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# A Brief Overview On Polymeric Delivery Of Nucleic Acid Vaccines

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**ABSTRACT**

Nucleic acid vaccines, in particular messenger RNA (mRNA) vaccines, show notable benefits in the current COVID-19 pandemic. The nucleic acid vaccine's potential as a preventative and therapeutic measure has been greatly increased by the use of polymeric materials as delivery vehicles. Improved in vivo stability, enhanced biosafety, selective cellular absorption, endolysosomal escape, and promoted antigen expression are among the features of polymeric nucleic acid vaccines. Nevertheless, polymeric the hurdles facing polymer-gene vaccination systems are still too great, despite significant advancements in the past few decades in the delivery of nucleic acid vaccines and clinical translation. An overview of different polymers and their properties, as well as sample formulations, are given in this review for the delivery of vaccines containing nucleic acids. It also explores the issues that are currently being faced in this field, how to solve them, and the potential uses of polymeric carriers and nucleic acid vaccines. This review's main objective is to protect against serious or emerging diseases by rationally designing and developing polymeric vaccine delivery systems. This review also includes information about recently developed novel delivery platforms and new vaccine vectors.

**Keywords:** Nucleic Acid Vaccine, Gene Delivery, Humoral Immunity, Cellular Immunity

## 1. INTRODUCTION

Contagious conditions, for case, coronavirus complaint 2019 (COVID- 19), excrescences, and vulnerable conditions are serious risks to public safety and health. The rush, spread, transmission, and long course of conditions bring great obstacles to the treatment process[1] By introducing exogenous genes and expressing antigens in the host cells, nucleic acid vaccines elicit potent T helper cell (Th)1 and cluster of differentiation CD8+ immune responses, making them appropriate for the treatment of chronic, recurrent, and metastatic diseases. Despite the fact that scientists have worked hard to make naked nucleic acid vaccines more immunogenic—for example, by using stronger promoter/enhancer systems, improving antigen-coding sequences, and improving immunization routes—bare DNA or RNA vaccines only slightly increase the ability of the host immune system to mount an attack. In this review,[2] We provide a comprehensive overview of the types, properties, and formulations of polymer carriers and delivery systems for nucleic acid vaccines (Figure 1). We also talk about the difficulties in using polymer-based technology to administer nucleic acid immunizations. Finally, we provide a summary of the approaches that have been taken to improve the efficacy of nucleic acid vaccines in the creation of polymeric delivery systems.[3]

## 2. Different kinds of polymer carriers for delivering nucleic acid vaccines

It will assist to use an appropriate vaccination delivery strategy. Since lysosome vaccines made of DNA have unfavourable pharmacokinetics of bare lithium due to their hydrophilicity, biological robustness, or simple nuclease degradation, the in vivo process is necessary for an effective decrease in vaccination potency. The presence of vaccine carriers reduces the body's natural nucleic acid degradation process. It has several desirable characteristics that may boost the vaccine's effectiveness. The most extensively used delivery systems for vaccines are lipid- and polymer-based.[4] Lipid-based delivery systems are biocompatible, capable of preventing nuclease from breaking down nucleic acids, and able to achieve nucleic acid endocytosis, which

increases transfection efficiency. Additionally, characteristics like long cycling and antigen-presenting cell (APC) targeting are conferred by lipid-related surface modifications. Conversely, polymer-based carrier delivery systems are becoming more and more promising since they can be precisely tailored by adding advantageous end groups.[5]

