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Self-Adjuvanted Nanovaccines: Concept and Applications

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ABSTRACT

The goal of modern vaccine development is to provide effective vaccines that are safe and well-tolerated. This has inspired the rational design of contemporary subunit vaccines that are both safe and well-characterized, combining essential immunogenic components of pathogen characteristics to induce tailored responses with the right strength, quality, and specificity. Because of their capacity to overcome biological barriers, prolong circulation periods, and create an improved long-lasting protective immunological impact, nano vaccines have been researched as an emerging field in cancer immunotherapy in recent years. Nanotechnology is a broad discipline that can be applied to a variety of fields, including vaccines. It offers a variety of approaches to vaccine administration. A combination of nanotechnology and vaccines, i.e., nanovaccines can be created and injected into the human body to improve health by various mechanisms. Many vaccines contain adjuvants, which boost immunity to vaccines and experimental antigens through several methods including the development of a depot, the activation of cytokines and chemokines, the recruitment of immune cells, the enhancement of antigen absorption and presentation, and the promotion of antigen transport to draining lymph nodes. Such adjuvants have also been reported to induce innate immune responses at the injection site, resulting in a local immuno-competent microenvironment. This review focuses on the study of Self-adjuvanted nano vaccines.

Keywords: Adjuvants, self-adjuvant, vaccines, nanoparticles.

INTRODUCTION

Pathogens such as bacteria or viruses that have been attenuated or inactivated and components of the pathogen's structure elicit the production of antibodies or cellular defense against the pathogen when administered to a patient. This is the underlying principle of vaccines. Vaccine production often involves the use of a suspending fluid (saline, sterile water, or protein-containing fluids), stabilizers and preservatives (such as albumin, phenols, and glycine), and adjuvants or enhancers that improve the vaccine's efficiency. [1]

Nanotechnology is the branch of science concerned with nanoparticles (NPs). Nanoparticles range from 10–100 nm in size of particles up to 1,000 nm. Material qualities can be strengthened or weakened at the nanoscale, or new properties may be discovered; several of these features have been documented, but many more remain undiscovered. Liposomes, micelles, buckminsterfullerene, dendrimers, metallic NPs, and carbon nanotubes are examples of nanoparticles. [2]

Nanotechnology is now being used in a variety of health sectors and can potentially provide solutions to several challenges. Nanotechnology can also aid in the improvement of the efficacy of vaccines. Adjuvants are used in conjunction with a

specific antigen to elicit a stronger immune response than if the antigen were employed alone. The adjuvant used is critical because it can induce high humoral and cell-mediated immunity, which is required for protection against some infections.

Nanovaccines:

Nanovaccines are vaccines based on nanoparticles that are developing as a new group of targeted vaccines that act at particular sites rather than the whole body. Nanovaccines have the potential to use the immune system of the body to fight pathogens and prevent diseases from spreading. As they induce both a humoral and a cell-mediated immune response, nano vaccines are reported to be more effective than traditional vaccinations. [1] Nanotechnology has aided in the formation of effective vaccine delivery methods that prevent the encapsulated antigen from exposure to a hostile environment and allow for a prolonged release that aids in the induction of the vaccine's immunostimulatory properties. Liposomes, nanoparticles, microparticles, dendrimers, and other nano vehicles are a few examples of such nano vaccine delivery systems. [3]

Advantages of Nanovaccine

Nanovaccines offer the potential to provide vaccines that are both safe and efficacious. Nanobeads covalently bonded with antigens have several advantages, including a low antigen dose, rapid antigen-presenting cell processing, and storage durability. Because of the delayed release of the antigen, encapsulated nanoparticles easily distribute antigen, protect it from degradation, and are found to be more effective with a single dose. Many nano vaccines are non-invasive and allow for painless delivery with minimum damage via the oral or nasal route, diffusion patches, or microneedle arrays. This provides an advantage over traditional vaccines, which are normally delivered in multiple injections and doses. [1]

