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A REVIEW ON VACCINE DELIVERY SYSTEMS

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ABSTRACT

Vaccines are the preparations given to patients to evoke immune responses leading to the production of antibodies (humoral) or cell-mediated responses that will combat infectious agents or noninfectious conditions such as malignancies. Alarming safety profile of live vaccines, weak immunogenicity of sub-unit vaccines and immunization, failure due to poor patient compliance to booster doses which should potentiate prime doses are few strong reasons, which necessitated the development of new generation of prophylactic and therapeutic vaccines to promote effective immunization. Attempts are being made to deliver vaccines through carriers as they control the spatial and temporal presentation of antigens to immune system thus leading to their sustained release and targeting. Hence, lower doses of weak immunogens can be effectively directed to stimulate immune responses and eliminate the need for the administration of prime and booster doses as a part of conventional vaccination regimen. This paper reviews carrier systems such as liposomes, microspheres, nanoparticles, dendrimers, micellar systems, ISCOMs, plant-derived viruses which are now being investigated and developed as vaccine delivery systems. This report also describes various aspects of "needle-free technologies" used to administer the vaccine delivery systems through different routes into the human body.

KEYWORDS: Edible vaccines, micro needles, microparticulates, needle-free delivery, vaccine delivery systems.

INTRODUCTION

Vaccine is a substance that stimulates an immunologically mediated resist to a disease but not necessarily an infection. Vaccines are generally composed of diminished organisms or

subunits of DNA encoding antigenic proteins of pathogens. Sub-unit vaccines though most selective and specific in reacting with antibodies. In order to raise an effective protective immunity these vaccines require enhance with agents called adjuvant. Adjuvant is believed to act by forming complexes with the agent to be administered from who immunogens are slowly released.

Vaccine delivery systems {e.g., emulsions, micro particles, immune- stimulating complexes ISCOMs,liposome'}Immunostimulatory adjuvant: Conserved molecular patterns of pathogen stimulate immunity as they are identified d by pattern recognition receptors like "Toll" receptors located mainly on B-cells, dendrites' cells of mammals {e.g., unmethylated CpG containing DNA}Adjuvants potentiate the Immunostimulatory property of the antigen while being non-immunogenic nontoxic and biodegradable by themselves. Aluminum salts such as aluminum hydroxide aluminum phosphate oil emulsions such as Fronds incomplete adjuvant particulate matter such as ISCOMs synthetic polynucleotide are other types of adjuvant Delivery of antigens from oil-based adjuvants such as Freundas adjuvants lead to a reduction in the number of doses of vaccine to be dispense but due to toxicity concerns like inductions of granulomas at the injection site such adjuvants are not widely used Hence search for safer and terrible adjuvants resulted in the formulation of antigen into delivery systems that administer antigen in particulate form rather than solution form, Elget *et al.* 2009.

Types of vaccine delivery system

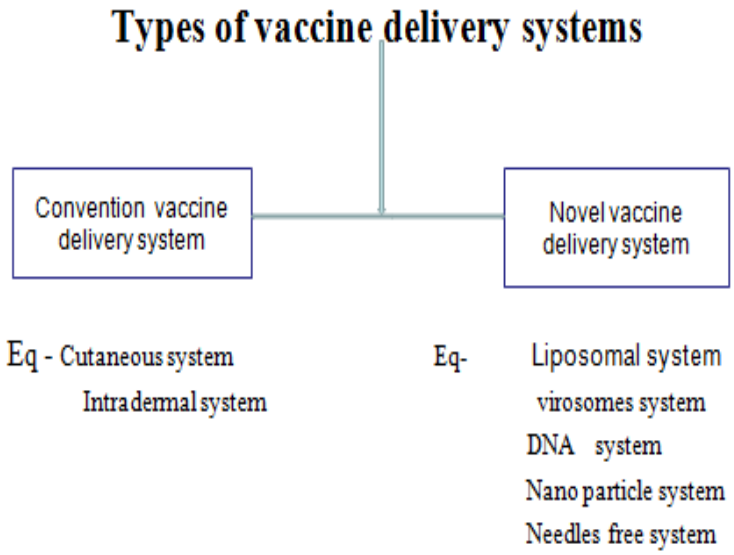

Fig 1: Types of vaccine delivery system.