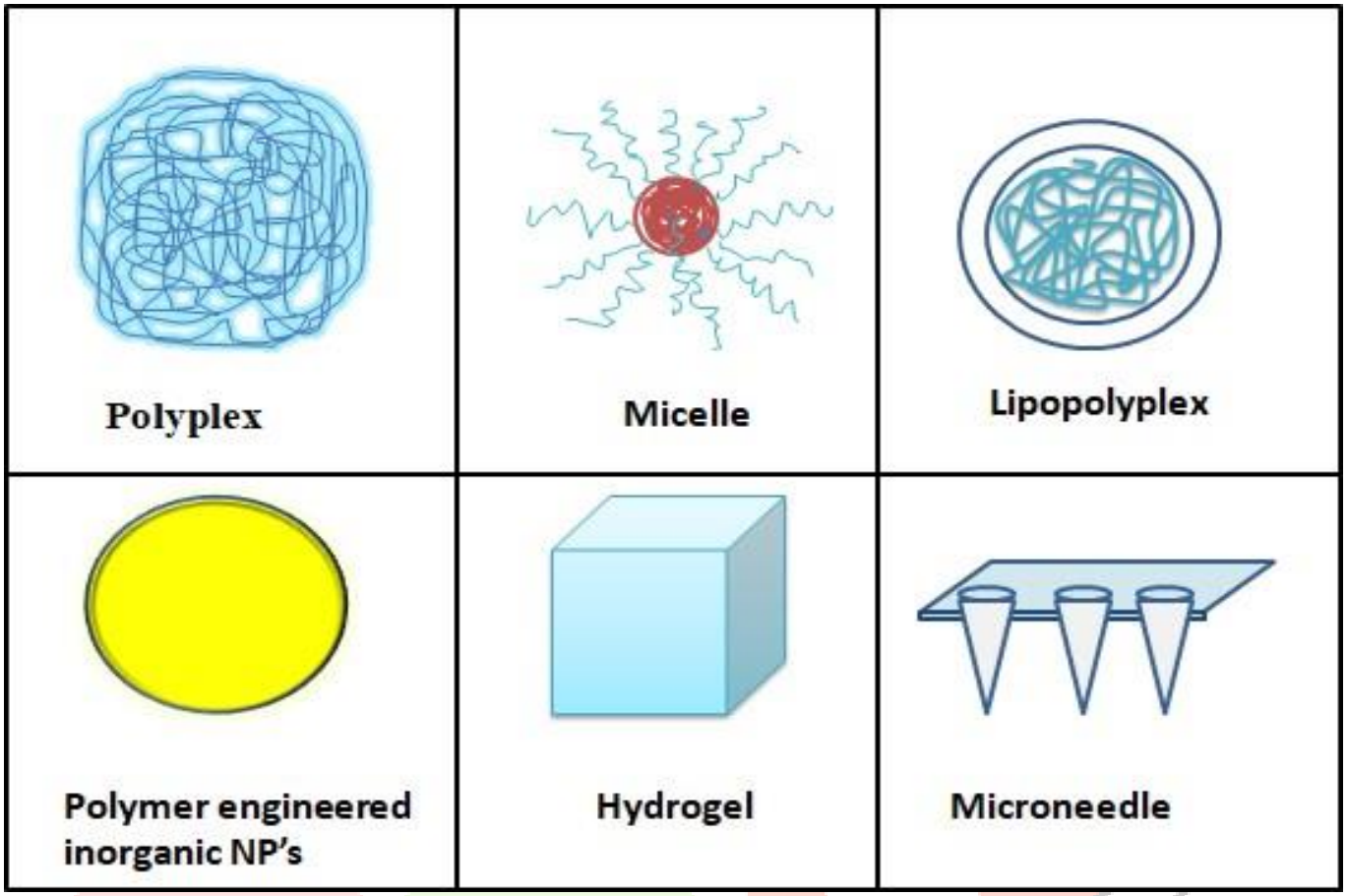


**Fig.1: representative polymeric formulations used for vaccine delivery including polyplex, micelle,lipopolyplex,polymer engineered inorganic nanoparticles (NPs), hydrogel, and microneedle.[6]**

### 2.1 Polysaccharides

Natural sources of polysaccharides that are valued for their immunoregulatory action, high biocompatibility and biodegradability, and low toxicity include mannan, dextran, beta-glucans, and chitosan. as excellent vaccine carriers.[7] D-glucosamine and N-acetyl-D-glucosamine are the building blocks of chitosan, and they are connected by -(1,4) linkages. It is among the cationic polysaccharides for nucleic acid delivery that has been researched and used the most. Most of it is produced by deacetylating chitin, which is achieved by converting over 50% of the acetyl groups into amino groups (Figure 2-A&B). Chitosan's natural immunomodulatory properties increase cellular immunity and post-vaccination antibody responses when given by injectable or mucosal routes.[8] Turley JL showed that only chitosan with a high degree of deacetylation (>90%) increases the production of mitochondrial reactive oxygen species, which causes dendritic cells (DCs) to become activated by the NLRP3 inflammasome and cGAS-STING. These findings open up new possibilities for the development of vaccine adjuvants by demonstrating the significance of chitosan's physicochemical characteristics in boosting immune activation.[9] Furthermore, low-molecular-weight chitosan exhibits increased intracellular nucleic acid release and better solubility, both of which support subsequent immune responses.[10] Mucosal immunization has been shown to be more effective when certain strategies, such as adding immunostimulatory molecules or decorating with targeting moieties to APCs, are used.[11]

