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REVIEW PAPER

The Role of Nanoparticles in Gene Therapy: A Review

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ABSTRACT

Nanotechnology helps design innovative and effective medicine delivery methods. Different particle characteristics are used in targeted delivery to elicit therapeutic responses. Recently, gene therapy nanoparticles have interested researchers. Regardless of their different atomic structures, they can penetrate cell walls effectively. Encapsulating various genetic materials for treatment has resulted in effective cellular uptakes. Nanoparticles have some unique properties in biological and non-biological systems, and the alteration of some physical and chemical properties of materials, such as their toxicity, has put nanomaterials in the focus of researchers. In addition to its main properties, shredded nanoparticles and their effects on surface properties can be formed into materials with important and sometimes different biological activities. These particles also have properties of the surface causing those biological responses such as inflammatory effects, DNA damage, cytotoxicity, hormonal changes, and so on. Changes in the biological effects of particles are due to: (1) nanoparticles are closely linked to the biological system and thus can easily enter the biological system of the cells; (2) their structural properties, which suddenly change when nanoparticles lose their capacity. Because of this, these particles have biological impacts on biological systems and are employed in cancer therapy, plant hormone operation, gene transfer, cell labeling, organic absorption, imaging, and more. To innovate, nanoscience research must be Manus. In an attempt to show the amazing advances in gene therapy, this review will define gene therapy and the vital role of nanoparticles in packaging and transferring genes for cancers.

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INTRODUCTION

Nanotechnology has proven to be advantageous in the realization of site-specific and efficient drug and gene delivery systems to different parts of body directly, particularly cancerous cells. One of the significant fields of research in pharmacy and medicine is the probable application of nanoparticles (NPs) in gene targeting, particularly in cancer treatment and diagnosis [1]. Among the NPs, iron oxide NPs (IONPs) and gold NPs (AuNPs) can be of considerable interest in cancer treatments. Developing gene therapy has different great potential with respect to viruses which are common carriers. They have great value in

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transducing dividing and not-dividing cells with a low host immunogenicity and long-lasting expressions by gene–infection into target cells. However, viruses can not transfer large genetic materials, and their limited capacity for genetic material carrying [2].

In recent years, gene therapy has emerged as one of the most sophisticated strategies in the evolving field of modern medicine. The term gene therapy refers to an entire class of transformative technologies that are all designed to introduce specific momentary changes into the genetic sequences of an organism. Given the promise of these powerful techniques for countless diseases, the underlying lack of difficulties that is faced for natural evolution only points to a few short-term obstacles amid viral uptake, immune system responses, and limited tissue targeting [3,4]. For the diverse clinical applications and the enhancement of gene therapy treatments, CRISPR/Cas9 genetic engineering and development of non-viral gene delivery systems including NPs have attracted more attention recently and provide a solution regarding the design of better vectors till the problem of immune responses is being solved completely. Gene therapeutic treatments have the potential to revolutionize human healthcare, and their success or failure will be based on the ability of scientists and clinicians to achieve precise and efficient genetic manipulation inside the living organism, with minimal adverse effects due to off-targeting, immunogenicity, and toxicity [5]. In this study, most recent scientific articles are reviewed about the effects of NPs as carriers for gene delivery in different cancers.

Definition and History of Gene Therapy

The advent of the second generation gene carriers developed for gene therapy demanded new applications, and their main distinction from the classical gene therapy in the first generation depend on the localization of the genes of transferred information. In the first generation gene therapy, the arrangement of this gene information was associated with sequences supposed to be localized within chromosomal structures. In the second generation, all genetic information being transferred, either gene or fragment of genes, or any targeted sequences, are factorized in two categories, each of which include: (i) a sequence enabling the penetration and the introduction of the gene/sequence into the cell (transduction), (ii)

