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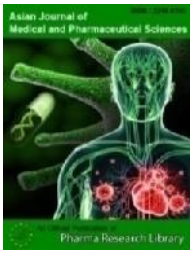

Synthetic Vaccine

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A B S T R A C T

Vaccination is among the most successful medical treatments ever developed. This prophylaxis had a long journey through history to become one of humanity's key achievements; from early immunisation in China, centuries ago, through to Edward Jenner's works in the eighteenth century–when the word "*vaccination*" was introduced for the first time – up to these modern times when recombinant protein-based vaccines are increasingly becoming popular. Despite the advances in the field, classical vaccination using whole organisms is still common. Whole pathogen immunisations usually produce long lasting immunity; however, they are not without drawbacks. The human body developed an extensive defense system against microbial pathogens. The particular microbes have evolved sophisticated mechanisms to evade immune surveillance, allowing persistence within the human host. In an effort to combat such infections, intensive research has focused on the development of effective prophylactic and therapeutic countermeasures to suppress or clear persistent viral infections. The DNA vaccines have now re-emerged as a promising candidate for therapeutic intervention due to the development of advanced optimization and delivery technologies. The genetic optimization of synthetic plasmid constructs and their encoded antigens, *in vivo* electroporation-mediated vaccine delivery, as well as codelivery with molecular adjuvants have collectively enhanced both transgene expression and the elicitation of vaccine-induced immunity. The development of potent heterologous prime–boost regimens has also provided significant contributions to DNA vaccine immunogenicity. Herein, the authors will focus on these recent improvements to this synthetic platform in relation to their application in combating persistent virus infection.

Keywords: DNA vaccine immunogenicity, microbes, human body, transgene expression, synthetic plasmid.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Vaccination is among the most successful medical treatments ever developed. This prophylaxis had a long journey through history to become one of humanity's key achievements; from early immunisation in China, centuries ago, through to Edward Jenner's works in the eighteenth century – when the word "*vaccination*" was introduced for the first time – up to these modern times when recombinant protein-based vaccines are increasingly becoming popular.

Despite the advances in the field, classical vaccination using whole organisms is still common. Whole pathogen immunisations usually produce long lasting immunity; however, they are not without drawbacks. For example, the safety of this form of vaccination is one of the major concerns as it may cause autoimmune or strong allergic responses. Interestingly, allergic shock is often related not to the presence of pathogen itself but rather, it is caused by contamination from the medium on which microorganism was grown (*e.g.* eggs, antibiotics). Attenuation or inactivation of such vaccines might not be perfect and the pathogen may return to its virulent state. One of the most prominent examples of such vaccine defectiveness was the "Lübeck disaster", when, in 1930, 67 babies among the 249 vaccinated with tuberculosis vaccine (BCG) died. Shedding of the pathogen to the environment, during vaccine manufacture, is the other problem and infections of staff during the production process have been also reported. Manufacturing difficulties of some pathogen (*e.g.* malaria sporozoites), poor vaccine stability and the need for a "cold chain" are other significant disadvantages of classical vaccines. Some of the vaccines cannot even use the whole cell approach (*e.g.* cancer vaccines, due to tumour similarity to healthy human cells). Subunit vaccines utilising only part of the whole pathogen are more controllable and can be produced without the use of the pathogen itself (*e.g.* recombinant proteins). They are a very attractive alternative to the whole pathogen approach and have become extensively popular in the modern era. However, they are still not perfectly safe, and cause side effects and production difficulties similar to whole pathogen strategies[1-6]. For example whole protein-based approach was largely abandoned in the case of the vaccine against Group A *Streptococcus* which was targeting surface protein (M-protein) of the bacteria due to potential protein-triggered autoimmunity.[3] In addition to problems associated with protein purities (these are normally produced using microorganisms), there are common stability issues, large scale protein expression difficulties, difficulties with the introduction of desired post-translational modification (*e.g.* glycosylation) into recombinant proteins and poor or undesired immune responses (inflammation, autoimmunity, *etc.*). Therefore, the use of only minimal antigenic epitopes which can trigger the desired immune responses appears to be the smart approach to develop safe vaccines. The synthetic peptide-based vaccines may have such a capacity. They may become the unique medication of the future capable of delivering not only protection against diseases but may turn into the therapeutic tool to treat them[7-15].

