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A Review

Nanotechnology in vaccine and immunology

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Nanotechnology exploits the exclusive characteristics of nanoparticles with size ranging from 1 to 1000 nanometers (nm). Various nanoparticles have presented magnificent potential for the fabrication of new drug carriers and vaccines. For designing vaccine significant attempts are done to engineer novel vaccines and to increase the efficiency of current vaccines for particular diseases. So far, few vaccines are engineered from killed pathogens or protein sub-units, while various vaccines are founded on live-inactivated pathogens that holds the danger of retrieval of their pathogenicity under some immune-compromised circumstances. To circumvent this designing of risk-free effectual vaccines in combination with satisfactory carrier systems are reflected as a vital requirement to attain preferred humoral and cellular immunity for various diseases. In the past years, utilization of vaccines based on nanoparticle has gained a pronounced responsiveness to increase aimed delivery, immunization approaches and vaccine effectiveness to attain preferred immune retorts at the cell level. To increase vaccine efficiency these nanoparticles mustguard the antigens from early proteolytic disintegration, controlled release, enable antigen internalization and management by antigen presenting cells for harmless human usage. Nanoparticles comprised of polymers, lipids, metals and proteins have previously been exploited to achievefew of these characteristics. In this context, various physicochemical characteristics of nanoparticles have a crucial part in the establishment of vaccine efficiency. This review emphases on the usage of nanoparticles centred vaccine and the importance of characteristics of nanoparticles to achieve effective vaccines delivery in order to prompt preferred host immunity against various diseases.

Keywords: Immunization, Nanoparticles, Nanotechnology, Vaccine

Introduction

Biomolecules such as proteins, polysaccharides and oligonucleotides works as allergens, antigens or pathogen associated molecular-patterns and are of nanometer size[1]. The size scatter of various immunological molecules have been displayed in (Table 1). Here, we will review how the porosity, shape, size, charge and hydrophobic characteristics of nanocarriers are essential for their influence on immune response and how the nanoparticles with these characteristics can be engineered with the help of nanotechnology[2]. Further the role of nanotechnology in fabrication of immunosuppressive drugs and vaccines will be discussed and how the regulation of nanoparticles properties can result in improved targeting and immune response generation. The arena of nanotechnology is very vast and to include every aspect of it is very difficult so, here we have only focused on the immunological usage of nanoparticles. Adjuvants were used to enhance the quality and quantity of humoral and cellular immune responses in inactive vaccines. However, nanoparticles boost the antigen delivery to the immune system and also increase immune responses[3]. Here, we present various nanocarriers like squalene founded oil in water emulsions and virus like particles (VLP) that have been exploited for years, however additional nanoparticles are yet in the initial phases of production.

Role of nanotechnology in vaccination

In-spite of the advancement of traditional vaccines, amendments are requisite owing to worries about the instability, toxicity and the necessity for manifold vaccine administrations. Lately, to overpower these limitations nanotechnology has been combined with development of vaccines. Nanotechnology has progressively showed a significant part in vaccine fabrication and delivery vehicles which propose a possibility to boost the humoral and cellular immune responses. The nanoparticles exploitation in vaccine development not only permits greater stability and immunogenicity of antigen, but also boost controlled release and targeted delivery. In the recent decade,

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Table 1 — The size scale allocation of few immunological molecules

	Structure	Size
Molecules	DNA	1-3 nm
	Polysaccharide	200-1000 nm
	Proteins	2-10 nm
Receptors	Toll-like receptors	2–10 nm
	Antibodies	10–15 nm
	T-cell receptor	10–15 nm
Pathogens	Viruses	10–200 nm
	Bacteria	0.1–8 μM
	Fungi	1–100 μM
	Protozoa	1–100 μm
Cells	Dendritic cells	10–22 μM
	Macrophages	10–22 μM
	B-cells	7–10 μM
	T-cells	7–10 μM
	Neutrophils	8–15 μM
	Eosinophils	10–12 μM