Novel vaccine delivery system

- Liposomal delivery system
- Virosomes delivery system
- Polymeric nanoparticles delivery system
- Micellar delivery system
- Dendrimers based delivery system
- Immunostimulatory complex (ISCOMS)
- Edible vaccine delivery system
- DNA vaccine delivery system
- Mucosal delivery system
- Needles free delivery system

Conventional vaccine delivery systems

At modern time rout of vaccination are intranasal by insufflations of scab material containg variable virus from smallpox patient described in china around the first millennium AD the Cutaneous route for such variolation involved breaking the skin with a sharp instrument and was used in India perhaps as early as china but not documented until the 16^{th} century after 15century experiment with hypodermic injection the introduction of the needles and syringes in the 19^{th} century began a new era in medicine

a) Cutaneous vaccination

The skin was one of the first tissue into which smallpox virus and later cross virus protecting cow pox virus where introduced to prevent smallpox. Cutaneous immunization remains today the standard rout for small pox vaccine as well as for administering Bacilli –calmett-Guerin (BCG) to prevent tuberculosis

(i) Tuberculosis vaccination

The Bacilli calmett Guerin (BCG) vaccine for the prevention of disease from mycobacterium tuberculosis in1927 administered in the cutaneous routes.

(ii) Influenza

In route of IM and SC is larger doses given as compared to needles syringes

b) Intradermal vaccines

Viral gives encoded in to bacterial DNA would how get expressed in vivo into their protein antigens a seminal gel expressed event in the modern era of recombinants nucleic acid vaccinology gene proto antigens to prevent influenza HIV/AIDS smallpox and many other disease Plotkin *et al.* 1994.

2. Need For Novel Drug Delivery System

- Immunization failure with conventional immunization regimen involving prime doses and booster doses as patients neglect the latter
- Control the spatial and temporal presentation of antigens to the immune system there by promoting their targeting straight to the immune cells
- Allow for the incorporation of doses of antigens so that booster doses are no longer necessary as antigens are released slowly in a controlled manner
- New avenues should be investigated to overcome the failure of clinical trials and other important issues including safety concerns related to live vaccines or viral vectors, the weak immunogenicity of subunit vaccines and side effects associated with the use of adjuvants
- A major hurdle of developing successful and effective vaccines is to design antigen delivery systems in such a way that optimizes antigen presentation and induces broad protective immune
- Patient's concern about pain associated with the injections disposal issues and potential for cross contamination of blood borne diseases is eliminated.
- Differentiate their products from the existing products as the pharmaceutical industry faces massive losses in revenues from the expired patents and to withstand pressure from generic companies
- Search for alternative ways to deliver growing list of new biopharmaceutical and molecular entities like vaccines, DNA, peptides and proteins that cannot be delivered orally (Plotkin *et al* .1994.

3. NOVEL DELIVERY SYSTEM

3.1 Liposomal vaccine delivery system

Liposomes and their derivatives “lipoplexes” are hollow spherical constructs of phospholipid bilayers capable of entangle hydrophilic moieties in the aqueous compartment and hydrophobic moieties in the lipid bilayers with cholesterol imparting rigidity to the bilayer

however lipoplexes tend to accumulate during storage due to neutralization of positive charge on liposomes by negative charge on DNA. This drawback is overcome by formulating liposomes/protamine/DNA (LPD). Protamine is an arginine rich peptide. It condenses with DNA before DNA can complex with positive lipids there by consulting stability to the preparation.

Viruses, proteins, glycoproteins, nucleic acids, carbohydrates, and lipids can be entrapped and targeted at cellular and subcellular level for evoking immune responses.

