate protein structure prediction being invaluable for vaccine design, MARIA and Alpha Fold are two new improved programs developed for MHC-II binding peptide prediction and protein folding, respectively, that show better results as they are based on better training data and better ML algorithms. MARIA (major histocompatibility complex analysis) is a multimodal recurrent neural network used for predicting antigen presentation by specific HLA class II alleles that have been trained on data generated by mass spectrometry, antigenic genes expression and protease cleavage information [120], where as Alpha fold is trained on protein data bank [3]. Positive-unlabeled Learning using AuTOml (PLATO) is a general semi-supervised approach to improving accuracy of model-based classifiers, which generates a set of high confidence positive calls by applying a stringent filter to model-based predictions. It has improved performance compared to model-based approaches for two key steps in tumor rejection mediating neoepitopes (TRMNs) prediction, namely somatic variant calling from exome sequencing data and peptide identification from MS/MS data [121]. AI has an important role to play in the clinical trial phase of vaccine candidates. It can analyze a large amount of clinical records of patients to determine their eligibility for a given study. Recruitment of volunteers is one of the many bottlenecks in conducting clinical trials [122]. It is often the most time-consuming and expensive step. Natural language processing (NLP) is a branch of AI that trains computers to analyze the written and spoken words [123]. This allows algorithms to search doctors' notes and pathology reports to check for the people eligible to participate in a particular clinical trial [124]. An open-source web tool called Criteria2Query uses NLP to search databases without requiring knowing a database query language [125]. With AI it is possible to replace human subjects in early phases of clinical trials. The company Novadiscovery (https://www.novadiscovery.com/) aims at creating virtual patients by running the trials first in-silico. It helps clinical trials directly from phase I to phase III and also reduces the size of the phase III trial by focusing only on profiles of responders who give optimum response. The technology Jinkō (https://www.novadiscovery.com/jinko-platform.html) uses real data collected from scientific studies regarding disease pathobiology and then uses drug data from existing studies to model its effect on patients. This predicts the clinical trial outcome. Computer models of disease progression and treatment response can represent each physical individual (digital twin) or a hypothetical individual whose key characteristics (described by the inputs of the model) are sampled from the joint distribution of a representative population (digital trials). Digitalizing clinical trials can be used to predict how an individual patient will respond to certain conditions.

T.N Chan School of public health at Harvard University and the Human Vaccines project have started a joint venture HII (Human Immunomics Initiative) to improve the understanding of the human immune system and speed up the process of vaccine development. They are developing AI assisted Immunological models based on huge data that has been collected from clinical research. Now with advances in computing, AI, genomics, systems biology and bioinformatics, HII plans to understand the mechanisms that govern the human immune system's fight against disease. This would accelerate the design and testing of vaccines for many diseases in the near future.

4. Concluding remark

Increase in the amount of experimentally validated data along with further development of better algorithms trained on better data sets will lead to better vaccine design strategies. The fact that the machine learning algorithms need to be trained on larger and reliable data sets of in vitro and in vivo experimental data requires collaborative projects to be designed for AI scientists and vaccinologists to work together. The advanced technologies such as the development of peptide presenting nanoparticles have shown to have the potential to overcome the challenge of weak immune response elicited by peptides, therefore making use of AI in developing peptide vaccines against RNA viruses, hold a great promise.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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