Nanovaccines can be used to target a particular location of the body where infection or disease develops, rather than the entire body as in the case of traditional vaccines. In some cases, nanoparticle systems are used to make hydrophobic compounds more soluble and increase the solubility of substances in solution so that they can be administered parenterally. They protect against the degradation of antigens, stabilize various pharmaceutical substances like proteins, nucleic acids, and peptides, and help minimize vaccine dosages.[4] The depot effect might be produced by these particles. The depot effect of NPs has been reported to be higher than that of microparticles. [5] Targeted delivery is also possible by covering nano-vaccine particles with antibodies that recognize receptors on the target cell. NPs improve or facilitate APC's ability to absorb and take up antigens. [6] Nanovaccines can cross-present antigens using the class of major histocompatibility complex and can also activate the humoral and cellular immune systems. As a result, they are more effective than traditional vaccinations. The lymph nodes, which are the focus of the immune cell battle, are easily accessible to the NPs without the aid of peripheral dendritic cells. [7]

Adjuvants:

Adjuvants work in a variety of ways to boost immunity to vaccinations and experimental antigens. Many communication pathways and receptors in the innate immune system have been identified in the last decade, and these innate responses have a significant impact on the adaptive immune response. Adjuvants are chemicals that boost their immunogenicity when added to or mixed with a vaccine formulation. The adjuvant used is critical because it can induce high humoral and cell-mediated immunity, which is required for protection against some infections. Furthermore, the balance between adjuvant properties and unfavorable effects is crucial in the selection

process. [10] Despite the present adjuvants' great performance in creating immunity against viral and bacterial infections, new adjuvants that boost protective antibody immune responses are still needed, particularly in groups that do not respond well to current vaccines. However, developing vaccines with pure or recombinant vaccine antigens that induce robust T-cell protection is a bigger problem. [11]

Adjuvants have traditionally been used to boost the size of physiological adaptations to vaccines, based on antibody levels or the capacity to prevent infection, but a new function for adjuvants has emerged: directing the type of physiological adaptations to result in the most potent forms of immunity for pathogens. [12] As a result, there are two unique reasons why an adjuvant should be included in a vaccine. Firstly adjuvants are presently used in clinical trials to (a) improve the general population's response to a vaccine by increasing mean levels of antibodies and /or the percentage of subjects who become securely immunized; and (b) the use of the MF59 adjuvant to boost the response of older participants to the influenza vaccination to groups with lower adaptability due to age (both newborns and the adults) or sickness. [13] (c) Allow for the use of lower antigen doses because the ability of an adjuvant to allow for comparable responses with significantly less antigen may be crucial in circumstances where mass vaccination is required but production facilities are constrained, as in the case of the measles virus. [14] and (d) allow for vaccination with fewer doses. The demand for several immunizations for multiple injections creates compliance concerns as well as considerable logistical challenges in many parts of the world. Adjuvants can help to cut down on the number of doses needed to achieve protection. [15] The second purpose for including an adjuvant in vaccination is to affect the immune response qualitatively. Adjuvants are increasingly being employed in vaccine development to boost kinds of immunity that aren't efficiently induced by non-adjuvanted antigens. [11]

Advantages of Adjuvants

Adjuvants are biological or chemical agents that cause non-specific immune system stimulation in response to the antigen(s) injected with them. Aluminium salts (alum), emulsions, saponins, non-ionic block copolymers, oil emulsions, cytokines, an assortment of bacterial derivatives, polymerized polysaccharides, immune stimulating complexes (ISCOMs), liposomes, and nanoparticles (NPs) are all examples of adjuvants. [3] Aluminum based compounds (alum) are one of the most significant and commonly utilized adjuvants in vaccines that have been licensed for human use. [16] These compounds can improve specific receptor-based recognition of nano vaccines and consequently cell activation, as well as strengthen the induced immune response [17]

Adjuvants have a variety of effects on the immune response:

- Make weak antigens more immunogenic
- Increase the duration and speed of immune response,
- Elicit and control humoral responses, including isotypes of antibodies,
- Enhance cell-mediated immunity,
- Boost mucosal immunity induction
- Enhance immune responses in immunologically immature patients, particularly infants,
- Reduce the dose of antigen required;
- Decrease overall cost of therapy
- Eliminate uncomfortable requirements for booster shots.

