Journal of Cell Science & Therapy
ISSN: 2157-7013

Agarwal, J Cell Sci Ther 2015, S8
DOI: 10.4172/2157-7013.S8-003

Review Article Open Access

Role of Nanovaccine in Immunotherapy

Megha Agarwal*

Indian Veterinary Research Institute, Izatnagar, Bareilly, India

Abstract

Nanotechnology, although not a new concept, has attained notable momentum in recent years. Due to the modern approach in material science and nano-engineering in the preceding decade, the nanoparticles have become incredibly striking for their applications in the fields of biology and medicine. There are significant applications of nanoscience in biology and biotechnology. Nanotechnology can be used to facilitate the therapy targeting immune system. The initiative that a nanostructure could be assembled, constructed and introduced into the human body to progress health, together with cellular repairs at the molecular level, is promising. The utilization of nanotechnology to medicine, known as nanomedicine, deal with the use of accurately engineered materials at this length scale to build up novel therapeutic and diagnostic modalities. Biodegradable nanoparticles are attaining amplified consideration for their capacity to serve as a feasible carrier for site specific distribution of vaccines, genes, drugs and other biomolecules in the body. They offer improved biocompatibility, superior drug/vaccine encapsulation, and expedient release profiles for several drugs, vaccines and biomolecules to be used in an array of applications in the area of medicine. The small size, customized surface, superior solubility, and multi-functionality of nanoparticles will persist to open numerous doors and generate novel biomedical applications. Certainly, the peculiar properties of nanoparticles offer the facility to interact with multifacet cellular functions in new ways. The nanomaterial is so minute that it can effortlessly enter the cell; therefore, nanomaterials can be used *in vivo* or *in vitro* for biological applications. Nanovaccine is rising as a novel path to the methodology of vaccination. Nanoparticles can also be used to cargo diverse types of cytokines like LIF and IL-6. This targeted nanoparticle approach is competent to harness endogenous immune-regulatory pathways, providing a potent new process to modulate T cell developmental plasticity in immune-mediated disease indications.

Keywords: Nanovaccine; Nanoparticles; Immunotherapy; Vaccination; IL-6; LIF

Introduction

Nanotechnology is an applied science that deals with the creation and fabrication of elements and hardware at the atomic plane within the range of 1-100 nanometers. Nanoparticles are any particles that are less than about 100 nanometers in diameter [1]. Nanotechnology targets therapeutic medicine by enabling three remarkably desirable therapeutic aims: Firstly, targeted drug delivery (for example, cytotoxins are used in treatment of cancer cells where comparatively high doses of drug can be focused upon the tumor to decrease off-target side effects); second is the utilization of endogenous regulatory systems, such as harnessing of the adaptive immune reaction towards immune self-tolerance in treatment of autoimmune disease and lastly, formation of an artificial transient microstroma as a place for endogenous repair following trauma or in age-related degenerative diseases [2]. Furthermore, since nanotherapeutic devices are distinct in configuration and molecular composition, and biodegradable where suitable, safety standards are promptly met. Nanotherapy not only exploits the discriminating property of antibodies to instruct the nanodevice but also utilize the power of the T lymphocyte to control either immune tolerance or immune-mediated destruction. Once the therapy is guided towards a desired lineage, that lineage will be maintained by endogenous regulation in subsequent responses to the target antigen. Such exploitation of the immune response capitalizes on both immune memory, especially relevant in vaccination, and immune surveillance throughout the host tissues.

Scientists in the expanding field of disease immunotherapy are applying bionanomedical techniques to design vaccines with the ability to harness the patient's own immune system. Scientists have found certain immunomodulatory agents called pathogen-associated molecular patterns (PAMPs) with the innate ability to initiate an immune response by blocking many of the immunosuppressive barriers. Within past few years, speedy developments have been made to employ nanomaterials in diversity of applications in various fields of medicine such as cardiovascular and orthopedic. In clinics, nanomaterials have been used in definite applications such as tissue engineered scaffolds and devices, site specific drug delivery systems, cancer therapy and clinical bioanalytical diagnostics and therapeutics. In recent years significant efforts have been made to use nanotechnology for the principle of drug and vaccine delivery. Therapeutic nanotechnology offers simply invasive therapies with high densities of function concentrated in small volumes, characters that may decrease patient morbidity and mortality. Emerging nanotherapeutics consequently haze the limitations between medical devices and traditional pharmaceuticals. Congregation of therapeutic nanodevices normally exploits either (bio) material self assembly properties or chemoselective bioconjugation techniques, or both. Thus, these unique nanoparticulate carrier systems have the potential to change the current scenario of research and diagnosis in real time.