3.1.1 Current research in liposomes as vaccine delivery systems

As vaccine adjuvants these systems exert immunomodulators effects by virtue of their particulate nature and their ability to bind with cell surface lipid receptors such as CD1a after contingent activation. The phospholipid bilayer fuses with cell wall hence tend to get incorporated into elements of reticuloendothelial system (RES) rapidly. The development of polymerized liposomes, which have shown increased stability in the gastrointestinal tract, also offers potential for use in mucosal vaccination. Polymerized liposomes coated with targeting molecules such as antibodies, antibody fragments, antigens and molecules are able of binding to specific cell surface receptors found in the mucosal tissues. Stealth liposomes or sterically stabilized liposomes contain hydrophilic surfaces due to coating of liposomes with PEG and this covalently binds with the polyethylene found in the lipid bilayer thereby decreasing the opsonization by serum proteins and increasing circulation half lives.

Purified and isolated nucleic acid molecules encoding a basal body rod protein of a strain of Campylobacter, specifically Campylobacter jejuni, encapsulated in liposomes along with adjuvants like aluminum phosphate, aluminum hydroxide, QS21, Quill A, calcium phosphate, calcium hydroxide, zinc hydroxide, a glycolipid analog, an octadecyl ester of an amino acid, a muramyl dipeptide and a lipoprotein served many purpose. Proteins expressed by nucleic acids are found to be immunogenic against the disease caused by Campylobacter, in the diagnosis of infection by Campylobacter, and as tools for the generation of immunological reagents. Monoclonal antibodies or antisera raised against these peptides are useful for the diagnosis of infection by Campylobacter, specific detection of Campylobacter in in-vitro and in-vivo assays, and for use in passive immunization for control and treatment of diseases caused by Campylobacter Sijun *et al.* 2009.

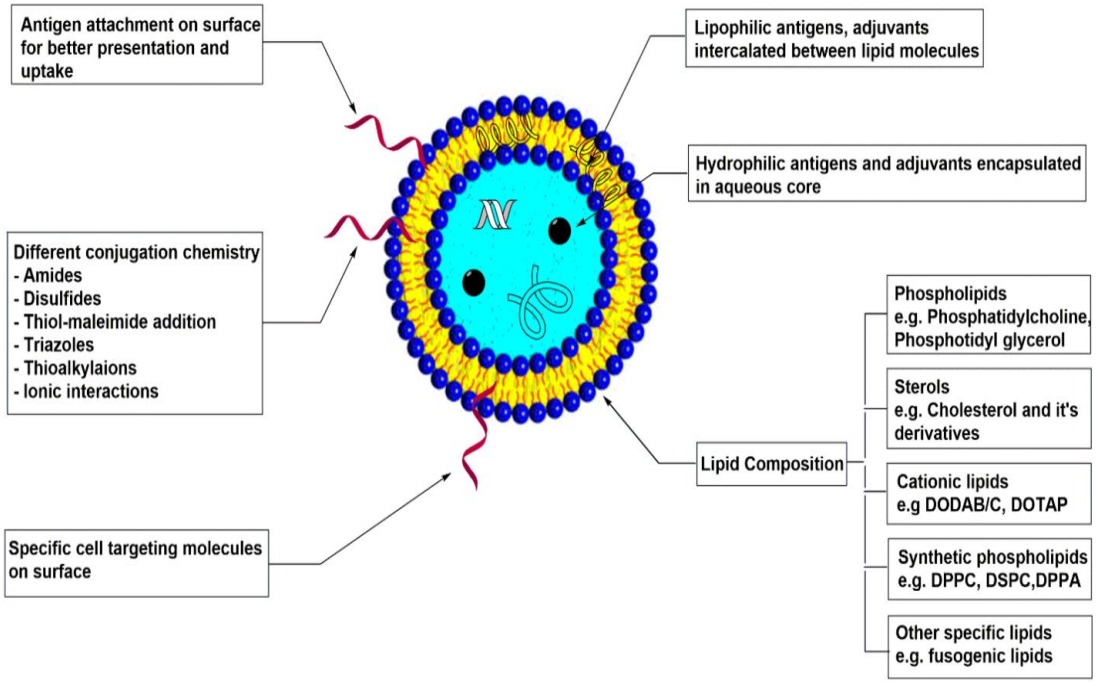

Fig 2: Systematic diagram of liposomal drug delivery system (Sijun *et al.* 2009).