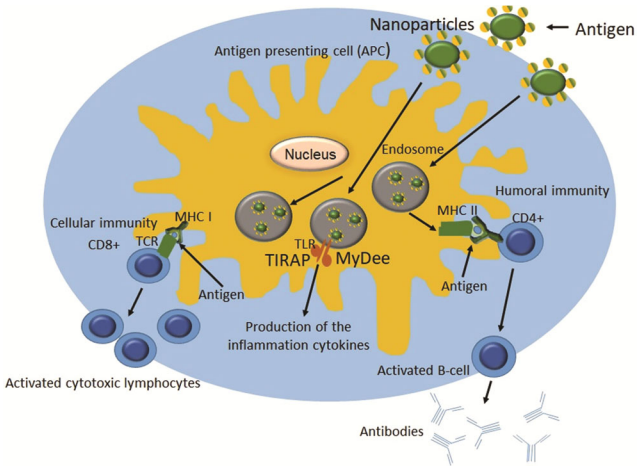

Fig. 1 — Targeted delivery of antigensubstancesutilizing surface modifiednanocarriers into the antigen presenting cells

nanosized materials like liposomes, polymeric, inorganic, virus-like particles and emulsions have received great responsiveness as possible delivery carriers for antigens that can stabilize antigen and also act as adjuvant. This superiority is credited to the size of nanoparticles that enables uptake by antigen presenting cells therefore, resulting in effective antigen recognition and presentation (Fig. 1). The surface modification of nanoparticles with various targeting molecules allows the antigen delivery to particular receptors on the cell surface, thus exciting precise immune responses.

Polymericnanoparticles

Recently, polymeric nanoparticles have attained remarkable responsiveness for their use in number of vaccines delivery owing to their biocompatibility, less toxicity, biodegradability, easy preparation and surface modification[4]. Furthermore, the regulation of vaccine release rate is comparatively simple by modifying the ratio or composition of co-polymers in the course of nanoparticles fabrication[4]. Most generally utilized polymeric nanoparticles for delivery of vaccine includes poly-lactic acid (PLA) and poly (lactic-co-glycolic acid) (PLGA). The employment of antigens loaded PLGA nanoparticles showed robust immunostimulatory effects by prompting nitric oxide and cytokine generation against mycobacteria infection[5].

PLGA based vaccine carriers have been widely used in animal models and clinical therapies as a milieu to conjugate, deliver and slow discharge of therapeutic agents[6]. In nanovaccine fabrication, PEGylated PLGA nanoparticles with size range of 150-200 nm has been exploited to conjugate to support the fast uptake of antigens in dendritic cells following elevated titers generation of antigen specific antibodies[7]. Recently, the mono-methoxy PEGylated PLGA thermo-responsive biodegradable hydrogel (<100 nm) has been utilized in mice to attain the subcutaneous hepatitis B antigen carriage and controlled liberation of macrophage/granulocyte colony-stimulating factor (critical cytokine for the endurance, differentiation and development of dendritic cells)[8]. The vaccine improved the dendritic precursor cells recruitment at injection site and supported the CD11c+ dendritic cells growth and migration to nearby lymph nodes. This was trailed by robust initiation of hepatitis B antigen selective antibody and T cell response, in mice which does not generally produce immune retorts for hepatitis B antigen or when less amount of hepatitis B antigen (≤2 μg) was employed. Notably, the outcomes propose that the adjuvant can possibly be utilized in vaccines which include weakly immunological antigens or in vaccines for weakened immune system patients. Moreover, along with synthetic polymers, various natural polymers like chitosan, pullans, alginate and inulins have been utilized as adjuvants[9,10]. Inulin, a recognized stimulator of complement system, presented enhanced defense against influenza viruses and hepatitis B[10]. Also, chitosan nanoparticles were established as delivery systems for DNA vaccine and HBV antigens. The PLGA and chitosan conjugated vaccines increased the immune retorts at the mucosal places. Latest report presented that *M. tuberculosis* lipids delivery in mice with the help of chitosan nanoparticles was capable of

prompting substantial humoral and cellular immune responses than lipids alone[11]. The intraperitoneal injection of this formulation exhibited improved stimulation of T-cells of splenic origin. Alternative report showed that intradermal injection of CpG loaded polymeric nanoparticles has amplified many fold activation of dendritic cell, showed equivalent vaccine efficiency at ~400 times lesser dose and produced lasting cellular immunity than free CpG[12]. The anticipated properties besides previously recognized less cytotoxicity and biocompatibility both *in vitro* and *in vivo* present polymeric nanoparticles as probable applicants for additional preclinical pharmacokinetics and therapeutic applications[13].