Vaccination and immunity

A vaccine, similar to a natural pathogen, at first, needs to be recognised by an animal/human defence system as an "enemy" to trigger a cascade of immune responses. The innate immune system serves as the first line of defence against microbial aggressors or toxins (produced by them). It also recognises pathogens/antigens as invaders and stimulates adaptive immunity, triggering antibodies and cellular responses. Antigen-presenting cells (APCs) such as dendritic cells (DCs) or macrophages are able to recognise pathogen-associated molecular patterns (PAMPs) *via* pattern recognition receptors (PRRs) such as toll-like receptors (TLRs). The PAMPs are recognised before or during the endocytosis process of an antigen by APCs. Once recognised, antigens are processed into small molecules (usually peptides) and loaded on MHC-I or MHC-II proteins. MHC-II loaded with small antigen trigger the activation of T-helper cells (CD4) which further activate cellular immunity (cytotoxic T-lymphocyte (CTL) responses) and/or humoral immunity (neutralising and/or opsonic antibodies production by B-cells). Antigens loaded on MHC-I interact directly with CD8+ cells stimulating cellular responses. Antigen can be recognised, processed and transported to lymph nodes by peripheral APCs, or it may travel on its own to lymphatic nodes and then be processed by lymph node resident APCs. Lymph nodes are composed mostly of T-cells, B-cells, DCs and macrophages, and one of the major sites for activation of adaptive immunity[16-22].

Peptide-based vaccine

The use of only a minimal microbial component which is able to stimulate long lasting protection against the pathogen is becoming the tendency in vaccine development. This type of vaccine may not replace the recent trend in development of recombinant protein-based vaccines in the near future; however, exciting development in peptide-based immunogens is already occurring.

Nano and micro-technology in vaccines

In general, peptide vaccines need an adjuvant for their efficacy. Adjuvants usually target APCs through TLRs recognition. However, delivery systems targeting APCs designed to mimic pathogen without the involvement of specific receptor recognition are also possible. Antigen uptake by APCs depends on the size, shape, surface, morphological and physicochemical properties. The mechanism of uptake/endocytosis varies depending on the size, and different sizes are preferentially uptaken by different subsets of APCs. These observations resulted in rapidly increased popularity of nano- and microparticles usage for vaccine delivery in recent years. It has been demonstrated that nanoparticles can be uptaken preferentially by APCs, especially when they are positively charged. Small nanoparticles (<100 nm) can easily travel to lymph nodes and therefore induce stronger and faster immune responses. Most of the reported studies suggested that 10–50 nm nanoparticles are optimal for induction of humoral and/or cellular immunity; however, the optimal size was different depending on material used for antigen delivery. It also needs to be taken into account that reported sizes of nanoparticles depend on the techniques used to determine their sizes. For example, the size of particles visualised by transmission electron microscopy (dried particles) may significantly differ from the perceived hydrodynamic size in solution as measured by dynamic light scattering. In contrast to small nanoparticles which are easily trafficking in lymphatic system, large nanoparticles and microparticles can induce a strong immune response due to depot effect (retention of the formulation and slow antigen release at the injection site).

Perrie and co-workers demonstrated that liposomes with longer retention at injection site induced stronger Th1 immune response. In addition, a particle-based delivery system may allow antigen cross-presentation toward inducing cellular immunity (for example, against cancer). Particles, similar to other delivery systems, can also trigger stronger immune responses due to the presence of multiple copies of epitope on their surface and protection of peptide against enzymatic degradation. Interestingly, shape (spherical over cylindrical) and enhanced hydrophobicity of the particles was also reported as factors influencing immune system activation[23-29].

Vaccines represent one of the greatest triumphs of modern medicine. The development of the first vaccine by Edward Jenner in 1796 to prevent infection by the smallpox virus was a watershed moment in the war against microbes. Over the next two centuries, human morbidity and mortality resulting from polio, measles, mumps, rubella, pertussis and diphtheria have dramatically declined by over 95% due to the development of prophylactic vaccines. While these strategies have been exceptionally successful against acute, self-limiting infections (Figure 1A), the development of vaccines effective against many microbes that persist within the human host remains challenging.[30-35]

Kinetics of viral load during viral infection and after different therapies

(A) The prevention of viral production and infection when a prophylactic vaccine is administered and establishes effective memory immune responses. (**B**) The course of an acute infection. Virus-specific T-cell effectors become activated and control the virus infection. After viral clearance, effector cells contract to become memory cells, which are pivotal in preventing reinfection with the same virus. (**C**) The cycle of a latent persistent viral infection that stays with the host indefinitely. After viral acquisition, virus production ceases; however, because the virus genome is not completely eradicated, the virus can reactivate. Upon the required stimulus for reactivation, the virus can begin producing viral progeny (lytic form of viral cycle), allowing disease to resurface. (**D**) The natural course of a chronic infection in which incessant viral production exhausts immune responses and disease can no longer be controlled or prevented. Continuous exposure of T cells to viral-specific antigens eventually causes effector cells to become exhausted, leading to deletion of these dysfunctional cells. (**E**) New therapeutic approaches for chronic viral infections might reconstitute virus-specific immune responses and lead to virus clearance and disease prevention.