Virosomes delivery system

Virosomes are small spherical unilamellar lipid membranes vesicles attach with viral membrane proteins such as hemagglutin and neuraminidase of influenza virus but without of nucleocapsid including the genetic substance of the origin virus. These proteins enable the virosome membranes to combine with cells of the immune system and thus deliver their contents—the specific antigens—directly to their target cells, educe a specific immune response even with weak-immunogenic antigens. Once they have hand down the antigens, the virosomes are completely degraded within the cells. A Viral protein intercalated into the phospholipid bilayer not only grants to anatomical stability and monotone to virosomal formulations, but it remarkable contributes to the immunological properties of virosomes, which are clearly different from other liposomal and proteoliposomal porter systems. It has been shown that a physical relation between the virosome and the antigen of interest is a condition for the full adjuvant effect of virosomes Moser *et al.* 2007.

3.3 DNA Vaccine delivery system

DNA Vaccines are composed of bacterial plasmids and Expression plasmids used in DNA-based vaccination normally contain two units:

[1] The antigen expression unit composed of promoter/enhancer sequences followed by antigen-encoding and polyadenylation sequences and

[2] The production unit composed of bacterial sequences necessary for plasmid amplification and selection.

- The construction of bacterial plasmids with vaccine inserts is adept using recombinant DNA technology once constructed the vaccine plasmid is transformed into bacteria where bacterial growth produces multiple plasmid copies.
- The plasmid DNA is then purified from the bacteria by separating the circular plasmid from the too larger bacterial DNA and other bacterial impurities. This purified plasmid DNA is used as the vaccine.
- A DNA vaccine against a microbe would generate a strong antibody response to the free-floating antigen secreted by cells and the vaccine would also stimulate a strong immune response against the microbial antigens displayed on cell surfaces.
- The DNA vaccine couldn't cause the disease because it wouldn't contain the microbes' just copies of a few of its genes. In addition, DNA vaccines are relatively easy and inexpensive to design and produce.
- So-called naked DNA vaccines structure of DNA that is administered directly into the body. These vaccines can be administered with a needle and syringe or with a needleless device that uses high-pressure gas to shoot microscopic gold particles coated with DNA directly into cells.
- Sometimes the DNA is assorted with molecules that facilitate its uptake by the body cells Naked DNA vaccines being tested in humans cover those against the influenza and herpes virus.

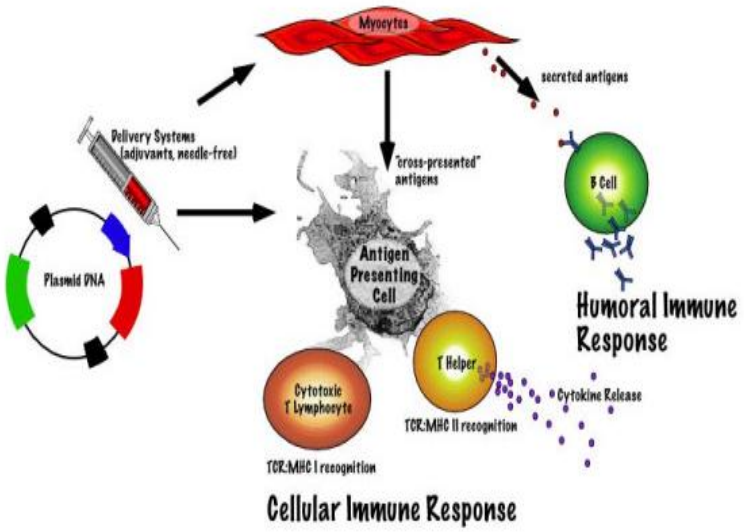

Fig 3: DNA vaccine delivery systems (Jane *et al.* 2004).