Nano-Particle Vaccine

Nanovaccines are vaccines that consist of nanoparticles and are rising as a new class of vaccines that directly target the site in

***Corresponding author:** Megha Agarwal, Indian Veterinary Research Institute, Izatnagar, Bareilly-243122, Uttar Pradesh, India, Tel: 094123 60917; E-mail: dr.meghaagarwal@gmail.com

Received April 28, 2015; **Accepted** July 11, 2015; **Published** July 11, 2015

Citation: Agarwal M (2015) Role of Nanovaccine in Immunotherapy. J Cell Sci Ther S8: 001. doi:10.4172/2157-7013.S8-003

the body where the disease or infection originated, as opposed to traditional drugs which affect all parts of the body. The motivation for nanoconstructs as vaccine systems develops from the idea that several components important for vaccine efficacy can be rationally assembled, optimized separately, and incorporated into a single vehicle to effect a potent immune response. These components may act additively or synergistically but in the end will work cooperatively to affect the desired immune response. Various advantages have been shown by the researchers working and investigating the different aspects related to nanovaccine.

Some of the important advantages of nanovaccine are as follows:

a) A small dose of antigen is desired, well-organized processing by antigen presenting cells and stability all along storage. Encapsulation of antigen has been extensively used as it is effortless to deliver, safeguards the antigen from degeneration and is found to be efficient with a single dose due to slow release of the antigen. The use of nanoparticles thus improves immunogenicity due to the absence of adjuvants such as alum, which are inflammatory mediators.

b) Alum, a common adjuvant used in various conventional vaccines, is known to cause irritation. In contrast, the use of needle-free nasal immunization with a combination of nanoemulsion and antigen is found to be tolerable and effective.

c) Refrigeration is not required for the nanoemulsion, as it is effective for a month at 25°C, and for 6 weeks at 40°C, thereby facilitating its final distribution in small areas/ villages of developing countries.

d) Innumerable nanovaccines are non-invasive, delivered by the oral or nasal route, diffusion patches or microneedle arrays, consequently allowing pain-free delivery with negligible damage. This is a benefit over conventional vaccines, which are generally multi-injection, multi-dose delivery systems.

Biodegradable nanoparticles can be made from a range of materials such as amino acids, polysaccharides and synthetic biodegradable polymers. The assortment of the foundation polymer is based on diverse designs and end application criteria. It depends on various factors such as 1) size of the preferred nanoparticles, 2) features of the drug (aqueous solubility, stability, etc.) to be enclosed in the polymer, 3) surface uniqueness and functionality, 4) extent of biodegradability and biocompatibility, and 5) drug release profile of the final product. Based upon selection of desired criteria for the preparation of the nanoparticles, the procedures can be categorized as following 1) dispersion of preformed polymers, 2) polymerization of monomers and 3) ionic gelation method for hydrophilic polymers. Traditional methods for increasing vaccine effectiveness have focused on coadministration of adjuvants, predominately montanide polymers or colloidal alum. However, these have a limited capacity to adsorb many antigens and greatly limited immunostimulatory properties. Despite the availability of a number of vaccines in the market for prevention of diseases, their cost per dose and delivery of multiple doses are the limiting factors of these vaccines. In addition to this, the requirement for cold storage is another disadvantage of conventional vaccines. In view of this, efforts have been made to develop nanoparticles prepared from biodegradable and biocompatible polymers as vaccine delivery systems to induce both humoral and cellular immune responses. Significant advantages of these biodegradable polymers are their long history of safety, proven biocompatibility, and their property to control the time and rate of polymer degradation and antigen release [3]. Entrapment efficiency, release kinetics and additional physical features like construction, porosity and size assortment, which determine the potency of the formulation, can be controlled by using a suitable aggregation of different polymers. This can lead to favorable formulation of a vaccine.