Viruses are sophisticated connoisseurs, hijacking their specific host cells and transforming them into virus-producing factories, an obligatory process essential for their survival. They can typically enter the human body via many routes, can be relatively pantropic and express complex evasion mechanisms to thwart virus-specific immune recognition. In general, viral infections result in one of two outcomes: an acute infection where the host is able to effectively eliminate the virus, or a chronic infection where incomplete clearance of the virus by the immune system results in viral persistence. Successfully controlling and clearing the spread of viruses requires the coordination of multiple immune effector mechanisms. The first line of defense is the innate immune system, which is activated in response to the detection of pathogens binding to pattern-recognition receptors, which then stimulate and mobilize the antiviral activities of innate cells (macrophages, dendritic cells [DCs] and NK cells) to help control viral spread. In some cases, these responses are enough to prevent the spread of the invading pathogen. However, when these mechanisms fail to control the infection, a more versatile line of defense, the adaptive immune response, is initiated. Cells of the adaptive immune system are activated by the innate response, causing their development into effector cells that promote viral clearance. However, several pathogens including HIV, HCV, HBV, HSV and HPV interfere with the effector mechanisms of the adaptive immune response, resulting in the establishment of persistent infection[36-39].

Chronic viral infections are typically the result of highly regulated evasion mechanisms employed to circumvent the adaptive immune system. Some of these pathogen-mediated approaches include inhibitors of antigen (Ag) presentation and the elicitation of cellular apoptosis, viral interference with interferon pathways and modulation of cytokine and chemokine activity, which favor pathogen persistence. In addition, in some cases, rapid mutation as facilitated by low-fidelity viral polymerases in response to selective immune pressure, allows viruses to escape immune recognition (e.g., HCV, HIV). Alternatively, some can escape altogether by establishing latency within host cells (e.g., HSV). They can also interfere with the function and differentiation of APCs and thereby prevent T- and B-cell activation and expansion. As a result of these strategies and others, the persistence of viral Ag and their prolonged presentation to the immune system contribute to inducing the progressive loss of function of virus-specific T cells. As a result, these T cells become anergic (exhausted) and are ultimately unable to express effector mechanisms critical to control or eliminate the pathogen[40-55]. While various therapeutic treatments targeting chronic infections have greatly helped in reducing the severity of disease, they are not 100% curative and may be associated with side effects and be cost prohibitive in some developing nations. For instance, the development of antiretroviral therapy (ART) has had an enormous impact in delaying the onset of AIDS and prolonging the lives of patients infected with HIV. However, the continuous use of ART drug cocktails can lead to undesirable side effects as well as contributing to the emergence of drug-resistant viruses. More importantly, the effective application of ART therapy requires that regimens be highly customized for each patient and is extremely expensive, and therefore not readily available in third world countries due to socioeconomic obstacles. As a result, over 90% of HIV-infected individuals worldwide do not benefit from this approach. In the case of HBV, currently available therapies such as lamivudine and IFN-α are not fully satisfactory in terms of safety and/or efficacy. Similarly, the

current standard of care for chronic HCV is pegylated interferon plus ribavirin, which exhibits a 50% efficacy rate in patients with HCV genotype 1 and is a costly therapy often accompanied by adverse effects. Thus, therapeutic vaccination strategies may help to treat persistent viral infections where drug intervention is limited, and where intracellular pathogens have established mechanisms to escape from host immune system surveillances.

