

Perspective

Towards Personalized Vaccines—Tailoring Peptide Vaccines to Demographic Groups and Individuals

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ABSTRACT

Traditional vaccines have seen spectacular successes in eradicating smallpox and have come close to eradicating poliomyelitis also. However, they have been short in combating viral epidemics which are now occurring with increasing frequency; the reasons are primarily due to rapid mutations in RNA viruses. Alternative procedures are to be found in the new science of vaccinomics where peptide vaccines have come to be recognized as a strong alternative strategy. While several issues still need to be resolved, and no license has yet been released for human use of peptide vaccines, such vaccines have found ready acceptance in cancer therapeutics where personalized vaccines are of necessity the de facto norm. This knowledge gives us the opportunity in the event of viral epidemics to tailor making vaccines for different communities for maximum efficiency and for immunocompromised individuals. We give a brief perspective on the current status and future prospects of new trends in vaccine research, specifically peptide vaccines development, in this paper.

KEYWORDS: peptide vaccines; traditional vaccines; vaccinomics; antibody design; viral epidemics; individualized therapeutics

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*“Come, my friends,
’Tis not too late to seek a newer world.”
—Ulysses, Lord Alfred Tennyson*

BACKGROUND

Traditional vaccines, when available, have a history of great efficiency against viral diseases that recurred time and again or were slow to mutate over time. This allowed for such spectacular successes as eradicating smallpox [1], and almost eliminating poliomyelitis except for resistances on non-medical grounds in some isolated pockets [2]. However, viral infections and epidemics are becoming increasingly frequent these days: epidemics like the SARS (Severe Acute Respiratory

Syndrome) epidemic of 2002–2003 affecting 8098 people in 37 countries [3], the H5N1 bird flu scare of 2005–2006 [4], the H1N1 swine flu of 2009 that caused over 200,000 fatalities [5], the West African Ebola crisis of 2014–2016 leading to 11,308 deaths [6], the Zika virus crisis of 2015–2016 [7] and the recent deadly but narrow-ranged Nipah virus with 40% fatalities among infected persons in Malaysia and 75% to 100% fatalities in Bangladesh and India [8,9], to name a few. The suddenness and pathologic intensity in each instance caught the world unaware, with no therapeutics to combat the diseases or provide relief to the patients except for palliatives and culling of domestic poultry and animals as suspected carriers of the virus. These were all either new viruses or, as in the case of the H1N1, a mutated form of an older version [10]. In any case, no existing drugs or vaccines were capable of meeting these onslaughts and generating new drugs and vaccines is time consuming and expensive. On average, it takes about 10–15 years [11] and costs approximately US\$1.8 to US\$2.6 billion [12,13] to discover and develop a new drug. Tens of thousands of compounds need to be introduced into the drug discovery pipeline for every successful drug that comes to the market [14]. The cost of developing a vaccine—from research and discovery to product registration—is estimated to be between US\$200 million and US\$500 million per vaccine. This figure includes vaccines that are abandoned during the development process. In short, vaccine research and product development is also a lengthy and complex process loaded with binary outcome risks [15]. Since viral epidemics generally die out within six to eighteen months, similar exercises would be clearly an inadequate approach to such epidemics and pandemics. In some instances, like the hypervariable ribonucleotide (RNA) viruses like influenza, the viruses mutate so rapidly that their vaccines have to be in a constant change regime.

Traditional vaccines such as attenuated or inactivated vaccines have to go through a lengthy process to breed, purify, store—sometimes, as in the case of the rVSV-ZEBOV Ebola vaccine, at -60 to -80 °C [16], and transport to the point of administration; there is also the other problem of necessarily the same vaccine having to target different communities, not all of which will exhibit the same level of response efficiency. To meet all this diversity, regular changes in the vaccines are required, which becomes a complex task and not commercially viable. Then also, sudden calls for increased supply often surpasses the ability to manufacture good quality vaccines as has happened in the Ebola virus outbreak in the Democratic Republic of Congo in 2019 where the supplies of the rVSV-ZEBOV Ebola vaccine is reported to be less than required and necessary production will require 6–18 months [17].