Nanoparticle – delivery system

In recent years, significant research has been done using nanoparticles as oral drug delivery vehicles. Oral delivery of drugs using nanoparticles has been shown to be far superior to the delivery of free drugs in terms of bioavialability, residence time, and biodistribution. Advances in biotechnology and biochemistry have led to the discovery of a large number of bioactive molecules and vaccines based on peptides and proteins. Development of appropriate carriers remains a challenge due to the fact that bioavailability of these molecules is restricted by the epithelial barriers of the gastrointestinal tract. The drugs may also be liable to gastrointestinal degradation by digestive enzymes. The benefit of using polymeric nanoparticles is to allow encapsulation of bioactive molecules and guard them against enzymatic and hydrolytic degradation. For illustration, it has been found that insulin-loaded nanoparticles have conserved insulin activity and produced blood glucose reduction in diabetic rats for up to 14 days following the oral administration.

Nanoparticles laden with plasmid DNA could also serve as a capable sustained release gene delivery system due to their quick escape from the degradative endo-lysosomal compartment to the cytoplasmic compartment. Because of their intracellular uptake and endolysosomal escape, nanoparticles could discharge DNA at a constant rate resulting in uninterrupted gene expression. This gene delivery strategy could be applied to facilitate bone healing by using PLGA nanoparticles containing therapeutic genes such as bone morphogenic protein. Nano particulate vaccine delivery system can also be helpful to enhance the weaker immune response generated by synthetic peptide vaccines [4].

The nanoparticle vaccine can also be used to elicit an anti-tumor response and can generate tumor antigen-specific CTLs. The CpG oligodeoxyribonucleotide (CpG ODN) vaccine complex includes an outer coat of a pharmaceutically novel protein derived directly from the serum of the patient, an agonist of TLR9 CpG ODN, cytokine granulocyte macrophage-colony stimulating factor (GM-CSF), and poly(lactic-co-glycolic-acid) (PLGA) biodegradable fluorescent nanoparticles. The mechanism of this vaccine complex is to draw in APCs around the tumor, using the protein coat (innate immune function) and the CTLs (adaptive immune function) to induce the recognition of tumor-associated antigens. The nanoparticle-based intracellular delivery system will aid in a prolonged and highly specific immune response that will enter into the endosomes or intracellular compartments of the APCs and begin immune stimulation. The vaccine complex is also cost effective and biologically specific because the main vaccine component of the human derived protein can be taken directly from the patient. This vaccine platform encapsulates new technologies in order to improve immune stimulation and elicit a strong and specific anti-tumor immune response against cancer.

Nanoparticle carrier system

In addition to the commonly used oral and injection routes, drugs can also be administered through other means, including transdermal, transmucosal, ocular, pulmonary, and implantation. The mechanisms used to achieve alternative drug delivery typically incorporate one or more of the following materials: biologics, polymers, silicon-based materials, carbon-based materials, or

metals. These materials are structured in microscale and, more recently, nanoscale formats. Biodegradable polymer nanoparticles, characteristically consisting of polylactic acid (PLA), polyglycolic acid (PGA), or a copolymer of PLA and PGA, are being studied for the delivery of proteins and genes, vaccines, anticancer drugs, ocular drugs, and cytokines. Other polymers being reviewed for nanoscale drug carriers include polyalkylcyanoacrylate, poly(3-hydroxybutanoic acid) (PHB), poly(organophosphazene), poly(ethylene glycol) (PEG), poly(caprolactone) (PCL), poly(ethylene oxide) (PEO), and copolymers such as PLA-PEG. Biodegradable nanoparticles of gelatin and human serum albumin show promise as pulmonary drug carriers. There have been a diversity of materials used to engineer solid nanoparticles, both with and without surface functionality. Conceivably the majority are the aliphatic polyesters, specifically the hydrophobic PLA [poly(lactic acid)], the more hydrophilic PGA [poly(glycolic acid)] and their copolymer PLGA [poly(lactide- co-glycolide)].

