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From Bench to Bedside: DNA Vaccines

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Abstract

DNA vaccines came into scientific limelight almost 25 years ago. Since that time, there have been many advancements in this field i.e. increased immunogenicity, use of improved formulations and improved physical methods of delivery. This review focuses on denoting the recent developments in the field of DNA Immunization. The recent studies demonstrated by a number of research centers showed that the DNA plasmid induced immune responses evoke protective immunity against several infectious diseases and cancers, which provides adequate support for the use of this approach. Four DNA vaccine products have recently been approved in the field of veterinary medicine indicating a constructive future for this technology. This review also highlights the advantages and disadvantages of DNA Vaccines.

Introduction

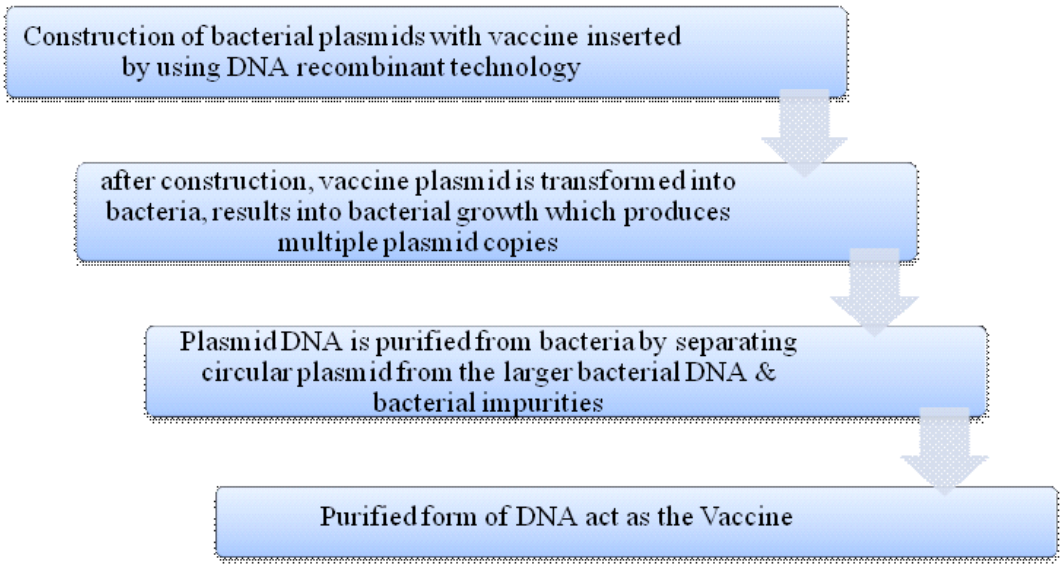
Currently, with the advance in the biotechnology and the utilization of novel techniques in molecular biology, it is possible to make new vaccines. The successful vaccine gives a fruitful opportunity to use it not just as a part of the term prophylaxis of infectious diseases but also to broaden their purposes in controlling existing and persisting infectious diseases. Currently, vaccines are being investigated as an approach to control HIV and other incessant viral infections as well as treatment of cancer and autoimmune ailments. In spite of all these accomplishment underway in production of vaccines, there are major challenges facing with difficulties, constraints and drawbacks confronting vaccination. Researchers were unable to produce a vaccine for pathogens with antigenic hyper variability including serogroup B meningococcus, HIV and HCV or against pathogens with

an intracellular phase, causing infections that are transcendently controlled by T cells, such as tuberculosis and malaria.[1] Likewise, development of conventional vaccination can be time and labor intensive, not permitting a quick action to the need of a new vaccine, as in the occurrence of an influenza pandemics. Also there are likewise hypothetical safety concerns linked with the approaches of using both non-live and attenuated concepts.[2][3]To overcome all these challenges, new approaches amid the most recent 30 years have been applied to vaccine advancement. These updated approaches in vaccination technology include DNA vaccines, beforehand characterized as impossible to make.[4]

Synthesis of DNA Vaccine[5]

DNA vaccines are composed of bacterial plasmid. Expression plasmid of DNA-based vaccination contain two units:

i. The antigen expression unit: contain promoter/enhancer sequence which is followed by antigen-encoding polyaldenylation sequences
ii. The production unit: contain bacterial sequence which is necessary for plasmid amplication& selection



Benefits

The ability of plasmid DNA to induce both cellular and humoral immune responses after inoculation has been demonstrated in several animal models, and hopes have been raised that its applications will lead to new therapies for a range of human diseases. [6]

It is potentially cheaper to produce than recombinant protein vaccines. It is much easier to transport and use, especially in developing countries, DNA-based immunisation exhibits several important advantages over conventional immunisation strategies that involved live-attenuated or killed pathogens, proteins, or synthetic peptides. It incorporates many of the most attractive features of each approach.

One of the important advantages of the DNA immunisation, is that the immune response to immunisation can be directed to elicit immune response without the need for live vectors or complex biochemical production techniques. [7]

DNA Vaccines are heat stable and do not require refrigeration. They can be transported and administered at far off places. [8]

Other advantages of DNA vaccines are that they are highly specific and the expressed immunizing antigen is subjected to the same glycosylation and post-translational modifications as natural viral infection. Moreover, it is relatively easier to insert multiple variants of an antigen into a single array of plasmid vaccine.