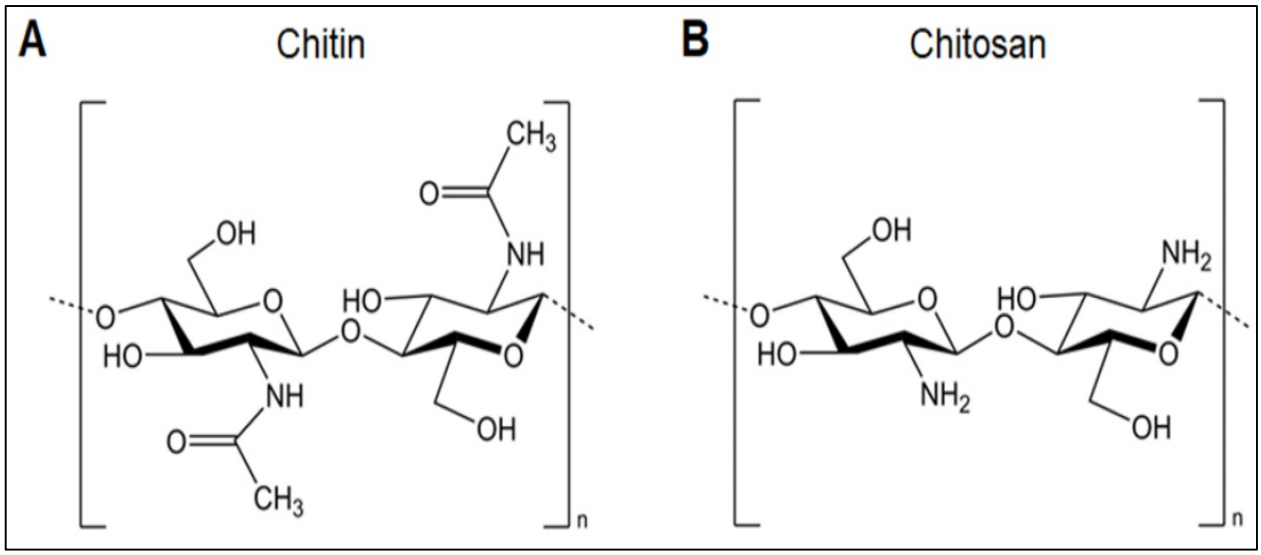


**Fig.2: A. Chemical structure of chitin. B. Chemical structure of chitosan.**

### 2.2 Polyamino acids

Amino acid-based polymers are thought to be promising biomaterials for biomedical applications; there are 20 types of essential amino acids in biological systems, and over 500 non-proteinogenic amino acids have been identified.[12] A wide range of poly (amino acid)s (or polypeptides) with varying chain lengths and compositions may be easily synthesized because of the diversity of functional side groups found in amino acids. Amino acid-based polymers are more soluble, biocompatible, and biodegradable when amino acid moieties are present in the framework.[13] Derived from lysines, polylysines (PLLs) are readily protonated and form complexes with nucleic acids that are negatively charged (Figure 3-A&B). At low concentrations, lysine-based cationic PLLs exhibit minimal cytotoxicity while achieving high gene transfection efficacy. By using a hybridised chain reaction, Yu W created a polymer wire with CpG motifs, which they then assembled with cationic PLLs to create nanospheres. Through the constant stimulation of immune cells' lysosomal Toll-like receptor (TLR)9, this readily made polymer carrier improved immune cell activation and further stimulated the death of cancer cells.[14] Zhao K. used electrostatic interactions to encapsulate the HA gene of the H9N2 influenza virus plasmid DNA (pDNA) into dendrigraft poly-L-lysines (DGLs). DGLs were effective non-viral nucleic acid vaccine delivery vehicles because, following intramuscular injection, they prevented pDNA degradation, helped pDNA escape from endosomes, enhanced antigen presentation, and produced strong cellular and humoral immune responses.[15] Much effort has gone into creating highly branched poly(amino acid)s as gene delivery vectors in order to boost positive charge densities in the polymer structure, which will also show great potential in vaccine delivery.[16]