Poly lactic-co-glycolic acid (PLGA): Among the nanoparticulate carriers, poly (lactic-co-glycolic acid) (PLGA) NPs have unbelievable prospective in the applications connecting targeting, imaging, diagnostics and therapy. Conjugation or encapsulation of drugs in PLGA nanocarriers decreases the undesirable shortcomings of other therapeutic agents, such as brief circulation half-life and non-site-specific targeting, ensuing in unacceptable systemic side effects. These drug-loaded PLGA conjugates not only lengthen the in vivo circulation time of the therapeutics from several minutes to several hours but in addition shrink cellular uptake along the endocytic route. Macromolecular drugs such as proteins, peptides, genes, vaccines, antigens and human growth factors, are effectively incorporated into PLGA or PLGA-based nano/microparticles. In 1999, the US FDA approved a PLGA microsphere formulation, Nutropin Depot, as a once-a month alternative to daily injections of human growth hormone. PLGA is a copolymer of lactic acid and glycolic acid. Depending on the ratio of lactide to glycolide, different forms of PLGA can be obtained, which are usually identified with regard to the monomers ratio used. PLGA is one of the most successfully used biodegradable polymers for the development of nanomedicines because it undergoes hydrolysis in the body to produce the biodegradable metabolite monomers, lactic acid and glycolic acid, which are successfully processed by the body, culminating in minimal systemic toxicity.

Targeted Therapy for Autoimmune Diseases

Within the immune system there is an exquisite ability to discriminate between "self" and "non-self" that is orchestrated by T lymphocytes. Inequitable approaches guide differentiation of these lymphocytes into either regulatory (Treg) or effector (Teff) T cells, influenced by cues from the naive T cell's immediate micro-environment as it responds to alike antigen. Reciprocal pathways may lead to commitment of naive T cells into either the protective tolerance-promoting Treg, or to the pro-inflammatory Th17 effector phenotype.

Treg

The guardians of 'self' Within the family of CD4+ T cells, a subset of CD4+Foxp3+ T cells recognized as "regulatory" T cells (Treg) retain peripheral self tolerance. It is at present documented that Tregs offer a probable resource for antigen-specific tolerogenic therapy for management of autoimmune diseases as well as reception of organ or tissue allografts, together with bone marrow and stem cell grafts in regenerative medicine [5]. CD4+CD25+ regulatory T cells, a naturally arising regulatory T (nTreg) cells have emerged as a unique subset of T cells that are critical for the maintenance of peripheral tolerance. Deficiency of Treg development and function can cause various autoimmune and inflammatory disorders (e.g., immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome [IPEX], multiple sclerosis, and type 1 diabetes).

Transcription factor: FOXP3, a forkhead transcriptional factor is particularly expressed in CD4+CD25+ Tregs and vital for the expansion and function of nTregs. Mutations in the FoxP3 gene direct to fatal autoimmune or inflammatory diseases (Scurfy disease in mice and IPEX in humans) due to the shortage or malfunction of nTregs [6]. A lack of Foxp3 results in a lack of Treg, leading to lethal autoimmune self-destruction in both mice and humans, illustrating their vital role in survival. Autoimmune diseases arise when autoantigen specific Treg populations become inadequate in protecting their target. Therefore the use of targeted nanotherapy to promote Treg function by harnessing recently discovered regulatory switches will progress this aim.

T-helper 17 cells

Effector CD4 T cells including T helper (Th) cell 1, Th2 and Th17 are essential to mount efficient adaptive immune responses by producing a unique set of cytokines. Th1 cells mainly produce IFN- γ and mediate cellular immune responses to intracellular pathogens, although Th2 cells classically produce IL-4 and control humoral immune responses to extra cellular pathogens [7]. T helper cells that produce IL-17 (Th17 cells) promote autoimmunity in mice and have been implicated in pathogenesis of human inflammatory diseases [8] although human Th17 cells have a different origin than in mice [9].