Therapeutic interventions

Live-attenuated vectors

Live-attenuated vectors have been classified as the most effective type of vaccine due to their ability to invade and cause infection that is greatly similar to the native pathogen, but without the associative pathogenic effects. This type of vector is constructed (by modern methods) by attenuating the infectious agent to reduce virulence while retaining microbial viability. Traditionally, one approach of attenuation is achieved by growing the virus in cultured cells of a different species until the virus can no longer grow well in human cells. Such vectors have been shown to be highly effective when used as prophylactic vaccines in nonchronic infections such as measles, mumps, rubella, yellow fever and polio. Despite these achievements, there is the possibility for reversion into virulence due to the viable nature of the vaccine vector, which has been observed for the live-attenuated oral polio vaccine developed by Albert Sabin as well as others. Further risks are associated with administering these vectors to immunocompromised individuals who may not be able to effectively respond to the vaccine. Therefore, the development of broad alternative approaches that are not limited by these attributes is an important goal of future vaccine platforms.

Viral vectors

Viral recombinant vector platforms, such as vaccinia virus (VV) or adenoviruses (Ad), are among the most developed and characterized candidates for gene therapy and vaccine applications. VV is the prototypical poxvirus, particularly well known for its role as the successful vaccine vector that helped eradicate the smallpox virus. Based on this success in the 1980s, VV became the first recombinant viral vector platform as an approach to preventing infectious diseases. Since then, research has focused on VV as a vaccine platform for a wide variety of infectious agents as well as for cancer immune therapy. Due to its large genome size, recombinant poxviral vectors can carry large amounts of foreign material while retaining their transcriptional and translational capacity. There is also little risk of viral integration into host DNA since replication takes place in the cytoplasm.

As a disadvantage of this platform, recombinant VV can be pathogenic in immunocompromised individuals, which is a major concern when considering its use as a therapeutic vaccine in HIV-infected individuals. Thus, current efforts are directed toward developing a more highly attenuated vector system. Examples of certain highly attenuated, nonreplicating poxvirus strains under development include: the orthopoxviruses, modified vaccinia Ankara (MVA) and NYVAC (derived from the Copenhagen vaccinia strain); and the avipoxviruses, ALVAC and TROVAC (derived from canarypox and fowlpox viruses, respectively). In addition, these attenuated pox vectors have shown effective boosting capabilities in prime–boost regimens. Priming with DNA vaccines and/or viral vector vaccines is being used in a number of studies involving therapeutic vaccination against SIV and HIV infections because of their successful induction of cellular and humoral immunity. During a recent preclinical study, the efficacy of a MVA virus was tested in SIV-infected macaques receiving ART. The authors observed a subset of vaccinated monkeys (five of 12) that had maintained low viral RNA levels below threshold levels had more than 30% $CD4^+$ cells, while the percentage of $CD4^+$ cells in the unvaccinated monkeys (five of six) with higher viral RNA levels had $CD4^+$ cells below 30%. Even though the therapeutic vaccine appeared to benefit several monkeys, there was no control over viral rebound after ART was stopped. While these viruses remain ideal vectors, their construction and production can be complex and expensive, and preparations are not always stable. In addition, prior immunogenicity to the vaccinia vector can limit application of the vaccine to individuals previously vaccinated against smallpox. Nonetheless, great interest remains for such attenuated vectors in vaccine approaches[56].

Another nonretroviral vector that has been extensively studied as a vaccine platform is Ad. This platform has been developed as a vaccine vector because of its capacity to infect a number of different cell types, its high transduction efficiency, ease of manipulation and its ability to induce strong cellular immune responses. Currently, there are over 50 adenovirus serotypes, but Ad5 is the most widely studied because of its greater immune potency. Recombinant adenovirus (rAd5) vectors have become attractive vaccines for HIV because they can be administered mucosally. Both SIV and HIV are known to be active in the mucosa. For instance, Mercier and colleagues demonstrated that enteric-coated capsules containing Ad5 vectors expressing HIV-1 Gag and Env peptides stimulated Ag-specific mucosal and systemic immune responses in adult rhesus macaques. While rAd5 has become a promising HIV vaccine candidate due to the induction of strong Ag-specific cellular immunity, their major limitation is the potential for generating antivector immunity upon repeat administration. Furthermore, another limitation is pre-existing immunity to Ad vectors among human populations that are in great need of an HIV vaccine, especially in sub-Saharan Africa where Ad5 seropositive responses are greater than 90%. For instance, more recently, the safety and efficacy of rAd5 as a HIV vaccine platform has shown that having established pre-existing anti-Ad5 may enhance or exacerbate the spread of virus as observed in the recent Merck Step trial. However, further testing is warranted. Overall, antivector immunity has proven to impair the reuse of vectors, such as adenovirus or poxvirus-based vaccines. This effect potentially limits the ability of these vector platforms for re-administration or to be used for multiple-dose regimens. However, one pivotal approach that investigators are using

to get around this issue is discovering and using rare serotype vectors. Overall, continued research is needed to improve the development of safe and effective nonretroviral vector vaccines[57].