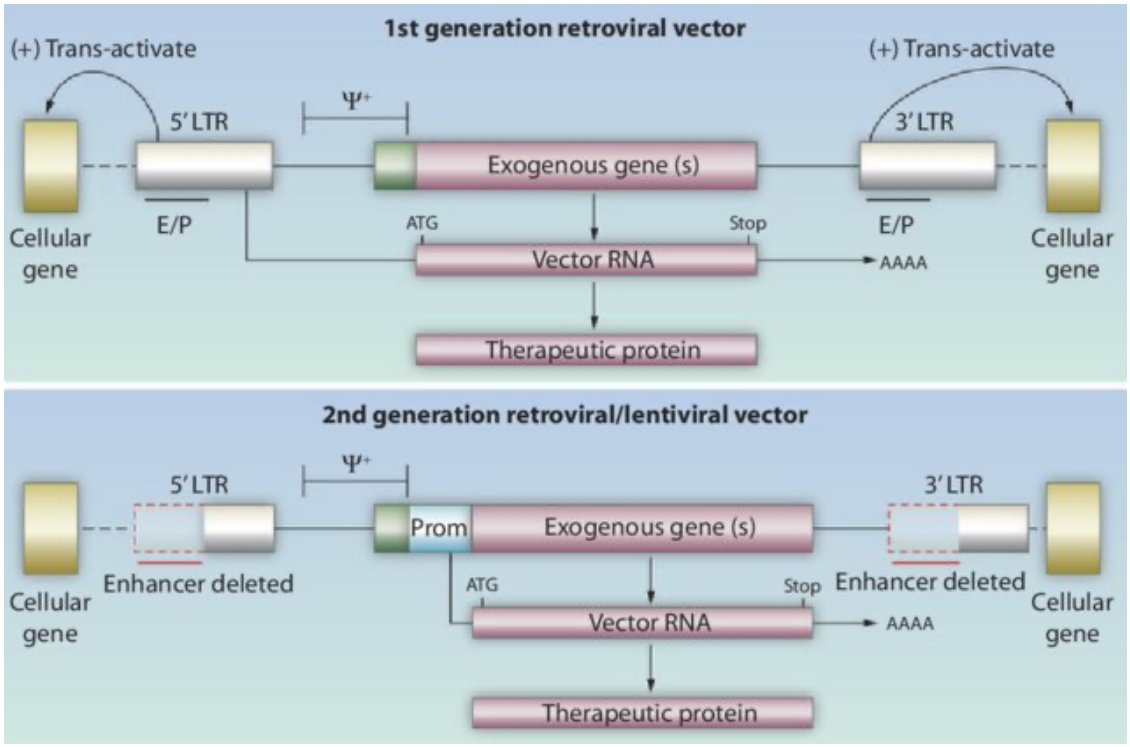

Fig. 1. First-and second-generation [10].

an expression specific part for gene in the form of a cassette, the expression of this sequence being regulated and taking place only in certain cells or tissues [6] (Fig. 1).

Gene therapy is the treatment of diseases by adding, replacing, or silencing specific genes of a patient [7,8]. Although materials that carry genes to the cells (termed as carriers) are crucial, they should be considered as part of a system that is set up to reach a specific therapeutic goal. For instance, the therapeutic goal may differ according to the disease; this implies carriers themselves should be designed based on the requirements of a specific application. There are numerous life-threatening and chronic hereditary diseases for which gene therapy may provide a solution. Viral gene therapy, somatic gene therapy, gene editing, immunotherapy, cancer therapies, and vaccines are different applications of gene therapy [9].

Types of Gene Therapy

Gene therapy, technically described, is understood by Friedmann as the use of genetic material to alter or modify a patient's genetic constitution, enabling them to resist and benefit from a broad range of disease processes without the introduction of exogenous material. Also it includes genetic or metabolic diseases and is classified into three basic types: Replacement, Knockout, and Knock-in, potentially based on the therapeutic aim [11]. Genes can be transferred *in vivo* by gatekeeper or nonviral vectors. Other genes can be transfected *in vitro* and returned to the host cell. A very strong player, at that time, in gene therapy, due to its profound influence, was observed a nuclear molecule that of DNA, which was demonstrated in 1972 by Friedmann and Roblin genes could be incepted into cells by a string of DNA. DNA has been most widely used to deliver genes to target cells because it is able to transfect both dividing and nondividing cells [12]. After the discovery of gene therapy in 1972 by Friedmann and Roblin, researchers were faced with a problem. According to [13], the researchers turned to using viral vectors, which have seen remarkable progress since this time. However, there is still a need for fine-tuning delivery systems to achieve specific therapeutic outcomes and avoid unwanted side effects.

Nanoparticles in Biomedical Applications

Gene therapy is the process of modifying cellular or extracellular genetic patrimony with the aim of curing a disease. To date, however, the clinical use of gene therapy has been limited by low transfection efficiency and the inability to systemically administer genetic material to the diseased cells within the human body. The most sought after gene therapy tools also should be biodegradable, controllable, and provoke sufficient immune responses *in vivo* [9]. NPs are a promising class of nucleic acid delivery vectors that can address many of these challenges. They can protect nucleic acids from degradation, increase their stability, mediate cellular uptake, release the nucleic acids, and may trigger cell-specific targeting. NPs are also biodegradable and can be tailored for tissue- or organ-specific delivery. NPs are the smallest unit of material that can be used to modify biological processes and are widely used in many fields, including biomedical applications. They have unique properties based on their nanometric size, such as a high phantom size, large surface area to volume ratio, tunable surface functionality, and tailored physiochemical properties [14]. NPs can be applied in drug targeting such as imaging, diagnostic, and therapeutic modalities [15,16]. Nanotechnology is the manipulation with substances at the level of approximately 10^{-9} m, with the primary goal of creating various devices with new mechanical and electrodynamic properties. Furthermore, several features make NPs excellent vehicles for gene delivery, including their ability to deliver a wide range of genetic material, their capacity to protect genetic materials from degradation, their low cytotoxicity, and their decreased immune response. Different types of NPs exist including carbon-based NPs, magnetic NPs, and polymeric NPs, and each has various advantages and disadvantages in gene delivery applications [12]. However, there are also other types of NPs, such as polymeric, liposomal or dendrimer NPs [17].

Overview of Nanoparticles

The introduction of the gene into the target cell involves a process known as transfection. For each gene, it can be carried out in virus form (viral vectors), in the form of non-viral vectors in various forms (complex-based, polymer-based or lipid-based) and by means other than the two preceding: Physical transfer through gene guns or electroporation found in clinical gene therapy so far only be an example of the Zolgensma tee

is an approved gene therapy [11]. Pluripotent stem cells (iPSCs) were created by three other genes—using *Oct4*, *Sox2* and *Klf4* from four [18]. Bioengineering is an emerging interdisciplinary field of research consisting of medical, chemical, electrical and mechanical problems, which, along with other challenges, also brings a number of ethical challenges [19].