Drawbacks of Adjuvants

The majority of today's vaccines work primarily through humoral immunity to provide protection. Vaccines that elicit responses include live attenuated microorganisms, toxoids, recombinant protein, and polysaccharide-protein conjugates. Various modern vaccines have

long-lasting antibody responses that require little or no further boosting to maintain protection. Despite the vaccinations' great performance, there are significant groups of persons for whom existing vaccines, even those with alum adjuvant, may not achieve appropriate antibody titers rates or protective antibody titers, owing to medical factors such as chronic kidney disease [18,19]. A list of several adjuvants that have been used in approved vaccines is given in Table 1.

ADJUVANT	DESCRIPTION	APPROVED VACCINE PRODUCTS
Aluminum based mineral salts (Alum)	E.g. Aluminium phosphate, Aluminium hydroxide Calcium phosphate,	E.g., Anthrax (Bio Thrax ®, Emergent Biosolutions) DTP (Triple AntigenTM, CSLlimited) Hepatitis A(Vaqta ®, Merck)
MF 59	Sub-micron oil-in-water emulsion	Influenza (FLUAD ®, Novartis)
Mono phosphoryl lipid A (MPL)	Bacteria-derived immune stimulant	Hepatitis B (Fendrix ®, GlaxoSmithKline)
Virosomes	Spherical vesicles containing viral membrane proteins in the lipid membranes	Hepatitis A 0(Fendrix ®, Berna Biotech) Influenza (Inflexal ®, Berna Biotech)

TABLE 1: Examples of adjuvants [37]

Mechanisms of immune response potentiation by adjuvants are discussed below. [20]

1. Depot formation at the site of injection

The primary method of adjuvant activity is the formation of a depot at the area of injection. High antibody titres are the result of the immune system being continuously activated by antigens trapping and slow release at the injection site. [21]

Antigens are adsorbed onto alum and bind because of a strong electrostatic contact between the two resulting in increased antigens uptake and presentation by APCs. [22,23] Other adjuvants, such as water-in-oil emulsions [Complete Freunds Adjuvant (CFA)] and biodegradable micro and nanoparticles, have been demonstrated to produce high antibody titers for lengthy periods. [24] $AS0_4$, an adjuvant made up of monophosphoryl lipid A (MPL) and alum, co-localized with antigen, is proven to generate optimum immune responses. The use of alum in $AS0_4$ aids in the stabilization of MPL and antigen with in the vaccine as well as creating a depot effect. [25] The cationic adjuvant formulation (CAF) 01, which combines dimethyl dioctadeclammonium and trehalose-6, 6-behenate (DDA /TDB) and is now being tested in a phase I clinical trial, is expected to create a long lasting depot effect. Surgical excision of the antigen-alum depot 14 days after immunization did not influence immunological responses, according to several investigations. [20]

2. Up regulation of cytokines and chemokines caused cellular recruitment at the injection site

The attraction of innate immune cells at the injection site has been the subject of the most recent study on adjuvant mechanisms. Particulate adjuvants have been proven to recruit immune cells by creating a local pro-inflammatory milieu. Researchers discovered a group of genes described as "adjuvant core response genes" that were frequently regulated at the injection site by alum, MF59, and CpG-ODN (Table 2). These genes encode cytokines, chemokines, innate immune receptors, interferon-induced genes, and gene-encoding adhesion molecules. [26]

Adjuvants	Associated Chemokine Ligand
Alum	CXCL1, CCL11b, CCL11c, Ly6C
MF59	CCL2, CCL3, CXCL8
ASO3	CCL2, CCL3, CCL5, CSF3, IL-6

TABLE 2: Adjuvant-associated chemokine ligands. [27,28]

Adjuvants work to achieve this by attracting a range of immune cells to the insertion site, some of which are in charge of transporting the antigen to draining lymph nodes and initiating specific immune responses.