3.3.1 DNA vaccine delivery strategies

3.3.1.1 Physical methods

Techniques such as tattooing, gene gun, electroporation, ultrasound, and laser provide energy [(electrical, ultrasonic, laser beam] that brings about a transient change in permeability of cell membrane thereby promoting the entry of immunogenic DNA into the cells. The cell permeability is restored on the removal of applied energy after a short time period.

Tattooing

It is a physical method for injecting DNA into skin cells. The effect of two adjuvants, cardiotoxin and plasmid DNA carrying the mouse granulocyte macrophage colony stimulating factor (GM-CSF) when given by tattooing and as intramuscular injections has been determined

. Model antigen used in this study was gene encoding the capsid protein of the human papillomavirus type 16 (HPV16). From the results.

It is concluded that the delivery of the HPV16 L1 DNA alone using a tattooing device elicited a stronger and more rapid humoral and cellular immune responses than intramuscular needle delivery together with molecular adjuvants Porkorna *et al.* 2008.

- **Gene gun**

Gene gun is a biolistic device that empowers the DNA to directly enter into the cell following bombardment of target DNA in the gene gun chamber kept against the target site.

In a study carried out by Jane McAllister and David Proll four groups of mice were immunized with plasmid DNA comprising the LacZ gene encoding β-galactosidase 3 groups of mice received shots of 1 μg of DNA coated onto gold micro carriers through gene gun intradermally (ID) Gold micro carriers of 0.6, 1.0, and 1.6 μm size were used respectively. The fourth group earned three doses of 100 μg DNA in salty as intramuscular (IM) injection. Antigen-specific IgG titres were found to be higher in mice receiving intradermal vaccination than IM vaccinated mice. From this it is educe that gene gun immunization is more effective over IM injection as DNA from former is directly shot into the target cells where as DNA from the latter must enter the cell before protein (antigen) synthesis. As a result, though the dose of DNA administered via gene gun is only $1/100^{th}$ of dose injected intramuscularly a

greater proportion of the administered DNA is used for antigen synthesis Mcallister *et al*. 2004.

- **Electroporation**

This technique involves application of electrical pulses to the skin thereby creating transient pores in the skin promoting the entry of DNA into the cell. On removal of electrical energy, skin regains its structure holding the entangled immunogenic agent due to closure of pores.

Chron Vac-C,a therapeutic DNA vaccine given to patients already infected with the virus in order clear the infection by boosting immune response, showed acceptable safety when hand over by electroporation in phase I/II clinical study at Karolinska University Hospital. This clinical study was carried out at the Infectious Disease Clinic and Center for Gastroenterology at the Karolinska University Hospital in Sweden. This was among the first contagious disease DNA vaccine to be delivered in humans using electroporation-based DNA delivery.

In addition, DNA vaccine delivery by electroporation is being investigated in many cancers such as prostate cancer, metastatic melanoma and is under clinical trial David *et al.* 2004.

3.4 Immunostimulatory complex

ISCOMs are spontaneously formed spherical open cage-like complexes when saponin, cholesterol, phospholipid, and immunogen, usually protein are mixed together and have typically a diameter of 30-80 nm. ISCOMs merge certain side of virus particles such as their size and orientation of surface proteins with the powerful Immunostimulatory activity of saponin Unlike other vaccine adjuvant ISCOMs have shown to encourage a broad immune response by cumulatively promoting high levels of antibody and strong T cell responses, including enhanced cytokine and activation of cytotoxic T lymphocyte responses in a variety of experimental animal models and has now progressed to phase 1and 2 human trials.

ISCOM-based veterinary vaccine against horse influenza is commercially available Shen *et al*. 2000.

3.5 Polymeric nanoparticles delivery system

Polymeric nanoparticles because of their size are preferentially taken up by the mucosa associated lymphoid tissue. They are broadly reviewed for nasal and oral delivery of

vaccines. Limited doses of antigen are suitable to screwed effective immunization. Hence the use of nanoparticles for oral delivery of antigens is suitable because of their ability to release proteins and to protect them from enzymatic degradation in the GIT.