Advantages of Nanoparticles in Biomedical Applications

One of the main challenges in designing cooperative drug/RNA delivery systems is to integrate materials with properties suitable for each of the encapsulated cargoes. As a consequence, the co-delivery of small molecule drugs and nucleic acids, siRNAs/miRNAs, mRNA and therapeutic mRNA presents a major frontier in this field [20] (Fig. 2). To this end theranostic nanomaterials featuring imaging modalities, eg FL, MRI, CT, have also been emerging in the context of gene delivery in the biological and clinical community [21]. Importantly, nanomedicines which incorporate RNA agents (various ncRNAs, antigene, mRNA, saRNA and shRNA) are perceived as the next-generation medicines for the treatment of cancer, infectious and immune diseases [22]. One of the key interests in advanced drug delivery carriers is to develop smart or activatable systems by which the release of therapeutic nucleic acid or drug occurs specifically at a passive or stimulus-driven active site with minimal side effects or off-target effects [23].

In health-related fields, NPs are celebrated for their properties such as high surface to volume ratio; distinct physicochemical properties, easy surface functionalization, targetability and therefore, are considered best suitable to deliver therapeutic gene molecules into the cells of interest [24]. A lot of detail-oriented investigations took place which subsequently resulted in the launch of a few nanoparticle-based products in the market to use for disease diagnosis and therapy. Specifically Camptosar (topoisomerase I inhibitor used for the treatment of cancer) and Renagel (4070 polymer) have been developed as examples of successful clinical advancements in NPs [25, 26].

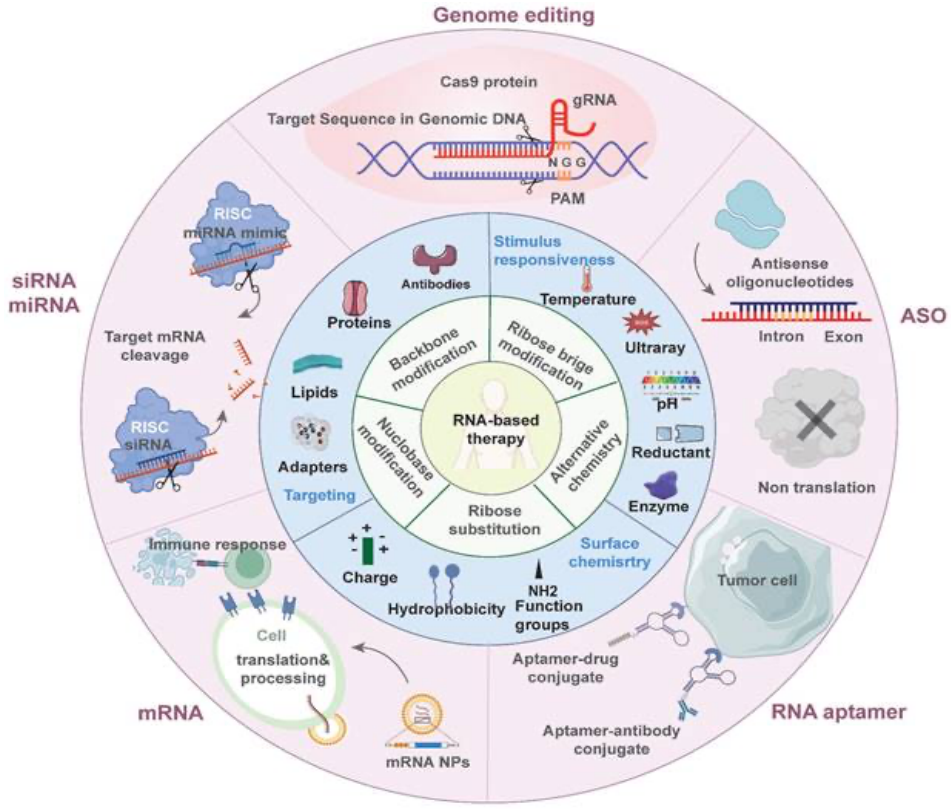

Fig. 2. Overview of RNA-based antitumor therapeutics [27].

Gene Delivery Systems

Gene delivery is a process to transfer exogenous genetic materials into living cells, which can be used as a biotechnological tool in gene functional studies. In the field of gene therapy, delivery vectors span from a simple plasmid construct in viral, nonviral, or cell-based delivery systems [28]. Both viral and nonviral strategies have some limitations, including immunogenicity (viral), low gene delivery efficiency (nonviral), and cytotoxicity concerns (both viral and nonviral vectors). Entrusted to nanotechnology, both the efficiency and safety concerns associated with these delivery systems can be addressed. Nucleic acid-based gene therapy refers to the therapeutic delivery of one or more functional genes or gene products to patients with genetic disorders, aiming to cure the disease or at least alleviate the symptoms. There are examples of success in gene therapy treating monogenic disorders; however, this does not hold for diseases involving multi gene/pathway dysfunction, which is often found in acquired, chronic, and complex diseases such as cancer, infectious diseases, and neurological diseases [29]. NPs are an essential component of gene delivery systems and nanotechnology is promising in this regard[11].

Viral Vectors

Various viruses such as human immune deficiency virus (HIV), hepatitis virus, parvovirus, and adenovirus have been tested to improve the treatment of various primary and secondary genetic disorders as well as gene therapy [30] Fig. 3. Due to their potential in evoking immune responses and insertion mutations in the genome, the clinical utility of these elementary vectors is limited [31]. In addition, these vectors have a small capacity for genetic transmission and are difficult to produce in large quantities. Therefore, aluminum antisense protection, virus transmission, and cell incorporation capacity have been applied [32]. Retrovirus, adeno-associated virus (AAV), and adeno-virus are the most stable viral vectors used in basic and clinical results, known as chromosome transduction vectors and non-viral vectors, respectively [33].