Dendrimers

Dendrimers are 3D, hyper-branched and monodispersed nanoparticles which consists of mixture of amides and amines. Limited researches have investigated the dendrimers application in various antigens delivery. The most frequently utilized dendrimers in delivery of vaccine includes polyamido amine (PAMAM) and polypropyleneimine (PPI). A single dose of multiple antigens loaded dendrimer was discovered to generate robust T-cell and antibody responses against *Toxoplasma gondii*, H1N1 influenza and Ebola virus[14]. The strong immune response production was attributed to the effective internalization of dendrimers by host. Also, a substantial upsurge in efficiency of HIV trans-activator of transcription centered DNA-vaccine was detected owing to improved internalization of PMAM dendrimer by the cells[15]. Therefore, the probability to modify the dendrimers to achieve particular physicochemical and biological characteristics as well the possibility to load numerous ligands have created dendrimers as potential applicants for new generation vaccines development with greater immunogenic characteristics.

Liposomes

Liposomes are the second greatest extensively investigated drug delivery systems and vaccine in the field of nanomedicine after polymeric nanoparticles. The liposomes fabrication is a natural procedure where lipids hydration permits the formation of lipid bilayer across an aqueous core. Until now, various types of liposomes such as unilamellar and multi-lamellar vesicles comprised of biodegradable phospholipids such as cholesterol, phosphatidyl choline (PC) and phosphatidylserine (PS) were involved in the vaccine investigations. Liposomes fuses target cell membrane to deliver vaccines[16]. The fundamentally adaptable and multipurpose liposomes are capable of encapsulating both hydrophobic as well as hydrophilic molecules. The hydrophobic substances are enclosed within the phospholipid bilayer while hydrophilic substances can be integrated in the aqueous core. Previous studies have revealed that antigenic proteins delivery encapsulated in multi-lamellar lipid vesicles prompt robust B and T-cell response[17]. Likewise, phosphatidylserine liposomes loaded with antigenic peptides can be easily internalized by antigen presenting cells to generate T-helper cell facilitated immune response[18] and heat-shock protein determining vaccine-DNA utilizing liposomes delivery provoked robust defensive immunity against fungal infection[19]. Owing to their predicted uses, various liposomes centred vaccine has been permitted for clinical examinations for intra-cellular pathogens such as *M. tuberculosis* and viruses. A report previously confirmed the effectiveness of liposome aerosol delivery systems in the production of defensive immunity for *M. tuberculosis* infection[20]. Another reports have attempted a mixture of several immune-modulators and dimethyl-di-octadecyl ammonium (DDA) lipid founded liposomes to improve immunity against tuberculosis, chlamydia, influenza and erythrocytic phase malaria[21,22]. In perspective of DNA-vaccines, DNA-lipid formulations have been effectively carried to the monkey lungs [16].

Inorganic nanoparticles

Various biocompatible inorganic nanoparticles like silica, carbon and gold have been utilized in the delivery of vaccine[23]. These nanoparticles can be manufactured in several sizes, shapes, and surface altered forms. Several viral antigens were effectively carried with the help of inorganic nanoparticles as delivery systems. This results in enhanced stability of antigen by shielding them from early disintegration by proteolytic enzymes. Bacterial and viral antigen delivery with gold nanoparticles results in relatively strong host immune retorts against tuberculosis, immune deficient virus, influenza and foot and mouth diseases in mice[24,25]. Plasmid DNA coding mycobacterial antigen (hsp65) loaded in gold nanoparticles showed substantial decrease in *M. tuberculosis* burden in infected mice[24,25]. Some studies have exploited spherical forms of carbon nanoparticles, nanotube and hollow mesosporous

silica as adjuvants to increase the delivery and immunogenicity of peptide and protein antigen against viral diseases[26,27]. Silica based nanoparticles comprise plentiful silanol groups on their surface which can be exploited to familiarize particular functional groups to achieve entrance for vaccine substances into target cells[27,28]. The main benefits of inorganic nanoparticles comprise reproducibility, little manufacturer and security in usage.

VLPs (Virus like Particles)

Various studies sufficiently demonstrated the usage of VLPs as a vaccine delivery system and their capability to activate the immune responses in host[29]. VLPs are comprised of virus sheath which is self-assembled and make a mono-meric complex exhibiting a great concentration of epitopes[29]. Fascinatingly, VLPs can too be fabricated to direct extra proteins either by fusion of proteins with the nanoparticles or by endogenous representation of numerous antigens. It can likely to attach antigens of non-protein in nature and tiny biological substances chemically onto the surface of virus to yield bio-conjugates with VLPs. Owing to the diverse equalities, VLPs may offer defense against virus as well as heterologous antigenic molecules. A precise immune retort was effectively produced post antigen carriage withSV40virus-capsid protein in mammalian cells[30]. VLPs are also established to upsurge the immunogenicity of feeble antigens. For instance, influenza A M2 protein, Salmonella typhi membrane antigen, and H1V1 Nef gonadotropin releasing hormone (GnRH) constructed VLPs generate robust antigen precise humoral and cellular immune responses[31]. It is supposed that the utilization of VLP based nano-formulations can allow the antigens to attain conformations like to natural antigen configuration, therefore it might cause superior activation of host immune response[31].