3. Presentation of an Antigen

An adaptive immune response must be induced before MHCs on APCs can effectively deliver antigens. It was once believed that several adjuvants, involving alum, microparticles, and oil-based emulsions, worked by "targeting" antigens to APCs, which increased the delivery of antigens via MHC. [29] Alum has been found to boost antigen absorption by DCs while also changing the size and ability of antigen delivery. Adsorption of antigen on alum increased antigen internalization. [30] To establish alum's capability to encourage antigen internalization, the impact of antigen delivery on alum adjuvanticity was recently investigated. The analysis also revealed that alum has a substantial role in slowing down the rate at which internalized antigens degrade. [31]

The effectiveness of antigen presentation appears to be modulated in a significant way by antigen size. Smaller lipid vesicles quickly localize to lysosomes which reduced antigen presentation, while large lipid vesicles end up in phagosomes, which enhances antigen presentation.

4. Activation and development of dendritic cells (DCs)

The production of adaptive immune responses requires the activation of DCs. Raised expression of MHC class II, activation marker CD-86, and maturation marker CD-83 enhance APCs' ability to activate and differentiate T lymphocytes. Freund's adjuvants like liposomes, lipo-polysaccharide (LPS), MF59, CpG -ODN, AS04, and –galactosylceramide (- GAL) have all been found to increase D C maturation to improve innate immunity. [32] OVA and alum injections into the peritoneal cavity resulted in antigen absorption and DC maturation. In vitro studies using human cells, although alum and MF-59 could not directly activate DCs, they did increase the surface expression of MHC class-II and costimulatory molecules (CD 83 and CD 86) on monocytes, macrophages, and granulocytes, leading to higher T cell proliferation. Furthermore, in vitro, alum activation of DCs has yielded mixed results. One study found that alum did not boost maturation or antigen presentation in DCs, whereas another found that the activation marker CD 86 and antigen presentation were increased. The source of alum could have played a role in the contradictory outcomes. [20]

AS04 has been discovered to mature antigen-specific T lymphocytes by maturing DCs (through TLR4), which subsequently travels to the draining lymph nodes. CpG enhances the production of MHC class II molecules, antigen production, and presentation in plasma-cytoid DCs.

- DOTAP (1,2-di oleoyl-3-tri methyl ammonium -propane) based cationic induce maturation of DCs through liposomes (vaccination in combination with DOTAP/ DC-chol liposomes increased serum IgG1 levels and induction of the production of specific IgA in tissues, suggested that the cationic DOTAP/DC- chol liposome leads to the induction of a Th-2 immune response. Immune responses are activated by DOTAP/DC- chol liposomes through an antigen specific Th-2 reaction.)
- TLR-independent adjuvants, mycobacterial cord factor trehalose -6-6- dimycolate (TDM), and Trehalose -6, 6- behenate (TDB) are directly activated DCs.
- diC14- amidine (3- tetra decyl amino-tert-butyl-N-tetradecylpropion- amidine) based cationic liposomes up regulate the expression of CD 80 and CD 86 on DCs.

Thus, adjuvants stimulate the maturation of DC and enhance the production of MHC and co-stimulatory molecules, which is necessary for effective T cell activation.

5. Inflammasome activation

Innate immunity cells express several pathogen recognition receptors (PRRs) to identify pathogens. Recent years have seen the discovery of TLRs, C type lectin like receptors (CLRs), nucleotide oligo-

merization domain (NOD) like receptors (NLRs), and Retinoic acid inducible gene-1 (RIG-1) like receptor (RLRs). Numerous immunological adjuvants communicate through PRRs or serve as ligands for innate immune receptors [[20]]

Inflammasomes have recently become one of the most extensively explored topics because of their potential role in adjuvant action. The NLR family, which also consists of NODS (NOD1-5), NLRPS (NLRP1-14), NLRP1 (NAIP), NLRC4 (IPAF), and v. Major Histo-compatibility Complex II (CIITA), comprises the inflammasome. Particulate adjuvants at the injection site cause localized tissue damage and cell death. Additionally, several adjuvants cause the injection site to release pro-inflammatory cytokines. These damage signals cause a generalized activation of the innate immune system, which gradually strengthens adaptive immunity. [20]

As observed above, individually, nano vaccines and adjuvants have an important role to play in the success of vaccination strategies to combat diseases.