Clearly, an effective alternative is urgently required.

PEPTIDE VACCINES

Recent advances in immune-informatics, genetics, information technology, bioinformatics and related sciences and technologies have opened up the possibility of such an alternative: the use of vaccinomics [18–21], the science of vaccine design that focuses attention on how vaccines operate and then build on that information, rather than blindly replicate old techniques. The main idea is to understand that the body's defense mechanism will operate upon the suitable surface exposed proteins, the epitopes, of the virion and act to eliminate the virus [22]; indeed, the first successful peptide vaccine was one used against the canine parvovirus [23], and since then several peptide vaccines for veterinary use have been licensed and marketed [24,25], though none for human use so far. Severing out the relevant surface exposed parts from the full virion and using appropriate peptides as vaccine candidates may help elicit the same defensive apparatus into action as for traditional vaccines (see Figure 1 for a simple schematic of peptide vaccines), but at less time and cost and thus spread the benefits of vaccination to cover more viruses and more people than current vaccines permit.

This is in principle a doable scenario once the genetic structure of the virus is known, and that is not difficult these days with superfast sequencer machines and advances in computational technology. The technique is to scan the pathogens' proteins for binding with Human Leukocyte Antigen (HLA) which vary from person to person and community to community. Peptide vaccines have been proposed against viral diseases [26] and human cancers [27], with notable successes against cancer tumors [28]. The pick of the peptides that could act as vaccines is determined by the binding of the processed peptide with the major histocompatibility complex (MHC) class I and II molecules coupled with the relevant HLA to be presented on the surface of the antigen presenting cells (APC) for determining the antibodies. Use of non-live vaccines so derived for humoral and cellular immunity avoids introducing any infectious organisms that may cause unintended illnesses in recipient individuals. Indeed, peptide vaccines have become very efficacious in cancer tumor treatment and has come to constitute a fourth pillar for such treatment complementing surgery, chemotherapy and radiation [28].

Compared with whole cell lysates or proteins, the peptide based approach has an advantage that only epitopes of interest are loaded onto the immune system instead of whole lot of irrelevant antigens that may lead to autoimmune response. The other advantage of peptide vaccines is that they can be fine-tuned by modifications to enhance the binding with MHCs to heighten the immunogenicity, a process called epitope enhancement [28]. Together, these attributes can be exploited for specific HLA profiles to make the peptide vaccines more relevant to a community or an individual.