Nano-emulsion

Nano-emulsions are a combination of water in oil and comprised of surfactants and solvents. MF59, is a nano-emulsion comprised of squalene oil in combination with sorbitantriolate (Span 85), polymorphic 80 (Tween 80) and is licensed for utilized as intramuscular injection for influenza vaccines in Europe[32]. The mechanisms of action seems to comprise improved inflammatory cytokines release, antigen uptake, buildup of granulocytes and monocytes at the administration site. MF59 is superior to alum as it offers both cellular and humoral immune reactions. After MF59 injection, enhanced pain and reactivity have been detected at the administration site that can be credited to amplified inflammation as result of greater immune response[33]. W805EC, is another nano-emulsion comprised of soybean-oil and is intra-muscularly administered in humans and animals ensuing robust humoral, mucosal and cellular immune retort. The exclusive action of this form of nano-emulsion is to sustain the assembly and cationic nature, assisting the penetration of mucosal layer and association with cell membrane. Moreover, nano-emulsions have no cytotoxicity conferring to widespread animal and human tests[34].

Other nanoparticles

Besides the above nano-formulations researchers are examining other smart nanoparticles for utilization in immunology and vaccine. For instance, hydroxyapatite or calcium-phosphate nanostructures could be a noble proposal for vaccine. Specific nanoplatforms may be prepared by means of DNA and plasmids expertise. An innovative approach in designing vaccine is to aim B-cells by encapsulating the nanocarriers with TLR-ligands. The surface modification and employment of indicator substances like aptamers are illustrations of aiming. Certainly, every technique has its own benefits and restrictions. Alternative expertise is vaccine founded on outer-membrane vesicles of bacteria, displaying both the receptor-binding area of MERS-CoV (OMV-H1/RBD) and antigenic steady chimeric-fusion protein of H1-type (haemagglutinin) of influenza A virus[35]. The bacterial outer membrane vesicles founded vaccines displaying viral antigens offer a nontoxic and trustworthy strategy to guard against two dissimilar viral infections[36].

Nanotechnologyin immunosuppression

Additionally, to initiate the immune reaction nanoparticles may be utilized curatively to prevent destructive immune comebacks which happen in transplant rejection, autoimmunity and allergies. The immunosuppressive outcomes of various nanoparticles are discussed in (Table 2). Nanoparticles may have an honest immunosuppressive consequence on constituents of immune system comprising T-cells, B-cells or antigen presenting cells may carry molecules that causes immunosuppression or can exploit both methods at the same period. Straight forward consequence comprise of increase in level of

Table 2 — Examples of immunosuppressive and immunostimulatory outcomes of nanovaccines

Effects	Nanoparticles	Disease	Bioactivity	size	use	Ref
Immunosuppressive	Poly(lactideco-glycolide)	Arthritis and autoimmune disease	Betamethasone, bifunctional peptide inhibitors and leukaemia-inhibitory factor	1–400 nm	In mice and rats	39
	Polyamidoaminedendrimers	Cerebral palsy, scar formation and gastroenteritis	N-acetyl- cysteine glycosamine	1-20 nm	in rabbits	40
	Liposomes	Arthritis, coronary artery stenosis and acute lung injury	Liposomal bisphosphanates	100-160 nm	In rats, rabbits and pigs	41
	Liposomes with DC-targeting ligands	Autoimmune disease	siRNA	50-92 nm	In mice	42
	Single-walled carbon nanotubules	Inhalation exposure	Suppression of DC function	1-4nm diameter; 1,000-3,000 nm length	In mice	43
	Multi-walled carbon nanotubules	Inhalation exposure	Suppression of T cell proliferation and function	10–20nm diameter; 5,000-15,000nm length	In mice	44
	Nanoemulsions	Autoimmune thyroiditis	Self antigen	3-400 nm	In mice	45
	Spherical fullerenes	Allergy	Suppression of mast cell and basophil degranulation	1 nm	In mice and in vitro	46
Immunostimulatory	Poly(lactideco-glycolide) nanoparticles	Vaccine carrier and adjuvant when combined with bioactive immunomodulators	Encapsulation for sustained local antigens and co-mediator release	100-200 nm	In mice	47
	Cationic liposomes	Vaccine carrier	Encapsulation and targeted antigen delivery or uptake by APCs, and recruitment of monocytes to the injection site	200-1000 nm	In humans and mice	48
	Virus-like particles	Vaccine carrier and adjuvant	Repetitive antigen display, structural or molecular mimicry of virus, particle size-dependent tissue penetration and trafficking to lymphatics, and TLR activation	15-30 nm	In humans and animals	49
	MF59 (squalene oil-in-water emulsion)	Vaccine adjuvant	Neutrophil, monocyte and DC recruitment, antigen uptake, and the induction of humoral and TH1-type immune responses	165 nm	In humans	50