DC vaccines

Therapeutic autologous DCs are currently being tested as personalized vaccine platforms for the control of chronic infection, such as HIV and HBV. As potent APCs, DCs are essential for initiating and maintaining virus-specific immunity and have been found to be impaired in patients with persistent infections. Therefore, DCs are thought to be ideal biological agents for use in immunotherapeutic strategies aiming to augment T-cell immunity in chronic infections. DC vaccines are generated by preparing donor monocyte-derived DCs *ex vivo* and loading them with Ags, and then administering them back into the patient. In 2010, the US FDA approval of Provenge® (Dendreon Corp., WA, USA), an immunotherapy for prostatic cancer that uses the patient's autologous blood cells stimulated with the disease-related protein prostatic acid phosphatase, demonstrated the possibility of this therapy to potentially be used as a future approach for targeting chronic infections. A recent study interested in polyfunctionality and memory T-cell responses following coculture of autologous lymphocytes found that Gag RNA-loaded DC therapy against HIV-1 induced polyfunctional T cells *ex vivo*, but a corresponding increase in the phenotype of central and memory T cells was not observed. On the other hand, peptide-pulsed DCs from healthy individuals and DCs isolated from infected individuals have been shown to be potent stimulators of primary and memory HIV/SIV-specific cytotoxic T lymphocytes *in vitro*. Therapeutic vaccination for SIV using the DC vaccine has also revealed a correlation between decreased SIV DNA and RNA levels and increased SIV-specific T-cell responses. Furthermore, a clinical trial reported by Lu *et al*. found that after administration of three doses of autologous DCs pulsed with whole aldrithiol-2-inactivated autologous virus, plasma viral load decreased by 90% for at least 1 year in eight of the 18 patients. By contrast, a different clinical trial observed a small difference in plasma viral load in HIV-infected patients vaccinated with monocyte-derived DCs pulsed with heat-inactivated autologous virus compared with the control group. These contrasting results may be the effect of different study designs. Even though preliminary results have demonstrated that a virus-pulsed vaccine is a promising strategy for treating patients with chronic infections, the challenge remains of sustaining substantially low viral loads in chronically infected patients. Furthermore, this approach is tempered by the difficulty of developing individualized treatment on a large scale. Thus, similar to the unavailability of HIV antiretrovirals to a majority of infected individuals due to socioeconomic issues, DC-based vaccines will remain focused on patient-specific immune therapy[58-61].

DNA vaccines

DNA as a vaccine platform first came into the scientific spotlight in the early 1990s, when it was reported that the delivery of plasmid DNA into the skin or muscle induced an immune response against encoded viral and nonviral Ags. Tang *et al*. were the first to report that delivering a DNA-coated gold microprojectile into the skin of a mouse could elicit antibody (Ab) responses against the delivered Ag, but Wang *et al*. were the first to show immune responses against a chronic viral infection. DNA vaccination has been suggested as an ideal therapeutic strategy due to numerous advantages over competing platforms. For example, DNA vaccines are nonlive and nonreplicating and thus unable to revert into virulent form, unlike live vaccines. Furthermore, DNA vaccines are highly customizable and hence, multiple Ags can be encoded within a single DNA plasmid. This allows for a much greater breadth in the host immune response and better protection as different epitopes within a single pathogen have been shown to elicit different types of immune responses. In addition, optimization of vaccine vectors and encoded Ags such as RNA/codon optimization and Ag consensus has also enhanced expression and cellular/humoral cross-reactivity. Individuals receiving DNA vaccines are unlikely to harbor antiplasmid vector immunity, as seen with adenovirus vectors. For this reason, DNA therapeutic vaccinations can be delivered repeatedly without initiating an immune response against the DNA plasmid. Finally, DNA vaccines are simple and inexpensive to construct, can easily be produced in large quantities, are more temperature-stable than conventional vaccines, and can be easily stored and transported. These advantages may help contribute to the successful delivery and administration of therapeutic vaccines to infected individuals in developing nations. By delivering DNA via different routes, DNA vaccines can generate a specific type of immune response – cellular versus humoral. For instance, needle injection of DNA mounts a predominately Th1 response while biolistic injections of the same plasmid mainly elicits a Th2 or balanced Th1/Th2 response. McCluskie and colleagues demonstrated that the type of Ab response (IgG, IgG1, IgG2a), level of Ab responses and cytotoxic T cell (CTL) activity vary depending on the route of administration in both mice and nonhuman primates (NHPs) as well as the immunization schedule in NHPs. Intranasal versus intramuscular immunization with a DNA–monophosphoryl lipid A vaccine against HIV Type 1 enhanced mucosal Ab responses and systemic cell-mediated immunity in mice. However, the intramuscular vaccine was more advantageous for eliciting Ab responses. The ease of manipulation of DNA vaccines allows for researchers to be selective in the type of immune response against a specific viral infection. The success of DNA vaccines in preclinical studies quickly lead to clinical trials, and the idea of using DNA to immunize people immediately gained widespread recognition. The first DNA vaccine studies in humans were conducted almost 20 years ago. The goals of the various studies were to evaluate and demonstrate the safety, tolerability and immune potency of the DNA vaccines. In the first Phase I clinical trial, a DNA-based vaccine for HIV-1 infection was evaluated for both therapeutic and prophylactic applications. Soon other DNA vaccine trials

