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Latency in Synthetic Peptide Vaccine

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ABSTRACT

Vaccine is a substance that induces immunity without causing disease. Vaccines can be made with live attenuated microorganisms, killed microorganisms or the product of the microorganisms. The product may be natural or synthetic.The peptide vaccines are considered as an alternative to classical vaccines that try to address the issue of possible side effects.The peptide vaccines are based on in vitro synthesised peptides of 20-30 amino acids,known to be highly immunogenic and to trigger the desired immune response.These peptide vaccines can be designed with self or non self -antigen to properly balance the immune responses,which is not possible for conventional vaccines.The series of limitations and failures in peptide vaccine in clinical trials include :limitations of single peptide epitopes as vaccine candidates;an immune invasion;failure to elicit controlled and prolonged immune response;lack of efficacy and inappropriate design. Better way to prove its efficacy is to produce the vaccine for a regional strain of the microbe.

KEY WORDS : Synthetic peptide vaccines; immune response; amino acids; drug delivery

INTRODUCTION

Vaccine is a substance that induces immunity without causing disease. Vaccines can be made with live attenuated microorganisms, killed microorganisms or the product of the microorganisms. The product may be natural or synthetic. Natural products are protective but not possible to procure them as the microorganism is non cultivable. In such cases recombinant technology or synthetic peptides are the other alternatives. The synthetic peptide vaccines are usually composed of 20-30 amino acids containing the specific epitopes of an antigen related to infectious or chronic diseases including cancers,these type of vaccines have several advantages over other kind of vaccines such as conventional vaccines and newly developed DNA of cellular vaccines (Arnon and Horwitz, 1992),(Ashwin and Muralidharan, 2015).The synthesis of these kinds of vaccines are

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comparatively easy and with low expenditure;increased stability and relatively safety and these are generally demonstrated in numerous preclinical and clinical studies. (Minor and Ferguson, 1986; 'Predicting Autoreactivity of Antibodies Elicited with Synthetic Peptide Vaccines', 2008; Girija *et al.*, 2019). In addition, these synthetic peptide vaccines have no limitations in targeted diseases from virus infections to Alzheimer's diseases and even allergy .('Predicting Autoreactivity of Antibodies Elicited with Synthetic Peptide Vaccines', 2008; de Paiva Cavalcanti, Pereira and Dessein, 2017),(Francis, 1991),(Selvakumar and Np, 2017) These can be designed with self and non self antigen to properly balance immune responses which is not possible for conventional vaccines. ('Predicting Autoreactivity of Antibodies Elicited with Synthetic Peptide Vaccines', 2008),(Shahana and Muralidharan, 2016). The series of failures in peptide vaccines in clinical trials suggest several issues critical for successful development of peptide vaccines .(Zom *et al.*, 2012),(Marickar, Geetha and Neelakantan, 2014). These include the task of efficacy,failure of prolonged immunogenic responses , not proper design for clinical trials , structural change and thus change in antigenic properties of the infectious agents during its life cycle in host organisms (Kastin and Kastin, 2011),(Skwarczynski and Toth, 2016). Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy *et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan *et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy *et al.*, 2019; Gheena and Ezhilarasan, 2019; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

PREPARATION OF SYNTHETIC PEPTIDE VACCINE

A variety of considerations is required to be made during the planning of a peptide vaccine in touch of the actual vaccine under development . The primary and foremost among them is the identification of immuno dominant domains of epitopes that are capable of including protective immune responses in terms of humoral immunity or cell mediated immunity against the specified antigen. The immunodominant epitopes are often chosen from Bcells,cytotoxic or helper T cells

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(Kunz, 2003).Epitopes solution will need to be directed toward not only inducing the specified effector responses but also for induction of helper T cell responses. Among the epitopes that induce specific sunsets of immune responses, they might be identifying the proper epitopes or peptides which will activate T cells to the magnitude which will confer protective immunity.
(Fagan, Toth and Simerska, 2014),(Marickar, Geetha and Neelakantan, 2014). Developments of a broad spectrum vaccine against multiple serovars of a pathogen may be required to identify highly conserved immunodominant epitopes (Masuko *et al.*, 2015).