transforming growth factor-β (TGFβ) that causes upsurgeof interleukin-10 (IL-10), prostangandin E2 (PGE2) and cyclooxygenase 2 (COX2) and reduced T-cell, B-cell action and apoptosis. The transport of immune suppress antleads to increased expression of forkhead box P3 (FOXP3), decreased expression of nuclear factor-κB (NF-κB) alongside steroids and reduced reaction against IL-2 alongside sirolimus that causes enhancement of regulatory T-cell function when self-antigens are displayed in a nano-emulsion. The fullerene (C60) has immunosuppressive outcomes[37]. C60 substances are entirely made up of carbon and generally utilized in nanotechnology for polymer composites, paints and electronics. Their incubation with mast cells results in reduction of IgE-facilitated signaling, reactive oxygen species generation and degranulation. In mice model, C60 inhibits the discharge of histamine and avoids a body temperature reduction that generally happens in bodypost an allergy encounter. C60 substances

prepared when resembles to cylindrical shapes, are known as carbon-nanotubes (CNTs) and are approximately 10 nm in diameter and numerous micro-meters in length. This assembly may be designed as single walled or multi walled pipes. Additionally, this has been discovered that they possesses immune suppressive outcomes. Dendritic cells subjected to lipopolysaccharides (LPS) and single walled CNTs were not as much talented of supporting T-cells multiplication, than dendritic cells that were subjected to only LPS. The mechanism of action for the consequence of single walled CNTs on dendritic cells functioning are not entirelyexplained[38].

Significance of physico-chemical features in fabricating nanoimmuno formulations

To increase the delivery and vaccine features various strategies have been exercised for conjugation of vaccine substances with diverse nanoparticles. These substances can possibly be encapsulated, surface adsorbed or conjugated with the nanoparticles. The adsorption of antigens on the surface of nanoparticles is mainly based on the hydrophobicity or charge of nanoparticles and antigen interaction[51]. This form of communication is commonly noncovalent that can result in fast disintegration of nanoparticles and release of antigens relianton external environment like temperature, antigen hydrophobicity, ionic strength and pH. In contrast, conjugation and encapsulation of antigenic molecules to nanoparticles is more stable because of robust chemical bond establishment and interactions amid the target substance and the nanoparticles. Additionally, nanoparticles can encapsulate antigenic molecules by modest mixing reaction during their fabrication, where the partial or complete disintegration of nanoparticles result in release of antigenic molecules. These methods have already been utilized with gold and silica nanoparticles. Likewise, dextran sulfate and chitosan nanoparticles were exploited for the synthesis of anionic and cationic antigenic nanoformulations. Several viral antigens are capable of conjugating with both anionic and cationic nanoparticles *via* immobilization method and hydrogen bonds[52]. The immobilization method reliant on pH, charge, nanoparticles and antigen ratio and the protein partition co-efficient among colloid and solution[52]. Various antigens were effectively carried to the targeted site by encapsulation, adsorption and chemical conjugation with the easy nanoparticles such as immune stimulating complexes, liposomes and VLPs. Immune stimulating complexes are a type of adjuvant preparations consisting of phospholipids, cholesterol and saponins in precise ratio. Antigens may be conjugated into immune stimulating complexes directly or after the surface alterations. Due to anionic nature of immune stimulating complexes directbinding of many of the solvable proteins is a restrictive issue. Nanoparticles may boost immunogenicity of the substances for instance, gold nanoparticles coated with Yersinia pestis F1-antigen and chitosan nanoparticles conjugated with influenza antigen H1N1 generate greater cytokine responses and antibody level as compared to mice injected with unconjugated antigens[53]. These results can be attributed to the increased immunogenicity and stabilization of vaccine antigens because of conjugation with nanoparticles. Alternative significant characteristic in the synthesis of nanoimmuno-formulations is that they increases the antigen presentation and delivery. The size, shape and charge are significant features that influence specificity, circulation, bioavailability and bio-distribution of nanoparticles by crossing biological barriers. Moreover, geometry of nanoparticles like surface to volume ratio have a significant part in the release of immunogen and disintegration kinetics[54].