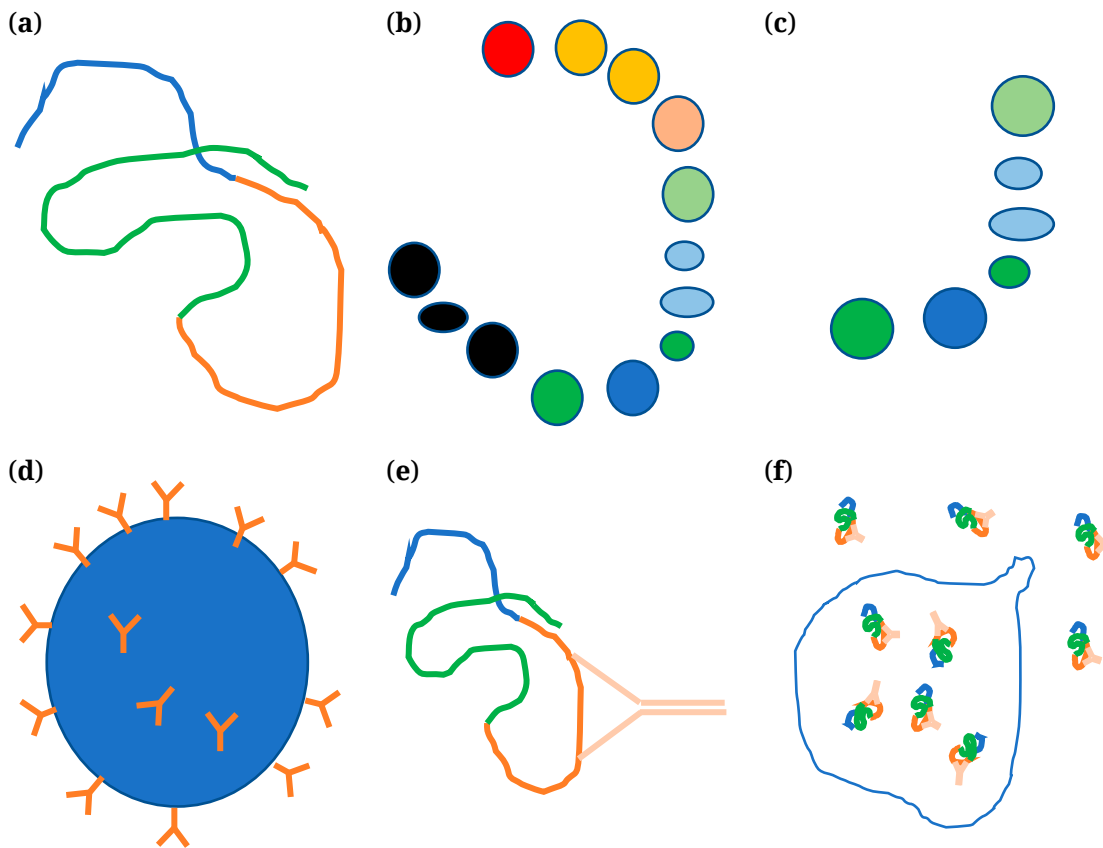


Figure 1. Schematic of peptide vaccine. **(a)** A schematic of an invading virion with three proteins—blue, green and red. We assume the red protein is surface exposed. **(b)** The amino acids that make up the red protein. The reddish part is covered slightly by the green protein, so it's not completely surface exposed. A presumed IEDB analysis shows that the blue-green residues have good epitope potential, the black ones do not. **(c)** The peptide with good epitope potential part shown separately. **(d)** Injecting this peptide into a body allows interaction with B-cells and T-cells that carry numerous potential antibodies (red Y's). If one of these can interact well with the epitope, in full or in part, then millions of copies are produced to fight the invading pathogen, *i.e.*, the inserted peptides work like a vaccine. **(e)** A schematic of an antigen-antibody interaction. This is an example of a linear epitope; there are also conformational epitopes arising from the folding of the protein, but this concept is not covered in this schematic. **(f)** A phagocyte clearing up Antigen-antibody complexes.

PERSONALIZED VACCINES

Personalized vaccines have made a huge impact in cancer treatment. Yoshida *et al.* [29] reports from a study of 500 advanced cancer patients administered personalized peptide vaccines that there were 215 cases of severe adverse events (SAEs) in 102 patients. These related to cancer progression, cancer treatment, other diseases and only 6 patients had SAEs related to peptide vaccines, consisting of skin reactions at and cellulitis around the injection sites, edemas of the head and neck regions, colitis, rectal bleeding and bladder-vaginal fistulae. Although the incidence of SAEs arising from peptide vaccination itself was rather low, the authors considered it prudent to advise physicians to be vigilant for these rare SAEs associated with augmented immune responses.

The prognosis for pancreatic cancer, however, remains rather bleak. In an earlier report, Yamamoto *et al.* [30] had reported that matching the HLA profiles of 11 pancreatic cancer individuals and administering only reactive peptide vaccines (max 4) that increased cellular and humoral immune responses to at least one of the peptides used for vaccination were observed in 10 patients and the survival rates for 6- and 12-months were seen to be 80% and 20% respectively. Injection sites were seen to be inflamed in 7 patients, but overall the regimen was well tolerated. The authors concluded that these encouraging results warranted further study of personalized peptide-based immunotherapy for pancreatic cancer.

