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A brief account of the search for peptide vaccines

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Abstract: An increasing trend of viral diseases have led to search for faster response systems for preventives and therapeutics. While traditional vaccinations have led to spectacular successes against smallpox and polio viruses, the need for rapid response to new viral epidemics, like in the case of Ebola and Zika viruses, has called for new ways of tackling such infections. The fact that viral diseases are notoriously difficult to control, due primarily to their nature of fast mutational changes leading to growth of new strains and development of strains resistant to prevailing medications, adds an extra layer of complexity to the task. Peptide vaccines provide one means of responding to the epidemics. Since they are developed based on the viral sequences and focused on the antigenic sites, peptide vaccines are amenable to rational design paradigms. The first such vaccine for the canine parvovirus was developed in the 1990s and many peptide vaccines against human viral diseases are under different stages of phase trials. While production of such vaccines can be fast and cost-effective, and there are several issues still to be resolved, peptide vaccines are expected to play a major role in the future. In this very bried review we recount current status and some of the different approaches to design of peptide vaccines.

Keywords: viral epidemics, peptide vaccines, Zika virus vaccine, coronavirus, dengue virus, papillomavirus

An increasing trend of viral diseases have led to search for faster response systems for preventives and therapeutics [1]. For some viruses the prevalent technique of vaccinations have led to spectacular successes such as in eradicatng smallpox and almost complete eradication of polio from the list of the most dreaded scourges in human history. The premise of vaccine technology is to expose the body to an attenuated form of the virus to enable the immune system to recognize the invading pathogen so that it is prepared to overcome the live viruses when infections do occur. In general, however, viral diseases are notoriously difficult to control due primarily to their nature of fast mutational changes.

The problem with traditional vaccines is two-fold. For one, the entire process of creating the vaccines through egg-cell technology is time consuming and costly. From lab to market, costs for development of drugs and vaccines are estimated to be upwards of $1.8 billion for drugs [2,3], and between $200 to 500 million for vaccines [4] and take up to 10 years; vaccine research and product development is lengthy, complex, and loaded with binary outcome risks. Secondly, by the time such a vaccine or drug

is put to use, mutational changes in the viral sequence may creating resistant strains that render the drug or vaccine futile; the fate of Relenza, an influenza drug, is a case in point. Influenza vaccines used for the last two years in the USA have turned out to be ineffective due to sequence changes in the virus.

These experiences have led to search for newer means to tackle the viral infectivities. One approach is to do in silico analysis to search for relevant molecules to inhibit viral endocytosis to reduce the lead time for drug discovery. An alternative approach is to elicit the body's own immunological response through targeted peptide vaccines. This method (Fig.1) is comparatively fast, less costly and more efficient in production of the vaccines [5]. As of November 2017, there were over 500 peptide vaccines in various phase trials listed in NIH, USA, ClinicalTrials.gov website testifying to the intense search for a breakthrough in this line of research. This method of rational design of peptide vaccines still has some issues such as vaccine delivery, protein folding and adjuvant use to be solved but holds great promise for rapid response in development and production. We briefly mention here some of the studies that have been done in this respect.

The first report of peptide vaccine was against the canine parvovirus [6], which was subsequently licensed. Studies of *in silico* identification of suitable peptides were carried out by Brossart *et al.* [7] from human cell-surface associated mucin encoded by MUC-1, gene as well as by Ludewig *et al.* [8] who observed anti-tumour and anti-viral immune responses upon administering peptide antigen vaccine against lymphocytic choriomeningitis virus. Liao *et al.* [9] validated that a peptide vaccine based on human papillomavirus protein E5 epitopes used in conjunction with a CpG adjuvant resulted in strong cell-mediated immunity and anti-tumour behaviour in mouse model; CpG is a short single-stranded DNA molecule. Oany et al [10] searched through 56 strains of human coronavirus spike protein for the peptides with best epitope potential and selected a 9-mer peptide for a T-cell vaccine and a 7-mer peptide for B-cell vaccine design. Islam et al [11] determined a conserved high-scoring epitope in the chikingunya virus using alignment techniques and predicted a B-cell vaccine target. Chakraborty et al [12] identified conserved segments of the envelope protein of all four types of dengue virus through sequence alignment, determined the best with good surface exposure and selected those with high antigenicity.

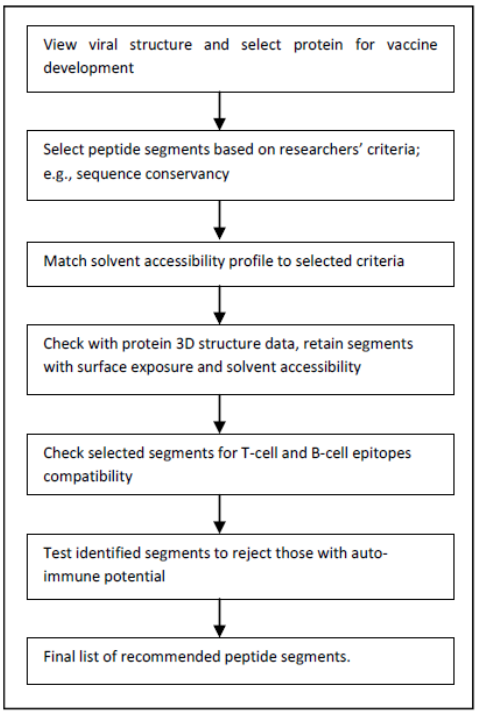

Fig. 1. Work flow chart of peptide selection process. *(Reproduced from Nandy, A and Basak, SC, Int. J. Mol. Sci.* ***2016****, 17, 666)*

The issue with these approaches is that those that have used current strains to determine peptides with strong epitope potential may fail with genetic drift and shift over even short time spans. To avoid such problems, we used graphical representation and numerical characterisation method for protein sequences to identify the best peptide vaccine candidates where a sufficiently large number of sequences of the relevant surface protein of the virion were scanned using such techniques to identify segments that were highly conserved over reasonably long time spans. These were then matched against the protein's Average Solvent Accessibility (ASA) profile to identify segments that were surface exposed, which were then verified using 3D crystal structure data wherever available. Those peptides that met these criteria were then matched against the target population's HLA profile to determine the best immunological response potential. The chosen segments were tested for autoimmune threats and a final list of candidate peptides for vaccines presented.

This approach enabled us to analyse several viruses which have caused epidemics acrtoss time and geography. Our first attempt was with avian (H5N1) influenza neuraminidase [13], which was later repeated for the H7N9 hemagglutinin protein [14]. A similar exercise for rotavirus [15] yielded four possible vaccine candidates. Application to several human papillomavirus envelope protein [16] showed that there could be peptide vaccines that can inhibit several papillomaviral types at a time. In a more recent example, the technique has been applied to comparatively sparse data of the Zika virus [17] that have caused severe disruptions in the Americas in 2015-16.

However, as mentioned earlier. there are still several problems to be overcome before peptide vaccines become a reality. Although there are several advantages of peptide vaccines over traditional types, and many are in advanced phase trial stages, no such vaccine has yet been licensed for human use. Issues such as adjuvants, stability, long term storage and the like need to be standardised. But when such problems are overcome, peptide vaccines hold the key for a cost-effective, fast response to deadly epidemics like the Ebola crisis or Zika virus rampage [18] in recent years.

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