Biodegradable PACA nanoparticles have been shown to enhance the secretary immune response after their oral administration in association with ovalbumin in rats. PMMA nanoparticles being very slowly degradable appear to be very suitable for vaccine purposes because prolonged contact between antigen and immunocompetent cells favors persistent immunity Jaeghere *et. al.* 1999.

Polymers Exploited For Vaccine Delivery

Sr.No.	Polymers & its nature	Used in	References
1	PGLA (semi-synthetic polymers)	Recombinant tuberculosis (TB) antigen	Shi *et al.* 2010
2	Chitosan **(Natural Water Soluble Polymers)**	Tetanus toxoid	Kumar *et al.* 2010
3	Polylactide *(natural*, biodegradable)	Recombinant malaria antigen	Domb *et al.* 1992
4	Crosslinked albumin gelatin *(Natural Polymer)*	Mild inflammatory response	Sexton *et al.* 2009
5	Phosphazenes (inorganic-organic *polymers)*	Dental periodontal cavities	Grooves *et al.* 1999

Vaccine Delivery Strategics

The direct injection of plasmid DNA into muscle or skin is still the most widely used. However, the biggest drawback of this delivery method is the low efficacy achieved in larger animals and humans. Therefore, development of physical delivery methods to increase the transfection efficiency of target cells has been a primary focus of research in more recent years.

Physical methods for pDNA transfection comprise electroporation, ballistic needle-free delivery systems and microporation.

Microporation involves use of hundreds of micro needles that enable topical immunization with naked plasmid DNA as they can bypass the stratum corneum thereby delivering plasmid DNA to APCs of the skin.

This induces stronger and less variable immune responses than via needle-based injection another physical method widely employed in DNA vaccination is particle-mediated epidermal delivery also called the “gene gun”. In this procedure, DNA-coated microparticles

composed of gold are accelerated to high velocity to penetrate cell membranes in the epidermis where a variety of cells including the Langerhans cells, the APCs of the skin, can be directly transfected as a result, the gene gun immunization have 10-100-fold more expression of the DNA-encoded protein than intramuscular vaccinations and 100-fold less DNA 22 is required for the same level of expression.

The gene gun technique has been used to immunize nonhuman primates against a variety of diseases, including HIV, Ebola, Japanese encephalitis, hepatitis E and B, influenza, smallpox etc. Thus, PMED can induce higher antibody and /or CD8+ T cell responses in mice and monkeys with substantially lower doses of DNA in comparison to needle-based approaches.

An alternative approach based on the use of electric pulses to transiently permeabilizing cell membranes, thus permitting cellular uptake of plasmid DNA is electroporation. It has been extensively studied in large animal species such as dogs, pigs, cattle and non-human primates to deliver DNA vaccines the potential of electroporation for DNA vaccination has been demonstrated by the increased protein expression and a robust stimulation of the immune response electroporation might permit for less frequent immunizations with the DNA vaccines and can renovate both cellular and humoral responses currently the DNA platform represents almost one quarter of all gene therapy vector systems under clinical evaluation The deal to further development of this vaccination strategy is strengthened by recent licenses in the area of animal health and by the improvement in immune potency protocol in the non-human primate model systems Abe *et al.* 2009.

COMMERCIALLY AVAILABLE NOVEL VACCINE PRODUCTS

S no	Disease	Brand name	Manufactured & Marketed by
1	Anthrax	AVA(BioThrax)	Emergent Bio Solutions
2	Diphtheria	Tdap (Adacel Boostrix)	Glaxo Smith Kline
3	Hepatitis A	HepA (Havrix,)	New Global Enterprises
4	Japanese Encephalitis	JE (Ixiaro)	Valneva

CONCLUSION

Vaccine drug delivery systems are gaining reputations these days due to the benefits they offer. Vaccine drug delivery systems are now being proven to be patient friendly as they avoid the need to administer booster doses and provide a long-term therapy in small doses. Their use is further encouraged by administering them via needle-free technologies. Edible vaccines on the other hand open an attractive avenue for the oral delivery of vaccines.

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