Obara *et al.* [31] reports that in urological cancer cases the immune response of small peptides has been rather limited due to various factors including poor immunogenicity of tumor associated antigens, immune escape of tumor cells, and tumor heterogeneity. In the case of prostate cancer, a phase II study of peptide vaccines consisting of four peptides and two adjuvants was seen to increase the overall survival rate compared to the control group. A novel peptide based renal cell carcinoma vaccine seems to hold good promise. Some urothelial cancer patients receiving peptide vaccine treatments showed injection site reactions, but continued treatment showed promising results. The best results were obtained by combination of peptide vaccines with other chemo therapies and several research groups worldwide are undertaking phase trials using such combination therapies.

Perhaps the most individualistic drug ever made is the case of manufacture of milasen, a splice-modulating antisense oligonucleotide drug tailored to one particular patient to treat a fatal but rare neurodegenerative condition [32]. The exercise was facilitated by molecular diagnosis that led to the rational design, testing and manufacture of the novel drug and offers a possible template for future development of patient-customized therapeutics. However, a number of ethical, commercial and social issues remain that needs to be carefully considered before such individualized approaches can become accessible for the many [33].

VIRAL EPIDEMICS STRATEGY

The case for peptide vaccines against viral epidemics is not as strong [34,35]. Generally, the community first facing the epidemic is the front-runner in the analyses and research for producing the vaccine which leads to T-cell and B-cell proliferation in case of strong binding. Further tests effectively guard against false positives, auto-immune threats and others. Unfortunately, as mentioned before, viral sequences, especially RNA viral sequences, can mutate very rapidly and lead to short lifespan for most vaccines. Design for vaccines against such viruses should encompass the conserved domains of the proteins being targeted. We have incorporated such ideas in our endeavor to design suitable

vaccines against several viruses: flus [36,37], rotavirus [38], human papilloma virus [39] and Zika virus [40] and arrived in each instance with a suggested library of possible vaccine candidates to be tested out in the wet-labs. The flowchart diagram (Figure 2) shows the protocol we have followed in this process, which, in brief, is as follows:

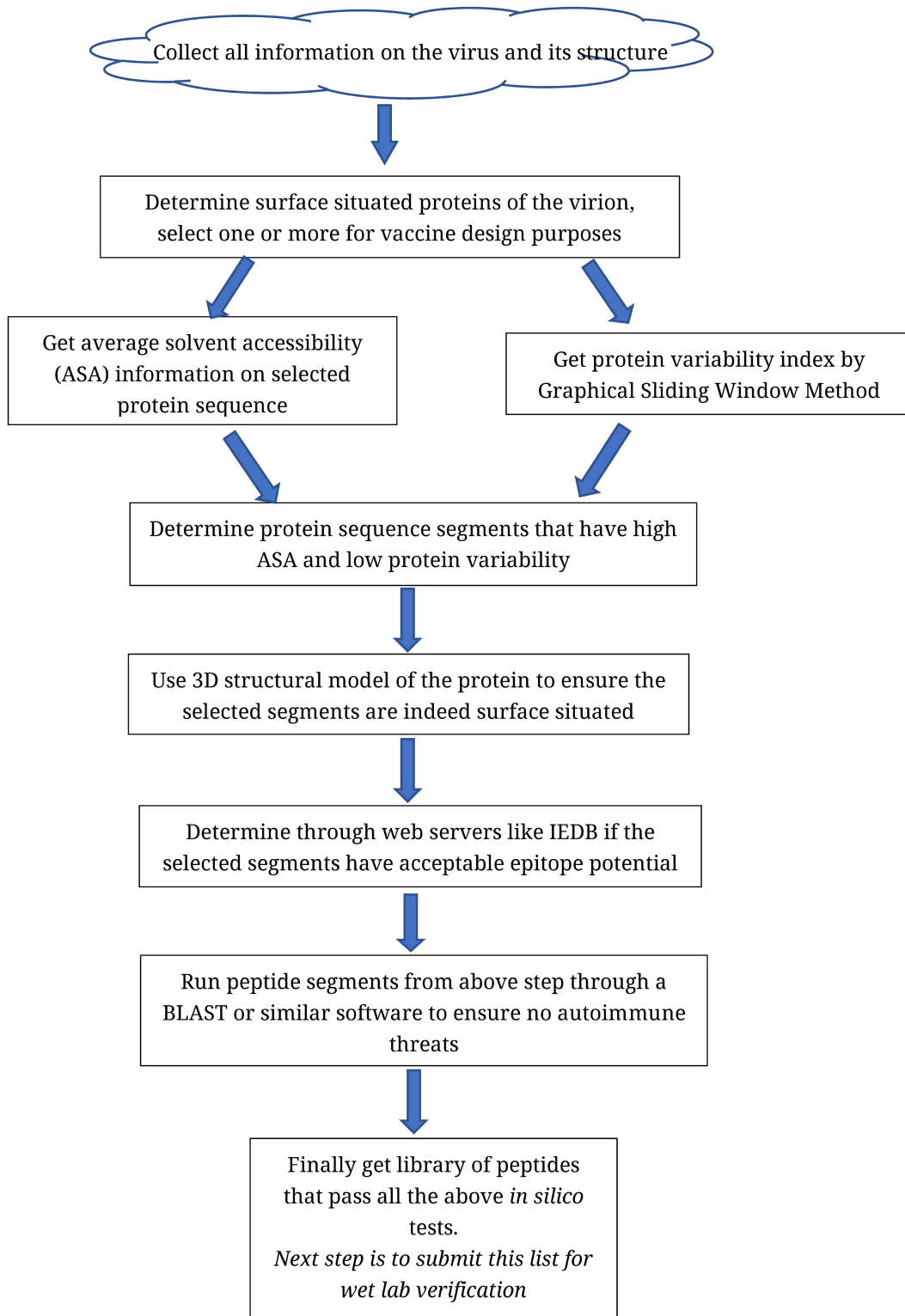


Figure 2. Flowchart for *in silico* peptide vaccine design.

We start off collecting as much information as we can about the surface proteins of the virus particles, then selecting complete sequences of the protein to make up a library of such protein sequences. For the influenza viruses, the hemagglutinin is a surface exposed protein; the L1 of HPV, the VP7 of rotavirus, the envelope protein of the Zika virus, *etc.* are examples of surface proteins of various viruses we have analyzed for peptide vaccines.

At the next stage we embark on two parallel exercises. Taking adequate number of the surface protein sequences, we use a web server like SABLE or iTASSER to determine the hydrophilicity levels of the sequence. At the same time we take all the sequences and determine which parts of the sequence remain most conserved through all the mutations that our library of these sequences suggest. To determine this, we use a simple 20-dimensional graphical representation and numerical characterization of protein sequences to map a window of 10 to 12 amino acids to a descriptor number (see Ref [41] for method, Ref [38] for application). We start from the beginning of a sequence to calculate the segment descriptor, then move the window by one amino acid position and calculate the second descriptor, and so on till the end of the sequence. We next do this for the remaining sequences until we have a matrix of amino acid position numbers versus segment descriptors for all the sequences. Running through the descriptors at each amino acid position, we can determine how many different descriptors there were, which implies that the lesser the variety of descriptors, the more conserved will that segment be. Such an exercise can be done by using other models of protein characterization (see Ref [42]), but we find our 20D method easier to use and sufficient for our purposes. Now, with the hydrophilicity profile and the protein variety profile on hand, we search for those domains where the surface exposure of the protein segment is highest and variability the least signifying the best regions for designing peptide vaccines, which may turn out to be more than one for a surface protein; we found six regions in influenza neuraminidase, four in the Zika envelope protein. One additional step we take is to check with the protein 3D structure diagram, if available, to ensure that the regions we pick for high surface exposure is not covered by neighboring protein structures.

The next step is to determine the epitope potential of the selected regions. For this we use the IEDB analyses resource with its library of HLA profiles of the community we wish to cover and also check for linear and conformational epitopes. If strong binding is seen between the antigen and the HLA in the regions we had selected in the process described above, then that would be indicative of strong vaccine possibility, else we have to delete that region from our list. Similarly, we need to check for autoimmune threats, if any, from these peptides and reduce the final list of peptides that meet all our criteria and form a part of our final library of possible peptide vaccines.