Though the majority of gene delivery techniques involve physically forcing uncomplexed nucleic acids through cellular barriers, gene delivery vehicles (also known as vectors or carriers) are entities that assist genetic materials in crossing biological barriers [34]. Gene delivery vehicles can be human or nonhuman, viral or non-viral, naturally or artificially occurring, and derived from chemical or biological sources. During the exogenous gene delivery process, genetic material is inserted into the viral vector and then delivered to the target cells, where it is released and expressed. The infected cells then transcribe and produce the encoded gene products, which function properly within these host cells, ultimately correcting the disease [35].

Non-Viral Vectors

Cationic polymers are a largely explored and attractive class of nonviral vectors acting as gene carriers. Several polymeric vectors are being studied for different applications, but the main ones are polyethylenimine (PEI) and poly (2-dimethylaminoethyl methacrylate) (PDMAEMA). PEI has a high cationic density that provides proton-buffering properties. These polymer capabilities are sufficient to facilitate prompt endosomal escape of polyplexes after endocytosis. Gene transfer efficacy and

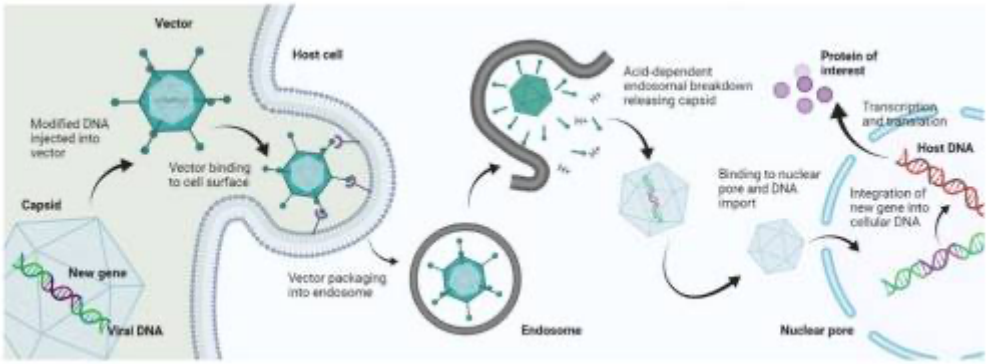

Fig. 3. Mechanism of viral gene delivery [35].

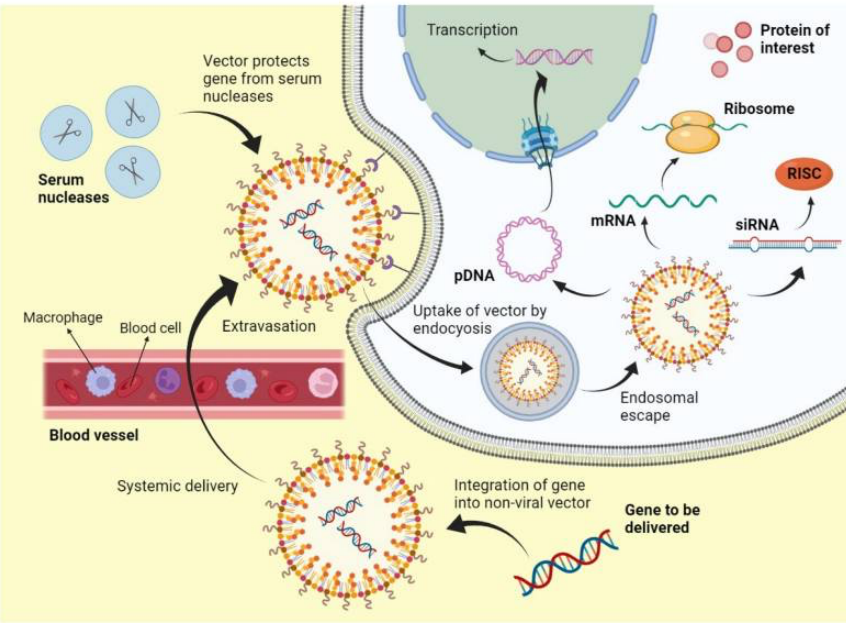

Fig. 4. Mechanism of nonviral gene delivery [35].

noncytotoxicity of their corresponding PEI-containing multiblocks have been confirmed in DA3–2-Lluc and TRAMP-C2 tumor models [36]. Polyion complex (PIC) micelles of stereo complex polylactide-polyethyleneglycol-block-poly(l-lysine) di-block copolymers were developed as a subtype of polymeric nanocarriers being able to condense large plasmid DNA into small sizes. First, their positive charges lead to electrostatic complexation with negatively charged genetic materials. Thus, PIC micelles were able to display rapid cellular entry. In the literature, these polymeric nanocarriers were also called stable and slow releasing carriers because of highly prolonged transfection activity [37]. In addition, non-viral gene delivery in medicine is increasingly recognized for its safety with limitation of relatively low efficiency of transfection [23] Fig. 4.