Transcription factor: IL-17 producing T cells express the transcription factor retinoic acid orphan nuclear receptor (ROR) γ thymus RORγt, which along with ROR, is critical for Th17 development [10].

LIF (Leukemia inhibitory factor)

Leukemia inhibitory factor (LIF) is a pleiotropic cytokine belonging to the interleukin-6 (IL-6) family of cytokines that share similar activities and receptors. Leukemia inhibitory factor (LIF) supports Treg maturation in contrast to IL-6 which drives development of the pathogenic Th17 effector phenotype. LIF is expressed in multiple tissues and involved in many biological processes, but its increased expression in dystrophic and injured skeletal muscle indicates an important role in skeletal muscle regeneration [11]. LIF is a neuropoietic cytokine for neural stem and precursor cells, and plays key roles in neuroprotection, axonal regeneration, and prevention of demyelination. This is confirmed that therapeutic stem cell transplantation for MS can be replaced by LIF therapy.

Nano-LIF

PLGA is decorated with functional avidin groups on the nanoparticle surface which enables modification of the surface through the robust attachment of biotinylated ligands such as PEG, T cell stimulating antibodies, and T cell-targeting antibodies. This technology is well-suited toward stimulation and manipulation of immune cell development through-

a) The presence of T cell-specific cell surface molecules that can be targeted by antibody

b) On the NP, presentation of multiple targeting ligands per nanoparticle ensuring high valency and avidity of contact with targeted cellular ligands

c) Delivery of multiple cytokine molecules per biorecognition

event to ensure relatively high concentration of cytokine specifically within the microenvironment of the targeted cell, although bypassing systemic exposure to the therapeutic cytokine.

Nano-LIF and Nano-IL6

LIF and IL-6, both representative of the IL-6 cytokine family, can be steadily encapsulated and liberated in bioactive form using PLGA nanoparticles. The outcome of nanoparticle delivered cytokine is extremely specific; nanoparticle- delivered LIF induces Foxp3+ and repress RORγT expression, while nanoparticle-delivered IL-6 induces the opposite effects. These effects are probably due to their own receptors, where IL-6 is composed of gp130 homodimers, and LIF of gp130/gp190 heterodimers. Targeting of LIF-encapsulating nanoparticles to CD4+ T cells enables specific, sustained delivery of LIF in the face of dynamic physiologic factors such as diffusion and clearance [5].

Advantages of Nanoparticle

These systems universally can be used to offer targeted (cellular or tissue) delivery of drugs, advanced bioavailability, prolong release of drugs or solubilize drugs for systemic delivery. This process can be modified to guard therapeutic agents against enzymatic degradation (i.e., nucleases and proteases). Thus, the advantages of using nanoparticles for drug delivery are a result of two fundamental properties: small size and use of biodegradable materials. Nanoparticles, for the reason that they have small size, can extravasate through the endothelium in inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or infiltrate microcapillaries. In general, the nanosize of these particles allows for proficient uptake by a variety of cell types and careful drug accretion at target sites. Countless studies have confirmed that nanoparticles have numerous edges over microparticles as a drug delivery system. Nanoparticles have a further assest over larger microparticles as they are superior suited for intravenous delivery. The smallest capillaries in the body are 5–6 μm in diameter. The dimension of particles being dispersed into the bloodstream must be considerably smaller than 5 μm, without forming aggregates, to guarantee that the particles do not cause an embolism [12].

Conclusion

Nanotechnology has become an authorizing technology for disease detection, diagnosis and therapy. In the past 100 years, vaccination has assisted enormously to public health by averting a number of virulent infections. Killed, attenuated, toxoid or part of the microorganism is used to provoke immune response against it. In recent years, nanovaccine is a novel path to the methodology of vaccination. Nanomaterials are delivered as microspheres, nanobeads or micro-nanoprojections. Gentle, competent and safe needle-free routes like the oral route or intranasal, or patches of microprojections to the skin are few of the ways which are in the trial stage at present but might have a remarkable future at the forefront in nanovaccination.