Challenges

DNA vaccines limited to protein immunogens (not useful for non-protein based antigens such as bacterial polysaccharides). Certain vaccines, such as those for pneumococcal and meningococcal infections, use protective polysaccharide antigens.

The disadvantages of DNA vaccines are based mainly on health and safety issues. Most of the safety issues concerning the system are based on the activation of oncogenes as a result of genomic incorporation of immunising DNA, as well as eliciting anti-DNA antibodies; however, this has rarely been detected in experimental studies. [9] Other drawback of plasmid vaccines is the reduced level of immunogenicity. Insertion of foreign DNA into the host genome may cause the cell to become cancerous.

Potential risks of integration of vaccine into cellular DNA of the host. A further concern is that an integrated vaccine might cause insertional mutagenesis through the activation of oncogenes or the inactivation of tumour suppressor genes. In addition, an integrated plasmid DNA vaccine could, in theory, result in chromosomal instability through the induction of chromosomal breaks or rearrangements. However, none of these concerns have been witnessed in the preclinical or clinical evaluation of DNA products. There is a chance of development of auto immunity. There is a possibility of development of antibiotic resistance. [6][10]

Ongoing clinical trials

A novel DNA vaccine has been developed the pre-membrane+ envelope proteins (prME) of ZIKA Virus. Mice and non-human primates were immunised with this prME DNA-based immunogen through electroporation-mediated enhanced DNA delivery. This study was partially successful, suggesting additional research for prevention of this disease in humans.[11]

In 2017, Scientists at the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, developed the NIAID

Zika virus investigational DNA vaccine. Vaccination have begun in multi-site phase 2/2b clinical trial testing an experimental DNA vaccine designed to protect against disease caused by Zika infection. [12]

20thCentuaryTimelines in DNA Vaccine Development

Year	Accomplishment
2010	Recombinant hepatitis B surface antigen (HBsAg)-vectored DNA vaccine encoding the E7 and E6 tumor-associated oncoproteins of human papillomavirus (HPV) type 16 was constructed and it was shown that the use of a HBsAg-based DNA vaccine as a vehicle to elicit responses to coencodedtumor antigens, and have specific implications for the development of a therapeutic vaccine for HPV-associated squamous carcinomas [13]
2011	li-PADRE-E6 represents a novel DNA Vaccine for the treatment of HPV-associated head and neck cancer [14] Pulmonary immunization with PEI-DNA is an efficient approach for inducing robust pulmonary CD8 + T-cell populations that are effective at protecting against respiratory pathogens.[15] Major advancements have been made in the field of vector design hold considerable promise for rabies DNA vaccine development. [16] Incorporation of TBK1 into a DNA vaccine was found to enhance the antigen-specific humoral immune responses targeting the Plasmodium falciparum serine repeat antigen (SERA), a candidate vaccine antigen expressed in the blood-stages of human malaria parasites. [17]

2013	Magnetic vectors comprising polyethylenimine (PEI)-coated superparamagnetic iron oxide nanoparticles were used for enhanced DNA Vaccine Delivery in combination with hyaluronic acid. [18] A DNA vaccine was designed against apolipoproein thus opening a new dimension for the treatment of cardiovascular diseases related to high lipoprotein (a). [19] An oral DNA vaccine against an Endoglin was developed and it showed significant inhibition of tumor growth. [20]
2014	Earlier it was reported that the short noncoding DNA fragments (sf-DNA) can significantly enhance EP-mediated transgene expression of reporter genes. Later a study showed that sf-DNA in EP-mediated HBV DNA vaccination leads to an enhanced expression of the HBV surface antigen, resulting in higher cellular and humoral responses. [21]
2015	Studies were conducted in order to improve the immunogenicity of DNA vaccines in humans. [22]
2016	ID injection of DNA vectors using an NF device (NF-ID) elicits a superior cell-mediated immune response, at much lesser DNA dosage, comparable in magnitude to the traditional intramuscular immunization. [23] A novel DNA vaccine has been developed the pre-membrane+ envelope proteins (prME) of ZIKA Virus. Mice and non-human primates were immunised with this prME DNA-based immunogen through electroporation-mediated enhanced DNA delivery. This study was partially successful, suggesting additional research for prevention of this disease in humans.[11]

DNA Vaccines Currently Being Used In the Market

There are only 4 licensed DNA vaccines available in the market for animal use: 1. Vaccine against West Nile virus for horse. [24] 2. Against infectious haematopoietic necrosis virus.[25] 3. Against melanoma in dogs [26] 4. Growth hormone releasing hormone (GHRH).[27]

Conclusion

Since the last 2 decades DNA vaccine technologies have generated great deal of excitement as well as disappointment. DNA Vaccines are potentially cheaper to produce than recombinant protein vaccines. It is much easier to transport and use, especially in developing countries. There is a lot of room for improvement in this field regarding the issue of low levels of immunogenicity. This opinion is strengthened by recent licenses in the area of animal health and by the improvements in immune potency reported in the non-human primate model systems. However, the coming years of clinical testing of new and more complex DNA vaccines will be pivotal for either creating a true clinical success based on immune potency, or for telling us that we still have much further to go. A developing country such as India should channelize its efforts to develop novel DNA vaccines for a variety of diseases in which non-human DNA vaccine models have sufficiently proven themselves. Its success will be built on a high level of participation cooperation between industry, the regulatory authorities, funding by non-governmental organizations, the public and academicians.

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