Nanoparticles as Gene Delivery Vehicles

NPs have been evaluated as promising gene delivery vectors owing to their simplicity of synthesis, low cytotoxicity, and ability to adsorb or wrap the nucleic acids on their surface with certain extent of protection under physiological conditions [38]. Among these, non-viral particles have widespread usage in the gene delivery process. The NP can offer distinct compacting and protection from intracellular nucleic acids degradation and overcoming various transport barriers, per se or in combination with another carrier to form nanocomplexes for improved efficacy, targeting, and controlled release of the therapeutic gene [21]. Polymeric, lipid, viral vectors are categorized on the basis of molecules from which they are made have their unique advantages and limitations; for example, polymeric NPs are known for their extended circulation time, targeted efficiency, and capacity to encapsulate both hydrophilic and hydrophobic drugs, whereas virus-based vectors have unfolded the targeted and sustained release delivery mechanism in gene delivery [36].

In viral gene therapy vectors, there is a risk of mutagenesis and trigger of an unwanted immune response in the recipient which can be reduced using NPs. In gene therapy, the functions of NPs are to stabilize the genetic material and protect it from degradation, target its specific site of action, and mediate the entry of DNA/RNA inside cells [39]. NPs offer several appealing features such as stimulus-responsiveness, easy manipulability, high transfection efficiency, controlled release profiles and subcellular targeting (Fig. 5) [40].

Properties of Nanoparticles for Gene Delivery

In the last decade, a significant contribution to the characterization of NPs in the biology of cells

has come from the field of biotechnology, called "nanomedicine", which opens up new innovation vistas for intracellular strategies, mobilized for combatting the onset and progression of various types of cancer [41]. Several critical factors about using NPs for anticancer DNA delivery, inclusive of cooperative vector/nucleic acid (NA) characterization, the requirements of a solid magnetic field for gene expression, and the necessity of using native promoters which are not degraded by histone packaging, remain elusive [34]. There is an imperative need to use future experimental studies with HIV in the heart of magnetically sensitive iron oxide core NPs that are transfected with a DNA plasmid that also includes a fluorescent protein or a luciferase reporter targeted to either a single or several cancer-related genes, or also to the HIV targets in individuals developed with AIDS [23].

The genetic materials are carried two routes including integrated DNA, which are predominantly used by viral vectors for gene therapy delivery and nucleic acid NPs (NAN) [42]. NAN comprises plasmids and viral genomes, wrapped by a self-forming core-shell composed of lipids, polymers, or inorganic NPs. The major mechanism of their gene delivery (i.e., to sustain their efficacy over time and elicit the best therapeutic response) comes from this core-shell composition, followed by the genetic content and the delivery protocol, in contrast with AAV or lentiviral vectors. NAN are easily produced in large quantity, are simple to engineer, and are non-genotoxic, thereby limiting the impact of NAN on the host cell genome [21]. NAN present other advantages over viral vectors, as they remain free of the problem of pre-existing immunity, and they can be renamed as platform carrier. Indeed, through simply changing the nanoparticle composition (host/target interaction), or the plasmid genome (i.e., choice of transgene for overexpression, silencing, gene editing, immunotherapy, CRISPR/Cas9) to be