The utilization of drug-loaded PLGA nanoparticulate technology is budding an innovative generation of additional effective therapies accomplished of overcoming many organic, biophysical and biomedical obstructions that the body stages against traditional therapies. The research signify that PLGA nanoparticulate systems have great potential in providing inventive treatment, and are being able to renovate feebly soluble, poorly absorbed and labile biologically active substances into hopeful deliverable drugs. Endogenous control mechanisms that normalize immune tolerance can be overburdened using nanotherapeutic devices to both deliver and release regulatory cytokines in a stable, physiological mode. LIF-nano-driven immune tolerogenesis indicates a unique, antigen definite approach to immune-mediated disease. Moreover, since LIF is in addition a significant factor for sustaining stem cells, the utilization of LIF-nano in regenerative medicine presents two-fold advantage, aiding engrafted stem cells in addition to shielding them from immune mediated rejection. As the functionality of nanoparticles becomes further composite, such as the addition of targeting ligands, there is a necessity to specifically engineer nanoparticles with the physicochemical and biological characteristics to accomplish each of the desired functions. Undeniably, this has been the uphill battle for the translation of targeted particles into clinical practice, emphasized by the reality that the first targeted liposome was portrayed more than 20 years ago, still barely a few of systems have ever made it to clinical trials and none have yet been permitted for use. We anticipate that with the introduction of safer nanomaterials simultaneously with new engineering approaches that lead to optimally designed nanoparticles, we will be perceived by an expanded number of multifunctional nanoparticles invading the clinic eventually.

However, the future remains exhilarating and broad open. Additional approaches are required to revolve the theory of drug-loaded nanoparticle technology into a rational sensible application as the next generation of drug-delivery systems.

References

1. Sekhon BS, Saluja V (2011) Nanovaccines-an overview. International Journal of Pharmaceutical Frontier Research 1: 101-109.
2. Metcalfe SM, Fahmy TM (2012) Targeted nanotherapy for induction of therapeutic immune responses. Trends Mol Med 18: 72-80.
3. Demento SL, Siefert AL, Bandyopadhyay A, Sharp FA, Fahmy TM (2011) Pathogen-associated molecular patterns on biomaterials: a paradigm for engineering new vaccines. Trends Biotechnol 29: 294-306.
4. Salvador A, Igartua M, Hernández RM, Pedraz JL (2011) An overview on the field of micro- and nanotechnologies for synthetic Peptide-based vaccines. J Drug Deliv 2011: 181646.
5. Park J, Gao W, Whiston R, Strom TB, Metcalfe S, et al. (2011) Modulation of CD4+ T lymphocyte lineage outcomes with targeted, nanoparticle-mediated cytokine delivery. Mol Pharm 8: 143-152.
6. Kim JY1, Kim HJ, Hurt EM, Chen X, Howard OM, et al. (2007) Functional and genomic analyses of FOXP3-transduced Jurkat-T cells as regulatory T (Treg)-like cells. Biochem Biophys Res Commun 362: 44-50.
7. Sofi MH, Liu Z, Zhu L, Yu Q, Kaplan MH (2010) Regulation of IL 17 expression by the developmental pathway of CD4 T cells in the thymus. Molecular Immunology 47: 1262–1268.
8. Zhou L, Lopes JE, Chong MM, Ivanov II, Min R, et al. (2008) TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. Nature 453: 236-240.
9. Romagnani S, Maggi E, Liotta F, Cosmi L, Annunziato F (2009) Properties and origin of human Th17 cells. Mol Immunol 47: 3-7.
10. Ghoreschi K, Laurence A, Yang XP, Hirahara K, O'Shea JJ (2011) T helper 17 cell heterogeneity and pathogenicity in autoimmune disease. Trends Immunol 32: 395-401.
11. Hunt LC, Tudor EM, White JD (2009) Leukemia inhibitory factor-dependent increase in myoblast cell number is associated with phosphotidylinositol 3-kinase-mediated inhibition of apoptosis and not mitosis. Experimental Cell Research 316: 1002-1009.
12. Acharya S, Sahoo SK (2011) PLGA nanoparticles containing various anticancer agents and tumour delivery by EPR effect. Adv Drug Deliv Rev 63: 170-183.