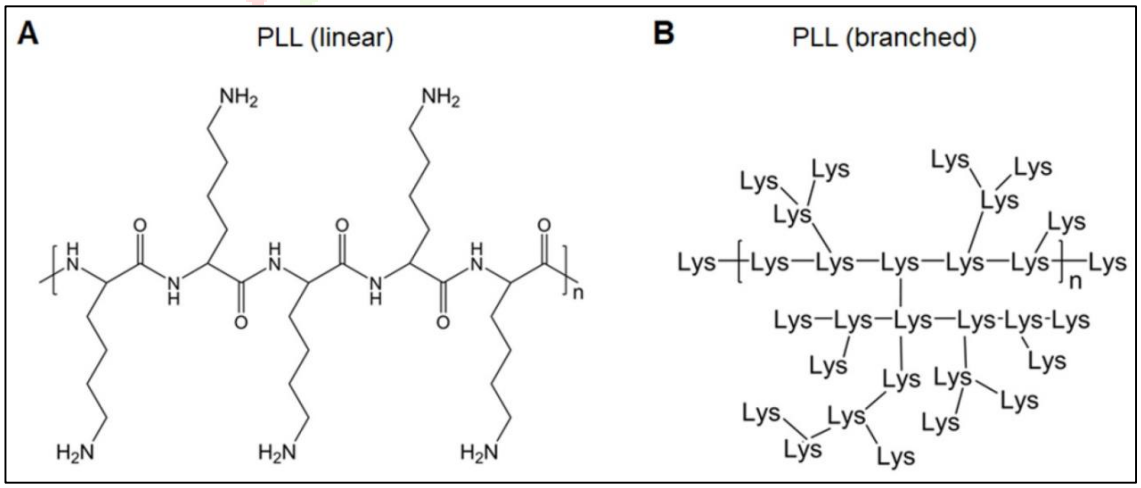


**Fig.3: chemical structure of linear PLL. B. Chemical structure of branched PLL**

### 2.3 Polyamines

Putrescine, spermine, and spermidine are examples of natural polyamines that are important in controlling gene expression, cell division, and viral translation and replication. Under physiological pH and ionic conditions, polyamines are positively charged and form complexes with negatively charged proteins, phospholipids, and nucleic acids inside cells.[17] Polyamines are important polycations for gene delivery because of their highly positive charges, ease of synthesis, and ability to form efficient polyplexes with nucleic acids. Synthetic polyamine analogues exhibit effective combinational therapy in both cancer and virus replication because they can target polyamine metabolism and the delivery of therapeutic nucleic acids at the same time.[18,19]. Because of its high charge density, poly(ethyleneimine) (PEI) is the most commonly used polyamine for nucleic acid delivery and is regarded as the "gold standard" in polymeric gene carriers (Figure 4)[20]. PEI has a great "proton sponge" effect that helps endolysosomal escape from cytoplasmic release and gene degradation. However, because effective gene transfer necessitates high-molecular-weight PEI, which invariably confers high cytotoxicity, the use of PEI is limited by its high toxicity. Several techniques, including PEGylation to protect the positive charge, coupling low-molecular-weight PEIs, and hydrophobic modification, have been used to reduce the toxicity while preserving the transfection efficacy of PEI.[21,22,23,24]. We found that anchoring PEI at the surface of perfluorodecalin reduces PEI toxicity. This is probably because perfluorodecalin's dissolved oxygen promotes cell growth, and PEI's decreased flexibility limits its interactions with cell membranes.[25]

### 2.4 Polyesters

Biologically synthesised polyesters, or polyhydroxyalkanoate (PHA), spontaneously self-assemble inside bacteria. These PHA particles are made up of an outer protein shell and a hydrophobic core. These proteins could serve as an anchor for the attachment of antigens, resulting in the production of PHA vaccines coated with antigens.[26] Polylactic-co-glycolic acid (PLGA), poly (lactic acid), and polycaprolactone are examples of chemically synthesised polyesters and their derivatives that have been used more recently in a variety of biomedical applications, such as drug delivery, tissue implants, scaffolds for tissue engineering, and the delivery of nucleic acid vaccines. Because of their unique ability to break down due to ester bond hydrolysis, polyesters are biodegradable, which is why many of them have found application in medicine.[27] A cationic polyester called Poly-β-amino ester (PBAE) can create complexes with nucleic acids to improve cellular uptake and polyplex endolysosomal escape (Figure 4-A&B).[28]; Polyplexes of PBAE have immune-stimulating properties. According to Jewell , DCs and macrophages were activated by PBAE particles.[29,30] An additional investigation showed that immune activation was significantly influenced by the molecular weight of PBAE. A range of PBAEs with varying molecular weights were produced by them. The immunogenicity peak was reached at 1.5–3 kDa, regardless of the initial molecular weight of the hydrolyzed PBAEs.[31]