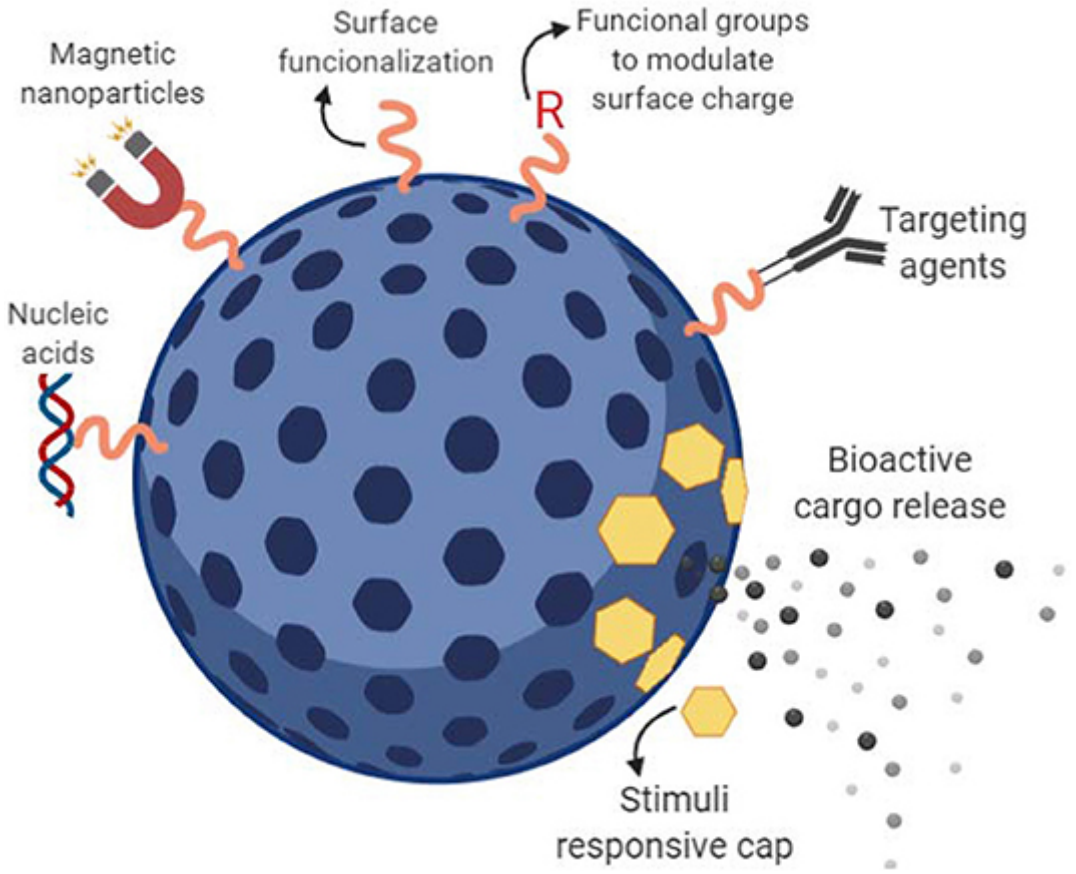

Fig. 5. Mechanisms of targeting and delivery of materials using NPs [40].

wrapped by the NAN the diversity of applications is clearly demonstrated [12, 43].

Types of Nanoparticles Used in Gene Therapy

Although virus vectors have shown wonderful gene transfection efficiency (in some studies, they can reach 90%), the possibility of invading the host organism poses a significant safety risk. This invasion has resulted in constraints for gene therapy and has highlighted the urgent need for the development of safe and efficient gene delivery systems [7] Fig. 6. Moreover, designing towards targeted therapy is a vital factor and additional studies shall be carried out to understand the interaction and fate of NPs in the biological fluids and cellular systems. Understanding the interaction of NPs with cells using different experimental methods (from room temperature to physiological temperature) is very important for future applications of these NPs in the human body [24]. NPs can be broadly classified into inorganic and organic types. Inorganic NPs include materials such as gold, silver, iron oxide, and silica. Organic NPs consist of lipids and liposomes, dendrimers, polymeric NPs such as chitosan, PLGA, and PNIPAM (poly N isopropyl acryl amide, a thermosensitive polymer), carbon nanotubes, and quantum dots [12]. Inorganic NPs are free from the risk of exposure to organic solvents and the degradation of genetic material inside the delivery system. This unique property makes inorganic NPs a safe and convenient delivery vehicle for gene therapy [44]. However, inorganic NPs may exert neuro-toxicity and inorganic delivery vehicles may fail to escape from the cell trafficking pathway resulting in the degradation of the internalized genetic material. In the case of organic NPs, the risk of toxicity and induction of immunogenic responses are less common. Organic NPs are easy to conjugate with ligands at the surface for targeted gene delivery compared to inorganic particles. However, the problems of poor biodegradability and in vivo instability limit the applications of organic NPs as gene carriers [45].

Key Considerations in Nanoparticle Design

Responsive NPs (Fig. 7) provide important possibilities for the regulated release of nucleic acid payloads in a heap of malignancy cell similar to physiology and pathology. This unlocks the door for flash treatments for malignancy as genes that otherwise are lethal to unrestricted cells can be shown to unified a material of regulatory tethering but no encrusted amounts of the

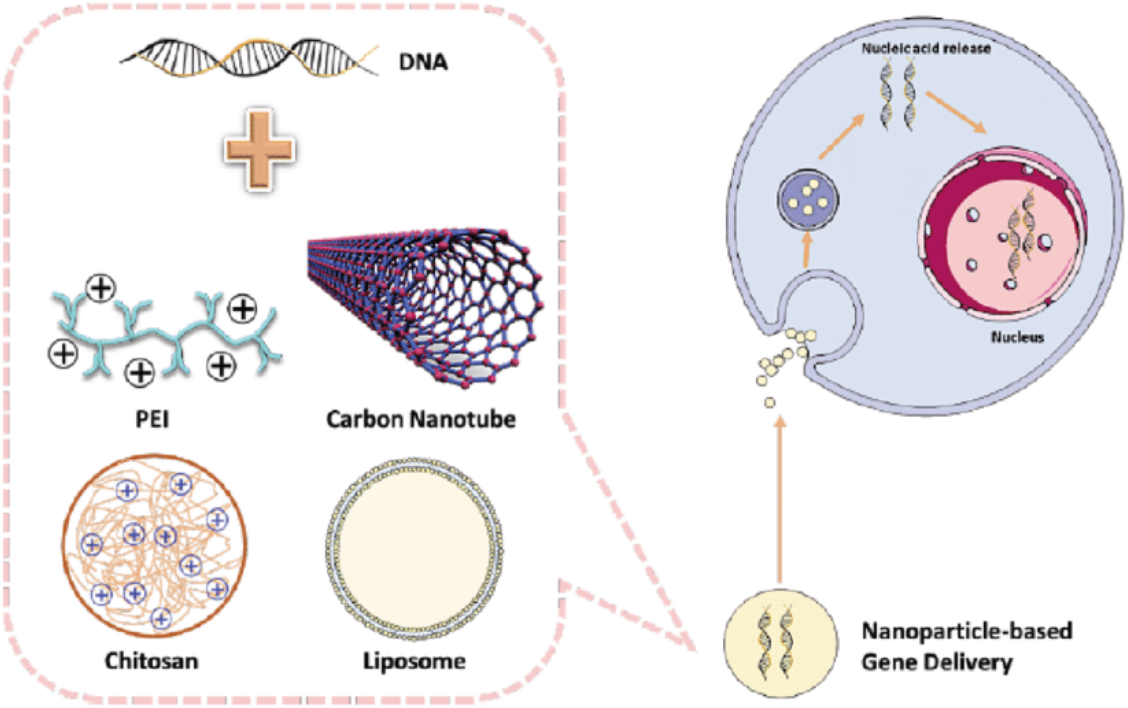

Fig. 6. Various NPs for gene delivery [46].

relevant nanoparticulated toxic dose [47]. As a result, packing-turning-off gene therapeutics are notable to improve gene treatment safety posed by non-tumor cell cytotoxicity. These possess dimers such as polymers, lipids/liners, carbon based materials, gold convert substances, drivers wear money agents, metal oxides, and geological minerals [48-57].