ADVANTAGE AND APPLICATION OF SYNTHETIC PEPTIDE VACCINE

The synthetic peptide vaccine represents fragments of peptide antigen sequence which are synthesised from amino acids and assembled into a single molecule or a supramolecular complex or just mechanically mixed,they are reorganised by the immune system and induce immune response (Voskens, Strome and Sewell, 2009),(Voskens, Strome and Sewell, 2009; Vaishali and Geetha, 2018).On comparing to traditional vaccines these are characterised to lots of advantages.These are relatively inexpensive and safe production technologies.Ability to induce the immune response to those structural elements of a protein antigen,which exhibits weak immunogenic within the whole antigen molecule. High standardisation.Lack of component processing high reterogenicity,possibility of removal of antigen fragments exhibiting allergenicity and cross reactivity to own molecules of the vaccinated organism possible of conjugation of various peptides from different antigens to one and the same carrier.(Wang *et al.*, 2018),(Palatnik-de-Sousa, da Silva Soares and Rosa, 2018; M, Geetha and Thangavelu, 2019)

SYNTHETIC PEPTIDE VACCINE COMBINED WITH IMMUNOMODULATORY COMPOUNDS

CYTOKINES

Cytokines are granulocyte macrophage colony stimulating factor (GM-CSF) which is used as adjuvants in vaccines due to its capacity to cause proliferation of dendritic cells and macrophage. In melanoma patients the additions of locally applied cytokines modestly increased the immune response against the peptide vaccines .(Powell and Newman, 2012). In other cases the peptide vaccine TERT administered with cytokines in pancreatic lung cancer patients induced detectable vaccines and survival advantage in immune responders.(Guenounou, 1995),(Girija *et al.*, 2019) .

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Where in the same case both the combinations are administered in pancreatic cancer patients resulted in demonstrated T-cell responses (Schijns and O'Hagan, 2005).

SYNTHETIC PEPTIDE VACCINE ON COMBINATION WITH CHEMOTHERAPY

A well defined chemotherapeutic agent combined with peptide vaccines in gemcitabine.This nucleoside analog is used in various carcinomas in bladder, breast, lung, pancreas and etc and has previously been shown to induce not only apoptosis in replicating cells but also immune stimulation of T.cells.(Institute and National Cancer Institute, 2020). Although the mechanisms for comparing chemotherapy with peptide vaccines are not completely resolved it is apparent that the aforementioned but also other chemotherapeutics have additive or even synergistic effects with peptide vaccine (Manivel and Rao, 1991) .

DELIVERY METHODS OF SYNTHETIC PEPTIDE VACCINES

Various particulate delivery systems are used for efficious delivery of peptides vaccines. These delivery systems can also serve as adjuvant.(Apostolopoulos, 2016),(Girija, Jayaseelan and Arumugam, 2018).The particulate vaccines carriers used as of emulsion, lipolysome, virosome and related particles , polymeric particles and some other particulate systems like nanoparticles carbon nanoparticles , Silicon nanoparticles , liposomes-poly cation complex , oligosaccharides Ester derivatives , micro particles and combination systems like liposomes and emulsions W/O.(Kumar, 2014).

PROTECTION LEVEL

The immunogenic of a mixture of peptides corresponding to cytotoxic T-epitopes is initially elevated by appearance of cytotoxic T-lymphocyte of certain specificities in immunised species . (Diaz-Dinamarca *et al.*, 2020),(Smiline, Vijayashree and Paramasivam, 2018; Diaz-Dinamarca *et al.*, 2020). The protection of the specific humoral responses induced by peptide immunogenic administration is determined by the neutralising effect of antibodies on the entry of an infectious agent into the target cell or by inactivation of a toxin produced by infectious agents. (Aghajani, Rasooli and Mousavi Gargari, 2019),(Paramasivam, Vijayashree Priyadharsini and Raghunandhakumar, 2020)

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ADJUVANTS FOR SYNTHETIC PEPTIDE VACCINE