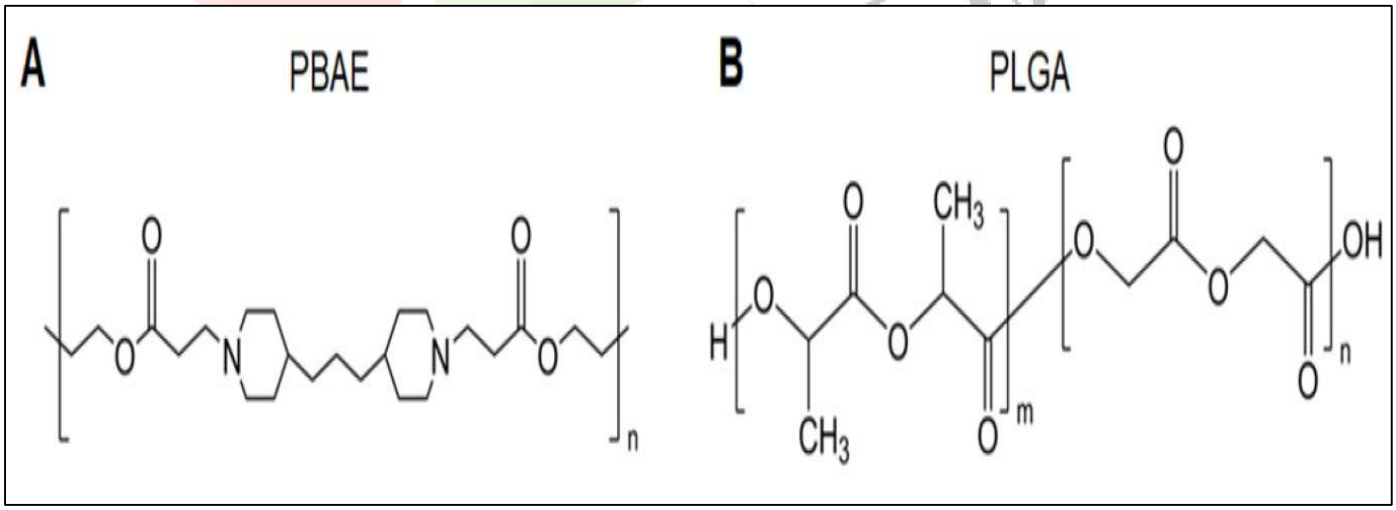


**Fig.4: chemical structure of PBAE. B. Chemical structure of PLGA**

### 3. Nucleic Acid Vaccines

In mice, intramuscular injection of plasmid DNA has been shown to result in long-term gene expression.[32]. These plasmids can be used to encode a viral antigen, which can trigger immune responses specific to the antigen in cells and humoral tissues.[33] Numerous studies investigating DNA-based vaccines against various diseases, including influenza, HIV, and lymphocytic choriomeningitis virus (LCMV), were prompted by these

findings.[34,35,36]. Since DNA can be synthesised using straightforward, scalable chemistry or produced in large quantities in bacteria, DNA vaccines are practically more affordable than protein, whole cell, or viral vectors. However, because DNA vaccines achieve a very low transfection rate, their main drawback is their low immunogenicity. Even if cell entry is successful, transcription cannot be achieved without highly inefficient localization to and entry into the nucleus.[37] Plasmids can be engineered to encode various antigens and other immunostimulatory molecules in order to enhance immunogenicity and trigger an adjuvanted immune response.[38] A number of DNA vaccines, such as those for West Nile (West Nile Innovator DNA) and salmon pancreas disease (Clynav), have been approved for use in animals but not in humans as of yet.[39,40] Due to the shortcomings of DNA vectors, RNA-based vaccinations have become more popular recently.[41] Similar to DNA-based vaccines, they are inexpensive and easily produced in large quantities. However, the instability of RNA and ineffective in-vivo delivery have previously limited their application.[41] Many structural modification techniques have been used to improve the RNA molecules' intracellular stability.[42] Importantly, RNA does not need to be targeted to and entered into the nucleus like DNA does, so the primary obstacle faced by RNA vaccines is cell entry.[43] Using polycationic carrier molecules in the formulation can help with this by condensing, protecting, and facilitating the RNA's quick cellular uptake.[44] Development of RNA-based vaccines has primarily targeted cancer, with multiple Phase I–III clinical trials currently underway.[45,46] Two main types of RNA vaccines have been used for infectious pathogens: self-amplifying and non-replicating. The duration and degree of expression that non-replicating RNA vaccines can achieve may be restricted, despite their ease of manufacture and lower manufacturing costs. Alphaviruses and other single-positive strand RNA viruses can provide sequences and concepts that can be used to create self-amplifying RNA systems (Alphavax). These vectors can theoretically accomplish a single replication cycle without the risk of infectious virus production because they only encode the immunogen and non-structural genes. They do not encode any structural genes. Thus, through intracellular amplification of the antigen-encoding RNA, they facilitate the production of a large amount of antigen from a small dose of vaccine. Numerous RNA-based vaccination clinical trials have been conducted for infectious pathogens, including HIV, rabies and zika.[47,48,49] Though DNA may offer advantages in terms of coding capacity and the amount and duration of immunogenic protein production, RNA may currently appear to be the more appealing of the nucleotide-based options. The argument for DNA vaccines' translatability is strengthened by the recent development of scalable, enzyme-driven, cell-free DNA production technologies.[50]