All the above work is *in silico*, implying a quick analysis to narrow down possible peptides for the next phase of actual experiments to determine the efficacy of the peptides identified for the purpose. The wet-labs experiments are long and rigorous. A large number of trials of peptide vaccines for humans are being carried out over the last many years: at last count there were 603 trials for peptide vaccines as per the National Institute of Health (NIH) website <https://ClinicalTrials.gov> (last accessed 2019 Oct 9). The vast majority—409/603, however, relates to cancers where the success rate is found to be comparatively very high.

PROS AND CONS OF PEPTIDE VACCINES

However, there are issues with peptide vaccines at this nascent stage. As remarked by Li *et al.* [43], the safety of particulate peptide vaccine delivery systems remains a major concern. Administration of the vaccines are commonly done through subcutaneous, intranasal, intravenous, and transdermal routes, of which transdermal has been the safest and easiest to use. Reducing the hydrophobicity of the polymer increases the safety of the vaccine administration, but such particulate delivery systems require repeated administration as per guidelines. It is also necessary to be prepared for immediate adverse events within 30 min of administration. Apellanz and Nieve [44] in their review of peptide vaccines in controlling Human Immunodeficiency Virus type-1 (HIV-1) suggested that the expected actions of peptide vaccines were limited due to various factors such as (1) single epitope vaccines are not powerful enough to elicit the required immune response; (2) they fail to provide the prolonged immune response necessary to control the pathogens (3) susceptibility of such vaccines to immune evasion and (4) a lack of efficacy. In practice, it turns out that the response realized by such peptide vaccines is significantly less than what the virus achieves when the full virion is exposed to the host immune system. Use of adjuvants helps rectify this deficiency to a large extent, but the science behind adjuvants is just beginning to be understood [45,46]. Then there are worries about stability of a peptide *in vivo*, for which carrier proteins need to be used.

But the positives outweigh the negatives by far [21]. More than one peptide can be combined as multivalent vaccines, the peptides being chemical entities can be manufactured to high levels of purity as well as scaled up to produce huge quantities in a short period of time, their storage at normal room temperature removes many worries of storing in refrigerated environments as required by traditional vaccines, transportation poses no novel issues and administering such vaccines in the field is a tried and tested technique as for traditional vaccines [47]. If the numbers of peptides in the vaccine candidate library become large, and wet-lab costs escalate, the set of peptides can be clustered into manageable number of groups and one or a small number of candidates from each cluster can be used for wet lab purposes. Such approaches

have been used for computer-assisted drug discovery protocols [48,49]. Because experimental data on such peptides designed *in silico* will be difficult to obtain, the clustering can be done using computed molecular descriptors which can be calculated from the structure (primary sequence) of the peptides without requirement of any other laboratory-generated data. Peptide vaccines, in short, are the answer to several of the problems that plague the development, production, dissemination and administration of traditional vaccines. These are of expeditious concern since many of the viral epidemics that plague a nation occur in the tropical and warmer temperate climates where funding issues often deter the use of the best of modern drugs and vaccines.

The fact remains, however, that to date no peptide vaccines have been licensed for human use. Given the positive feedbacks received from trials of peptide vaccines against cancer tumors [28] and infectious diseases [50], as well as the many advantages of peptide vaccines [21,51], it would appear possible that impediments to successful implementation of such vaccines will be overcome and licensure for peptide vaccines will ensue sometime in the near future.

If and when that does happen, there can be special benefits of peptide vaccine technology in the face of viral epidemics and pandemics. One can envisage a scenario where a string of peptide vaccine factories will be spread strategically located around the globe, while one or two labs are designated for detailed analysis of the epidemic/pandemic virus. On successful identification of the peptides through *in silico* and *in vitro/in vivo* analyses, the peptide sequences can be distributed to the peptide vaccine factories that can then commence to minor adjustments for epitope enhancement [52] to ensure best fit to the prevailing community HLA profiles. The same procedure can be adopted to cater to the requirements of immunocompromised individuals to ensure vaccination in these cases also. In the case of cancer victims, personalized vaccine development is a necessary condition for further treatment.