Formation of strong and specific immune reaction to the antigens is a crucial task within the creation of any vaccines. It's achieved by a further nonspecific stimulation of the system cells, specific targeted antigen delivery to immunocompetent cells and their constant activation by the antigen because of its deposition and protection against protease cleavage. These functions are attributed to adjuvants, which are included into vaccine preparations of strong and long term specific immune response to the antigens is an important task in the creation of any vaccines. It is achieved by an additional nonspecific stimulation of the immune system cells, specific targeted antigen delivery to immunocompetent cells and their constant activation by the antigen due to its deposition and protection against protease cleavage. These functions are attributed to adjuvants, which are included into vaccine preparations .(Aguilar and Rodríguez, 2007) . In vaccines prepared using attenuated and killed infectious agents structural elements of the microorganisms like cell walls, membranes and their components like polysaccharides, lipopolysaccharides, phospholipids, etc. act as adjuvants . Subunit vaccines contain added adjuvants, which promote antigen deposition and nonspecific stimu□ lation of the immune reaction , usually they represent aluminum salts or aluminium hydroxide . Adjuvant selection becomes especially important for the event of synthetic peptide vaccines, because as a rule peptides are well soluble in aqueous solutions, readily subjected to proteolysis and aren't deposited at the administration site. Peptide constructs are targeted at the activation of the immune reaction of a narrow specificity, and that they don't provide attraction and activation of nonspecific immune reaction cell components that potentiate and direct the precise response. Salts and aluminium hydroxide loosely adsorb peptides, weakly activated immunocompetent cells and don't potentiate the immune reaction to peptide antigens .(Jiang and Koganty, 2003) Seeking for new adjuvants for peptide vaccines against human infectious diseases includes adjuvants approved for animal use and also immunomodulators . Oil□based adjuvants, for instance , Freund’s complete adjuvant (which contains a suspension of killed tubercle bacillus cells or their lipopolysaccharides during a oil with lanolin) are utilized in laboratory studies of immunogenicity on animals for an extended time . However, the Freund’s adjuvant is quite toxic, exhibits high reactogenicity and should induce formation of necrotic ulcers at the injection site . Now less toxic and reactogenic oil□based adjuvants (Montanide series) are developed; they're utilized in some peptide vaccines passing clinical trials .

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The first approved vaccine adjuvants was alum, where diphtheria toxoid adsorbed to alum and has been used for long periods.Later an emulsion of water and oil including killed mycobacteria is developed referred to as (FCA) (freund's complete adjuvants)- a gold standard adjuvant for efficacy.(Riccione, 2017),(Priyadharsini *et al.*, 2018a).

More bacterial components Were studied as adjuvants after LPS and lipophilic phospholipid A we're found to exhibit adjuvant activity. In some cases a variety of natural and artificial compounds are demonstrated to possess adjuvants activity but many of them are more toxic for human use in comparison to alum bacterial components have been studied as adjuvants after LPS and lipophilic phospholipid A were found to exhibit adjuvant activity. In some cases a number of natural and synthetic compounds have been demonstrated to have adjuvants activity but many of them are more toxic for human use when compared to alum. (Ishizaka and Hawkins, 2007).

INDUCTION OF PROTECTIVE T-CELL AND B-CELL MEDIATED IMMUNITY PEPTIDE VACCINE

A successful vaccine must induce a strong and long memory humoral and cellular immunity response, but most importantly protection against the disease being targeted evaluation of protective property is an important aspect .('Peptide-free Synthetic Nicotine Vaccine Candidates with Galactosylceramide as Adjuvant', no date; Selvakumar and Np, 2017) . In later studies, a number of synthetic peptide from influenza LCMV and Sendai virus were tested in different group where many of them have been successfully shown to induce specific CD8 toxicity T-lymphocytes in immunised animals.Peptide recognised by CD8 T cells have been shown to be both selective and extremely sensitive.(Riccione, 2017),(Leggatt, 2014). Since, specific CD8 T-cell mediated immunity also play a central role in controller tumour growth peptide vaccines also have been designed to use for tumour therapeutic applications. There have been several reports of peptide vaccines being successful in controlling tumour growth.(Brostoff, 1995). The longer peptide needs to be trimmed to minimal MHC-1 binding ligand by protease and peptides or by Antigen presenting cells (APC) process followed by loading on MHC-1 groves . In fact minimal peptides used in most of the studies induced lower immune response compared to longer peptides. (Elsawa, Rodeberg and Celis, 2004),(Priyadharsini *et al.*, 2018b) (Shahzan *et al.*, 2019)

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EXAMPLES

- Long peptides need uptake and processing before the minimal epitopes are able to bind to MHC-1 molecules and they can indive sustained CD8-CTL responses .(Donev, 2015)
- Long peptide vaccines against HPV 16 E6/E7 are superior over vaccination with short peptides, an aspect confirmed worth later studies.(Collins, 1974).