## 4. Nucleic Acid Vaccine Development

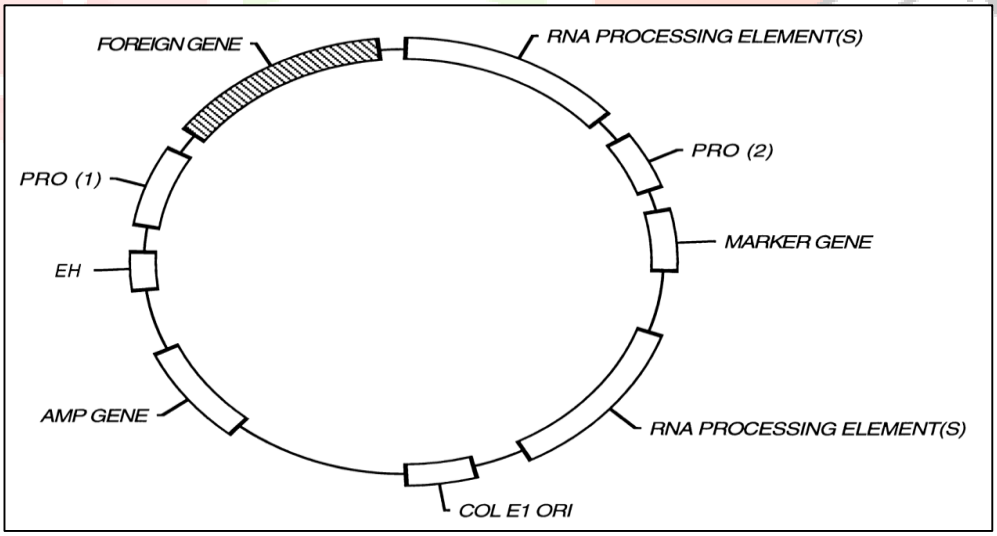


**Fig.5: A prototype plasmid vector for nucleic acid immunization.**

A prototype plasmid vector for nucleic acid immunization. Starting at 9 o'clock and moving in a clockwise direction, the genetic elements are as follows. First is a transcriptional enhancer (EH) element (optional) appended to a transcriptional promoter positioned upstream of the foreign gene. The transcriptional cassette terminates with RNA-processing elements, including a polyadenylation signal and an intro sequence (optional). An optional transcriptional cassette for marker gene expression may also be included with its transcriptional promoter, the marker gene, and RNA-processing elements. The bacterial origin of replication (ColE1) and a gene conferring antibiotic resistance (in this case ampicillin, or AMP) are also included. Refer to the text for details. In studies examining whether direct injection of DNA or RNA expression vectors for gene therapy could eliminate the need for live-virus vectors, the development of nucleic acid vaccines happened by accident.[51,52] Wolff discovered that gene products were expressed in muscle cells upon intramuscular (i.m.)

injection of nonreplicative DNA or RNA expression vectors in cationic lipid vesicles.[52] Remarkably, they discovered that this happened for plasmid DNA vectors even in the absence of the lipid delivery mechanism. To measure gene expression in these investigations, reporter genes including the bacterial b-galactosidase gene, firefly luciferase (luc), and chloramphenicol acetyl transferase gene were employed. Using a luciferase-expressing plasmid, the persistence of the gene expression was demonstrated. In these investigations, luciferase was found in the mice's skeletal muscles for 19 months.[53] Davis employed retroviral, adenovirus, and recombinant plasmid DNA vectors.[54] investigated the efficacy of gene transfer into mouse muscle that has reached maturity (mitotically inactive) and muscle that is regenerating (mitotically active). An expression of the luc Subsequently, it was found that, in terms of regeneration, the b-galactosidase reporter genes in mice were greater than those in mature muscle more effective than an at expressing the viral retrovector and reporter genes. These researchers had previously shown that preinjection of a hypertonic sucrose solution decreased the variability of gene transfer in normal muscle. It was suggested that the hypertonic sucrose's ability to shrink or force apart muscle fibres would be the cause of the increased gene transfer efficiency and improve plasmid DNA distribution.[55] Williams conducted comparable research[56] showed how to insert a plasmid vector into the skin and liver of a mouse that carried the luc gene under the control of the human b-actin promoter. DNA was delivered into the tissues using "biolistic" technology, which involved firing gold micro projectiles coated in DNA into the tissues. Luciferase activity was detected for 14 days. Using plasmid vectors encoding human a 1-antitrypsin that were transcribed from the cytomegalovirus promoter, these researchers were able to immunise mice in subsequent studies. They also demonstrated that animals that were co-immunized with both the human growth hormone and the human a 1-antitrypsin plasmids produced antibodies to both proteins. It has been demonstrated that DNA-based vaccinations can elicit immune responses in a range of animal species against a variety of pathogens. Mice and cows were shown to have antibodies against the glycoproteins of the bovine herpes virus[57] Furthermore, cattle immunized with DNA encoding bovine herpes virus 1 g Iv glycoprotein and subsequently challenged with live virus showed protective neutralizing antibody responses, as indicated by a decrease in nasal viral shedding.[57] Leishmaniasis is one of many infectious diseases that may be protected against with experimental nucleic acid vaccines , tuberculosis, malaria, and hepatitis B, are in the process of being developed.[58,59,60,61]

**5. DNA Vaccines Against Retroviruses**

Wang administered four injections every two weeks of a plasmid vector (pM160) that expressed HIV-1 HXB2 gp160. Immunized mice (BALB/c). The plasmid contained two eukaryotic transcriptional cassettes. The first one was controlled by the transcriptional enhancer of the Rous sarcoma virus and the long terminal repeat promoter of the mouse mammary tumour virus, and it expressed the HIV-1 env, tat, and rev genes. All of these results indicate that the gp160 antigen generated in vivo by DNA immunization in mice is highly immunogenic and may be effective in eliciting broadly cross-reactive antibodies, which is particularly significant for HIV infection immunity.[62] Notable is the additional finding that mice immunised with pM160 had their lymphocytes proliferate in vitro when exposed to recombinant gp120 glycoprotein (rgp120). This group assessed DNA immunization against HIV in primates in a concurrent study. The cynomolgus macaques gathered three times a week in the morning. injection of the HIV-1Z6 envelope region along with 100 µg of plasmid DNA (pM160-Z6).HIV-1 tat and rev genes' coding regions were also present in plasmid pM160-Z6. Immunised macaque mice were obtained two weeks following the third immunization, and they were used to incubate cell-free HIV-1MN with MT-2 cells in accordance with (a). assay for syncytium inhibition.[0]