would follow, including trials that tested DNA-based vaccines against other HIV Ags, HBV and malaria [70–72].

These introductory studies established that DNA vaccines were tolerable in humans, and that they could enhance T-cell proliferation and CTL activity, although the immune responses elicited were weaker than expected based on preclinical data. While 'first-generation' DNA vaccines failed to demonstrate a robust level of vaccine-specific immunity in humans, exhaustive research has continued to develop new modifications and improvements to the technology to enhance DNA efficacy. To date, a plethora of approaches have been conducted to improve or augment the immunogenicity elicited by DNA vaccines. These efforts have included: optimization of the vaccine vectors (e.g., RNA/codon optimization) and Ags encoded by the plasmids (e.g., consensus sequences) to enhance Ag expression and cellular/humoral cross-reactivity; inclusion of molecular adjuvants to enhance, modulate and skew immune responses; and *in vivo* electroporation (EP), a promising delivery method that improves the expression and presentation of Ags expressed by DNA vectors. Refer to references for a more detailed overview of how DNA vaccines prime immune responses[62-68]. Finally, the novel protocol of heterologous prime–boost immunization has markedly heightened the immunopotency of DNA vaccination, and as result has sparked great excitement and interest in the DNA platforms to be examined for therapeutic approaches. Although we are far from a complete understanding of how DNA vaccines fully work, recent studies are beginning to shed light on this subject.

Current therapeutic DNA vaccines

The recent advancement of DNA vaccine Ag design and optimization, inclusion of molecular adjuvants and improved delivery methods have greatly enhanced their immunological performance. This is highly reflected by the numerous ongoing clinical trials investigating DNA vaccines for therapeutic applications. Although the use of therapeutic vaccines against chronic infections is still in the early stages of research and development, recent studies have shown that the use of DNA vaccines in preclinical and clinical trials is a safe and effective strategy that can provide beneficial effects for individuals with persistent viral infections. Therefore, such promising results from preclinical studies using DNA vaccines have subsequently advanced these gene-based vaccines into clinical trials. While all of these current studies have demonstrated tolerance and safety among healthy and infected subjects, many of these vaccines still require additional optimizations to enhance immunogenicity. For instance, although Alvarez-Lajonchere and colleagues demonstrated that viral capsid proteins encapsulating a HCV DNA vaccine might play an important role as adjuvants and delivery vehicles by demonstrating vaccine-induced cellular and humoral responses, the immune response generated by the vaccine did not reduce HCV viral load and future studies with further optimized plasmids will shed more light on the potential of CIGB-230 HCV vaccines[69-70]

2. Conclusion

The enormous advances in molecular engineering and biotechnology in recent decades have enabled the development of increasingly efficient generation of vaccines. The vaccine platforms have numerous advantages, such as greater safety; better immune response directioning; the possibility of coverage against multiple viral subtypes; the fast development, production, and ease of storage, which justifies the growing effort to establish these vaccine strategies. The databases and the bioinformatics tools currently available allow the prediction of the most promising epitopes to use in essays in vivo, also allowing rapid replacement of these epitopes in other vaccine constructs in response to pathogen mutations, thus preventing epidemics with emerging viral subtypes. The development of peptide vaccines to combat human disease holds great promise but also will face continued challenges. The vaccines have been highly beneficial for reducing mortality and illness due to infectious disease and have the potential to have a similar impact in chronic diseases.

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