Nanoparticle engineering is essential for installation into gene delivery applications to improve intrinsic stability, sustained gene release, and intracellular transport, as well as its ability to internalize target cells both *in vitro* and *in vivo* [21]. NPs with a diameter >100 nm are negatively correlated with their yield in most of the cells due to low particle uptake, whereas smaller particles (40-nm size) are taken up, being more effective for plasmid delivery [9]. The cost and complexity of NPs preparation, quantification of optimal therapeutic agent dose, photo/chemical convergence before gene reach, inadequate specific delivery with a cumulative accuracy, and apoptosis mechanism exploitation for cancer therapy are all needed [58]. Moreover, food and drug administration perception through the regulation of toxicity and clearance programs, the availability of protective forth, and government regulatory support are important to take preventive measures for their efficient use.

Size and Surface Properties

Strict control of the size of NPs is necessary in experiments Fig. 8. Smaller particles <100 nm curved in plasma dispersion medium are accumulated in lymphoid and reticuloendothelial organs (spleen and liver) and trigger rapid clearance from the bloodstream [60]; intermediate particles (100–300 nm) infer the

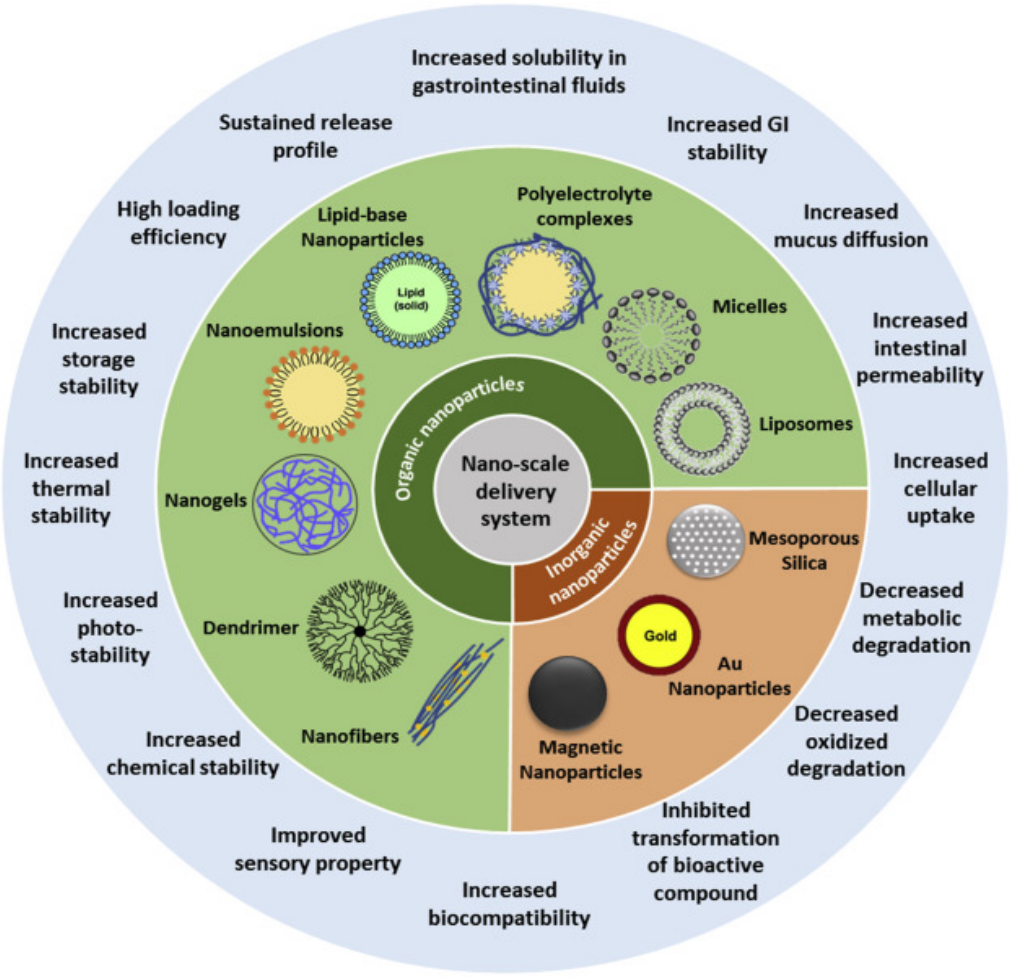

Fig. 7. Design of various nanoparticles and its effects on encapsulated bioactive compounds [59].

highest selective accumulation in tumoral tissue; and greater particles with a hydrophobic nature hasten alternating from the plasma to the tumoral interstitium but atomize in the interstitial space and scarcely penetrate into the tumor. To increase the selectivity of the entrance of mesenchymal tissue cells at the tumor place, it is important for particles to have a size of <300 nm. Hence, NPs measuring between 100 and 300 nm have critical importance in *in vivo* targeting [61]. All of these studies on NP delivery provide a general idea of what is most possible for gene delivery through physiological properties.