**6. Retrovirus-Mediated Gene Transfer**

A successful technique for transferring genes encoding foreign proteins into mammalian cells is retrovirus-mediated gene transfer. Actually, the most often used vector in human gene therapy clinical trials is retroviral gene transfer. Genes are transmitted by retrovirus vectors that are inserted into the host's chromosome, guaranteeing the persistence of genetic information in the target cells. One major worry regarding the delivery of retroviral genes is insertional mutagenesis, which is a harmful process that results in the inactivation of crucial genes due to chromosomal integration occurring at the wrong places. The decision to choose plasmids over retroviral gene delivery is therefore a trade-off between risk factors and transplant efficacy that is still being made. Irwin[64] Direct injection of a non-replicating N2 III Benv retroviral vector containing HIV env and rev genes was recently reported by Irwin The employed vector (Figure 2) HIV-1IIIB env and rev genes were inserted into the non-replicating amphotropic Moloney murine leukaemia virus (N2) backbone. CTL Because (i) Rev is an early viral protein and removing the infected cells before the virus spreads widely can impact the virus's spread, as well as (ii) rev is a highly conserved gene suggesting that the ensuing immune responses may cross-react with different virus isolates, the response to Rev determinants is especially critical.

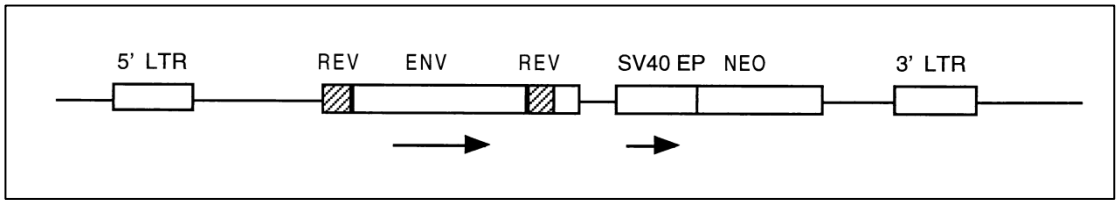


**Fig.6: Retrovirus-based vector for genetic immunization**

Vector for genetic immunization based on retroviruses. The application of this genetic immunization technique is approved by the FDA, and clinical trials involving sero positive individuals have been started for the first time. Details about this and future research will soon be available.[65]

**7. Parameters Affecting Gene Expression and Immunogenesity of DNA Vaccines**

The immunogenicity of DNA vaccines and the effectiveness of antigenic gene expression can both be impacted by several paKUVs. The env gene, including those two rev gene exons. Factors such as (i) the creation of the plasmid vector, in particular, the selection of the promoter utilised to drive the expression of the antigenic gene;The factors that determine whether a cell will secrete an antigen or keep it bound inside the cell membrane are (ii) the mode of administration; (iii) the tissue or organ in which the antigen is expressed; and (iv) the physical nature and properties of the expressed antigen. Cheng used bombardment with gold particles to move the luc gene cells from various tissues.[66] examined the impact of various target tissues and promoters on gene expression. DNA was applied to one-meter-diameter gold particles, which were subsequently delivered to different tissues via the Accelli gene delivery system and #40;Agracetus, Middleton, Wis. and#41;. All tested species, including rhesus macaques, mice, rats, and rabbits, showed evidence of gene expression. The pancreas, muscle, liver, epidermis, and dermis were among the organs and tissues whose Luc gene expression was assessed. One and five days following transfection, the liver showed signs of inducing the pPEPluc and pmMTluc gene promoters. The expression antigen's location is another factor that affects the type of immune responses that DNA immunization elicits. Rhodes[67] observed that when DNA vaccines, like influenza virus NP or HIV gp120, secreted forms of the antigen, mice would develop antibody responses as a result of DNA immunization. For HIV-gp120, antibody titers greater than 10,000 have been found. The muscle would then function as a reservoir for antigens that would gradually be released.[67]