Inferences of nanoparticles in the vaccine engineering

Emergent findings have demonstrated that nanoparticles can be valuable moderators in the vaccines development against several diseases. Therefore, it is crucial to synthesize nano formulations that are capable of delivering immunogens to antigen presenting cells specifically to dendritic cells and initiate successful antigen specific T-cell response. Various nanoparticles have been revealed to precisely stimulate dendritic cells to generate antitumor or antiviral immune responses[55,56]. A study projected that Fe3O4-TiO2 and nano-TiO2 nanoparticles can perform as a valuable vector to support delivery of vaccine in immune cells[55]. Fe3O4-TiO2 and nano-TiO2 co-incubation with dendritic cells leads to an enhanced TNF-α generation and increased theCD86, MHC class II molecules and CD80 expression *via* NF-κB pathway[57]. Thus, immunization efficiency of numerous nanoparticles like chitosan-coated EphrinA1-PE38/GM-CSF, VLPs expressing RSV glycoproteins and erythrocyte

membrane-enveloped PLGA nanoparticles for antigenic peptide (hgp10025-33) and various others have been upgraded[58,59]. Nanoparticles can also regulate polarization and differentiation of cells. Branched poly-ethylenimine super paramagnetic iron oxide nanoparticles supported polarization of Th1 to dendritic cells. Sehgal *et al*. revealed that nanoparticles can also be exploited for targeting specific sub-sets of immune cells. This have been resented that concurrent aiming of dendritic sub-sets for instance, BDCA3+ dendritic cells and dendritic cells-SIGN+ by nanoparticles improved the initiation of T cell-facilitated immunity as compared to aiming of each dendritic cells subset individually[60]. Preclinical reports by numerous researchers have effectively confirmed the effectiveness of nanoparticles founded vaccines in the initiation of precise immune retorts against tuberculosis[61,62]. Feng *et al*. designed a nanoparticles centred recombinant-DNA vaccine consisting of fms-like tyrosine kinase-3-ligand and Esat-6 coated with chitosan nanoparticles[63]. Intramuscular primary injection trailed with nasal lift of the above recombinant-DNA vaccine amazingly improved T-cell retorts in M. tuberculosis confronted mice[63]. Alternative report has presented that CpG adjuvant and M. tuberculosis antigen (Ag85B) loaded polypropylene-sulfide nanoparticles when administrated by pulmonary route can initiate *M. tuberculosis* precise poly-functional T-helper responses and lessen the bacterial load in lungs[64].

Conclusion

Nanotechnology is presently utilized for protective and therapeutic uses[65]. Sooner, the utilization of nanocarriers with exclusive immunological characteristics will allow investigators to modify immune retorts in innovative and unforeseen manner. The hydrophobicity, shape, size, porosity, surface charge of nanocarriers are crucial. Stimulation of cytotoxic T-cells by nanocarriers can aim tumors and virus infested cells. Nanoparticles may be enclosed with viral antigens to boost the action of cytotoxic T-cells. They also generate cytokines like IL-12, GM-CSF and IL-15. Besides, we can exploit immunosuppressive nanoparticles to regulate autoimmune diseases and inhibit illness advancement. Along with the remedial effects of nanotechnology, nanoparticles can assist us to identify immune system related ailments and determine vaccines and new agents/drugs. These emergent approaches presents novel ways for immune cells differentiation and equilibrate T-Reg and T-helper cells. These approaches can too offer additional efficient treatments in the upcoming year to control immune response and lessen side-effects. Concisely, nanotechnology will remain to offer visions into the characteristics of the immune reaction. The exploitation of nanotechnology in immunology can too impacts novel approaches for the inhibition or management of human ailments.

Conflict of interest

The authors declare no conflict of interest.

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