SUMMARY

Traditional vaccines have been found wanting in the recent history of viral epidemics that are happening with increasing frequency. Recent trends and advancements in knowledge of vaccinomics have enabled development of alternative strategies exemplified by peptide vaccines [34,35]. Although several issues remain to be resolved, peptide vaccines have found ready acceptance in cancer therapeutics where personalized vaccines are of necessity the *de facto* norm. But this also gives us the opportunity to use such advanced knowledge to tailor make vaccines for different communities for maximum efficiency and for immunocompromised individuals who would otherwise have been left to the mercy of chance against a viral onslaught. Setting up a few super specialized centers for preliminary analyses and adjustments and

manufacturing in satellite factories around the globe could lead to faster response to new epidemics and pandemics.

While vaccination remains an attractive proposition as an anti-cancer therapy, in practice several obstacles still need to be overcome before it can find widespread clinical acceptance. Recently, a novel type of biomimetic platform, the cell membrane-coated nanoparticle, is emerging as a strong support for nanovaccines [53]. Nanoparticles like liposomes, emulsions, *etc.* can provide platform for various combinations of adjuvants and antigens that lead to nanovaccines. These can be fine-tuned to deliver maximum immune activation through the antigen processing cells (APCs). The use of cancer cell membranes as the coating material offers vaccines rich in tumor antigens. With the nanoparticulate core carrying potent immune stimulators and targeting APCs, nanoparticles with such coating can provide strong inhibition to tumor growth. Developing techniques for obtaining tumor cell membranes from particular patients carries the potential for fabrication of personalized vaccines.

More recent advances in immune science and technology have raised the possibilities of other approaches to preventive therapeutics. Use of artificial intelligence (AI) to scan all genes and proteins comprising the human immune response over millions of individuals holds the possibility to discover and engineer precision vaccine for an individual. Such a shift in design strategy will signal a change from hypothesis-driven to a discovery-driven science. There is already precedence for this: IBM Watson program is reputed to be more efficient in detecting cancer symptoms than humans; precision vaccine design for individuals or communities by AI may not be too far off [54,55].

An exciting new approach to vaccinology is developing protocols in computational design of antibodies. Among the first researchers to consider design of new antibodies from structures of existing antibodies, Maranas and his group have developed OptMAVEN software [56,57] for de novo design of variable antibody regions against specific targeted antigen epitopes. Based on the 1000s of experimentally determined three-dimensional structures of antibodies that are available in the database, Dunbrack and his group developed a new more general framework [58] that combines pieces of these structures to create new antibodies better able to bind with the pathogen's epitopes. Called the RosettaAntibodyDesign (RABD) within the Rosetta protein modelling program [59], the authors have reported that the new method has yielded experimental confirmation of improving existing antibodies by 10 to 50 fold.

CONCLUSION

Peptide based vaccines have shown significant promise in certain types of cancer treatment, but have had limited success in combating several viral infectious diseases. Vaccines based on peptides appear to

hold the possibility of a quick response against sudden outbreaks of viral epidemics and pandemics, both for communities and individuals; however, as remarked by the Global Health Security Index [60], among 195 countries surveyed, none is thoroughly prepared to contain a viral outbreak at this time. But, recent advances in treatment with multiple peptides, new knowledge of their interaction with the immune system and understanding of characteristics of peptides in *in vivo* environment lead us to believe that the prospects of peptide vaccinology are more promising than hitherto observed and the spate of peptide vaccine trials will provide more clinical successes than we have seen so far leading to licensure for human use and a viable resource in the face of sudden epidemic and pandemic outbreaks.

AUTHOR CONTRIBUTIONS

AN conceived the design of this perspective. AN and SCB wrote the manuscript.

CONFLICT OF INTEREST

Both authors declare no conflict of interest.

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