**8. Safety Considerations for Nucleic Acid Vaccines**

Thus far, research has demonstrated that plasmid DNA is only extrachromosomally present and does not integrate into the chromosome of the host cell.[68].Myocytes do not divide further because they have reached the end of their differentiation process. Therefore, in comparison to cells that are actively dividing, these muscle cells would have a lower chance of integrating the plasmid DNA into the host chromosome. Moreover, retention of a bacterial methylation pattern has been shown by PCR amplification of DNA recovered from vaccine-injected muscles up to 19 months after administration, suggesting that DNA replication did not take place in the mammalian host.[68] The possibility of integration will need to be carefully considered in light of the low probability of plasmid DNA integration, the low chance that such an event would activate or disrupt a gene, and the clinical experience already available with live DNA virus immunization (smallpox and varicella-zoster viruses). To establish that no integration takes place and that other cells do not take up or integrate trace amounts of the injected DNA, more thorough and sensitive analyses of the fate of the injected DNA will need to be performed. Whether the injected DNA will cause anti-DNA antibodies comparable to those linked to autoimmune disorders is another possible safety concern. It has been demonstrated that double-stranded chromosomal DNA is nonimmunogenic.[69] ,even though single-stranded DNA that has been denatured and complexed with protein is immunogenic. On the other hand, the latter produced antibodies that are unique to the protein in the complex and do not identify the DNA of the mammalian chromosome. Crucially, research on nonhuman primates has not shown anti-DNA antibodies after plasmid DNA immunization. These results are consistent with research demonstrating that double-stranded DNA is not immunogenic. To rule out the chance that receiving a nucleic acid vaccine could cause or worsen an autoimmune reaction, more research is required.[70]

**9. RNA Vaccines**

Initially, it was demonstrated that mRNA could induce the production of proteins in situ after intramuscular injection. Recent research has shown that mRNA delivered intravenously or subcutaneously in liposome form

successfully produced CTLs and antibodies that were targeted at the encoded protein.[71] Yang have also documented that high antibody responses to human a 1-antitrypsin were elicited by particle-mediated (biolistic) delivery of RNA encoding the protein into the mouse epidermis.[72] Since RNA does not integrate into chromosomal DNA, the use of mRNA as a vaccine vector would eliminate the possible safety concern of insertional mutagenesis associated with DNA immunization. However, RNA vaccines may not be a feasible method of immunization due to the challenges and costs associated with producing RNA on a large scale, as well as the relative instability of mRNA in comparison to DNA.[73]

## 10. FUTURE PROSPECTIVE

Nucleic acid vaccines are expected to undergo exciting developments on a number of fronts in the near future. In order to improve vaccine stability and efficacy, research will probably first improve delivery techniques by investigating cutting-edge strategies like targeted delivery systems or carriers based on nanoparticles. Multi-antigen constructs, which allow for simultaneous protection against several strains or even distinct pathogens, are one example of how vaccine design has advanced. This could provide more widespread immunity and lessen the need for frequent updates, which would completely change how infectious diseases are treated. There is considerable potential in customising nucleic acid vaccines to treat non-infectious diseases like cancer. The development of tailored cancer vaccines based on individual genetic profiles could lead to a major advancement in immunotherapy's precision medicine approach. Nucleic acid vaccines will probably become more widely available as efforts to address issues with cold chain requirements and storage stability pick up steam, particularly in environments with limited resources. Moreover, further investigation may reveal novel uses for nucleic acid vaccines, such as autoimmune diseases or allergic reactions, outside the realm of cancer and infectious diseases. In general, nucleic acid vaccines will go forward by improving technologies, broadening their uses, and realising their potential to treat a variety of health issues. This will usher in a revolutionary period for vaccination and preventive medicine.

## CONCLUSION

Nucleic acids have been extensively researched in a variety of biomedical application domains and have been transported via polymers. The development of high potential polymers for the delivery of nucleic acid vaccines for the prevention and treatment of a wide range of diseases, including infections, cancer, and autoimmune disorders, has advanced significantly. Over the past few years, artificial intelligence and highly computational advances have improved our ability to analyse genetic variations in pathogens and tumours and create new, powerful DNA or RNA vaccines. Novel techniques for the synthesis and modification of different functional polymers were created. During the delivery of a vaccine, adjuvant integration activity in polymeric carriers may be a useful strategy for boosting the immune response. The final objective Vaccination produces a lasting immune memory as opposed to a transient immune response. Consequently, the remarkable and thorough in vitro and in vivo evaluation of a nucleic acid vaccine and its polymer carrier is due to its rational design. Additional research on the physiological principles and properties of polymers is warranted. In any case, nucleic acid vaccines delivered via polymeric carriers Preclinical research showed significant progress; in contrast, only PEI and PLGA, which are lipid-based carriers, showed success in clinical trials. When it comes to scalability, versatility, and configurability, polymers can offer advantages over lipids. However, as these translate in the clinic into vaccine candidates, and ultimately into vaccine candidates for the market, a comprehensive security evaluation of polymers and the products that result from their degradation, as well as an adequate quality control complexity of polymer structures. With any luck, this review will serve as a useful manual for applying nucleic acid polymeric materials to vaccine delivery.

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