SYNTHETIC PEPTIDE VACCINE THAT REACHED CLINICAL TRIALS

Malaria

In clinical trials the primary synthetic anti malarial vaccine "spf66" against p.flaciparum in asexual stage of development started. This consists of three fragments of three arious surface antigens of the merozoite with the repeated PNANP fragments of sporozoite CS protein between them, where the efficacy of "spf66" in clinical trials significantly varied counting on geographical location. (Nardin, 2010).

HCV-(Hepatitis -C-Virus)

HCV exhibit extremely high genetic variability and therefore employers of the traditional approach for vaccine developed based on attenuated or inactivate virus consist of 5 synthetic peptides which is of 2 fragments of core protein residues , 2 fragments of non structural protein , 1 fragments of NS4 protein.(Kang, 2006)(Pratha, Ashwatha Pratha and Geetha, 2017)

Foot And Mouth Diseases

Although now available inactivated vaccines against foot and mouth disease can effectively protect animals it's some drawbacks. The vaccine for this disease is predicated on VP1 peptide fragments containing virus neutralising B-epitopes and fragments of an equivalent protein. This vaccine has been approved and has been in use for veterinary purposes in Russia. ((Rowlands, 2019) (Smiline Girija AS, 2019)

Current Application In Covid19

Extensive mutations, insertion, and deletion were discovered in the COVID-19 strain using the comparative sequencing. The T-cell epitope-based peptide vaccine was designed for COVID-19 using the envelope pro- tein as an immunogenic target; nevertheless, the proposed vaccine rapidly

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needs to be validated clinically ensuring its safety and immunogenic profile to help stop this epidemic before it leads to devastating global outbreaks.

FUTURE THERAPEUTIC ASPECTS

In the ongoing fight against communicable disease there's accelerating progress within the identification of relevant peptides and, where appropriate, design of smaller drug molecules supported them should be applied .Such progress provides many additional tools and methods that could be used. In some cases, one might find that repurposing existing drugs or herbal extracts with suspected genuine efficacy may help within the challenge. As a sort of "stop press", note that at the time of this study it seemed plausible that angiotensin converting enzyme inhibitors could do an equivalent job as a peptidomimetic. This has supported certain molecular similarities, but recent studies have highlighted that customary ACE inhibitors are likely to possess a counterproductive effect, although an ACE 2 inhibitor might well work usefully. It's likely that the concentrations required may have an excessive effect on vital signs , but aerosol preparation could be useful. However, much research on this is often needed. However, a peptidomimetic supported the above motif perhaps also delivered as an aerosol, could perhaps be more specific and have less side effects. Design or discovery of more rigid molecules with similar van der Waals and electrostatic surfaces would be the more traditional pharmaceutical choice. (Shimonishi, 2007)

DRAWBACKS

The disadvantage is due to the technology which is not frequently used because the preparations and use is associated with problems. It needs a high knowledge and idea on the immune complex , high cost of cultivation of pathogenic bacteria , viruses or Protozoa for industrial productions, risk of leak of infectious agents, high cost for purification and detoxification of vaccine produced . High genetic variability of infectious agents, significant structures Chand thus change in antigenic properties .(A. and F., 2012).Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

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CONCLUSION

Some of the biological activity of the synthetic peptide vaccines is being potentially used for clinical and laboratory analysis. It acts as an infection control against several infectious agents and retards their development. Elaborated research and works are needed for further study and future need. Identifying a suitable vaccine candidate is the major task in the successful production of synthetic peptide vaccines. Efficacy will vary in different serotypes and ethnic groups. Better way to prove its efficacy is to produce the vaccine for a regional strain of the microbe. This way it can be a better alternative for recombinant and plasma derived vaccines.

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