Further, we look at the combination of these two approaches and their applications.

a) Self-adjuvant nano vaccines in cancer immunotherapy

Along with surgery, chemotherapy, and radiation, immunotherapy is regarded as the most important pillar of cancer treatment. Immune check-point inhibitors (anti-CTLA-4, anti-PD-1, and anti-PD-L 1), chimeric antigen receptor T cell treatments can all help patients with advanced cancer live longer. In preclinical and clinical trials, cancer vaccines containing tumor-associated antigens (TAAs) and adjuvants have produced antibodies and TAA-specific T cells. Tumor neoantigens, which arise from genetic and non-synonymous mutation changes without activation in healthy tissues, have been widely employed in the creation of neoantigen-based vaccines to address these difficulties. [33]

i. Example of synthesized and designed self-adjuvant and neoantigen-harvesting nano vaccines are Mal-PEG5000-b-PC7A45 nanoparticles (described as Mal -NPs), while NH2-PEG5000-b-PC7A45 nanoparticles (defined as NH2-NPs)
ii. Both NH2- NPs and Mal -NPs promoted BMDC (Bone marrow DCs) maturation
iii. Both NH2- NPs and Mal- NPs enhanced TNF- α markedly, but with a slight improvement in IL- 1β production.
iv. Both kinds of nanoparticles can record damage associated molecular pattern proteins (DAMPs), which are pro inflammatory macromolecules known to enhance immune responses.
v. Both PDT/ NH2- NPs and PDT /MalNPs increased the number of tumor- infiltrating Treg cells. [34]

b) Self-adjuvant nano vaccines in mRNA

Although long thought to be inappropriate for widespread usage due to hereditary instability, mRNA has several properties that make it an intriguing tool in the search for an effective vaccination platform. First, it has a better safety profile than plasmid DNA and viral vectors, with no risk of gene integration, transitory expression, or anti-vector immunity. Importantly, plasmid DNA's efficiency is hampered by the need to traverse both the cellular and nuclear membranes. mRNA, on the other hand, is already fully functional in the cytoplasm. Second, the efficiency of vaccine-induced adaptive immunity is highly dependent on the intensity of the innate immune responses that were initially triggered [35]

- Self-adjuvanted mRNA-based vaccines (termed RN Active vaccines) induce balanced immune responses comprising both humoral and cellular effectors as well as memory responses.
- Local innate immune responses are induced by self-adjuvanted mRNA vaccines which lead to robust and boostable adaptive immunity.
- Endosomal Toll-like receptors (e.g., TLR7, TLR8) and cytoplasmic sensors (e.g., RIG-I or MDA-5) mRNA, has inherent adjuvant activity

- Triggering of these receptors leads to the production of proinflammatory cytokines which is a prerequisite of a successful immunization. [36]

CONCLUSION

While nanotechnology is being applied to a wide range of medical sectors, a key area that has benefitted is that of vaccines. Nanovaccines have piqued researchers' interest due to their numerous advantages, raising hopes for the development of more effective and less harmful vaccines. Since the last hundred years, adjuvants have been employed to boost vaccine immunogenicity. The adjuvant selection was empirical until recently, but significant developments in the field have enabled their rational/targeted use. This knowledge, together with a growing understanding of the immune system, will pave the way for the development of effective mutation vaccines. Although all adjuvants appear to boost innate immune system components, the mechanisms used vary. Many new adjuvants in clinical or pre-clinical development are aimed at increasing certain types of T cell responses and creating the varied immune responses that may be required for difficult diseases like malaria and HIV-AIDS.

Declaration by Authors

Ethical Approval: Not Applicable

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