NPs should have specific characteristics for effective gene delivery [1,62]. Indeed, NPs on the order of 10–100 nm and possessing cationic ligand, autofluorescence, and antigen role properties are effective in gene delivery. Selecting the suitable size of NPs results in invariable cellular distribution patterns in different specific tissues, lower hepatic clearance, and controlled renal filtration within the sites of interest [63]. The administration of NPs with a zeta potential of 15–30 mV helps to obtain more effective gene loading and a charge balance between NPs and gene; besides, as it is more convenient to protect gene from nuclease degradation [24]. Longitudinal studies reveal the decreased efficacy of particles with positive zeta potential due to their aggregation. Influences of the size and surface properties of NPs on *in vitro* and *in vivo* gene delivery are also substantial.

Biocompatibility and Biodegradability

NPs-base gene therapy enhance the efficiency, decrease the adverse immune responses and increase the cellular uptake of the genetic material. The biocompatibility and biodegradability of a nanoparticle depend on the physico-chemical and biological properties, and their effect on the intended approach in nanomaterial design for different biomedical applications [65]. The particles could be degraded in the environment based on the physico-chemical properties of the nanoscale materials such as surface, structure, size, and shape. The biodegradation of metallic NPs may lead to the release of toxic ions in the cellular environment that may induce cellular toxicity [66]. Novel metal, metal oxide, and hybrid NPs combined with polymeric, lipid, peptide, or protein-based NPs for gene delivery have been developed and are commonly used in addressing the limitations in the gene delivery processes [54].

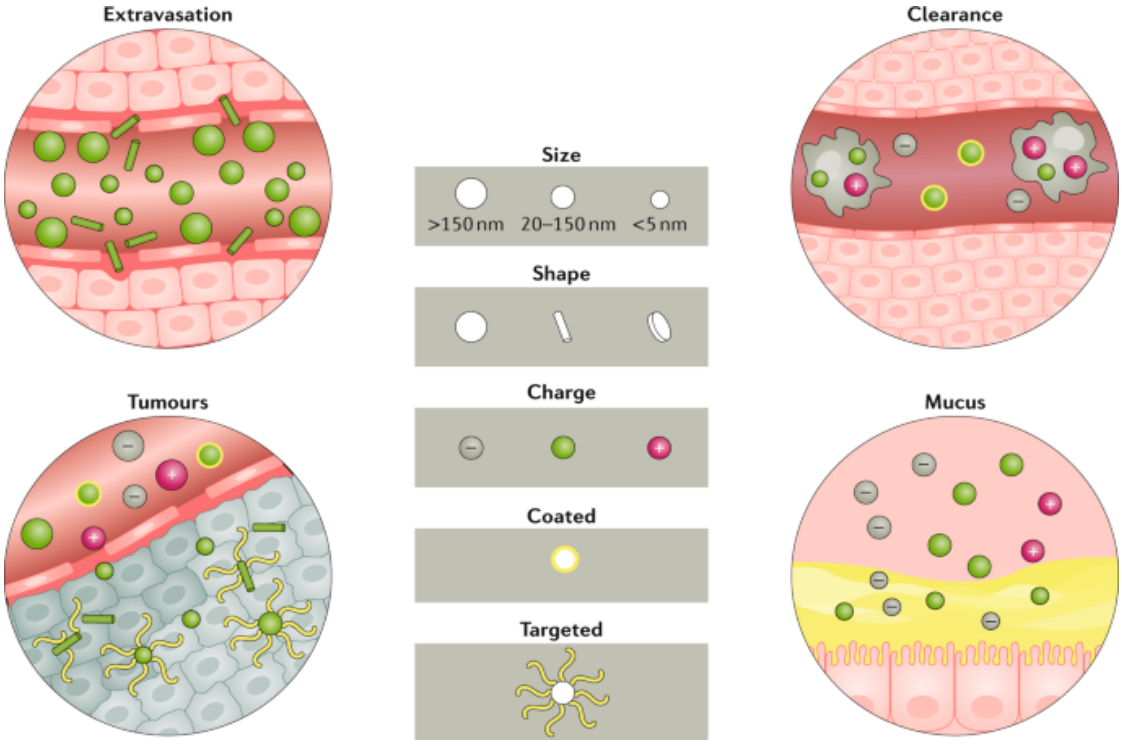

Fig. 8. NP characteristics impact distribution [64].

The synthesis, properties, and challenges with respect to the gene delivery aspects of the NPs are outlined [67]. Nanomaterials offer particular interest in biomedicine due to the target delivery of drugs, increased therapeutic efficacy, reduced toxicity, specific tissue interaction, and improve the diagnosis and treatment of many diseases [86-70]. Among them, metallic NPs are commonly exploited in gene therapy. Gene therapy implies the treatment of genetic diseases and currently, nanomaterials are developed to target all the major genetic disease therapies which include cancer, hereditary, and infectious diseases [29,97].

Applications of Nanoparticles in Gene Therapy

Nanotechnology and particles have been effective tools in the design of novel and efficient drug delivery systems [14,71]. These particles, with various features, can be used in targeted delivery and achieve desired therapeutic responses. Regardless of their different atomic structures, they can penetrate cell walls effectively. Encapsulating various genetic materials for treatment, these materials showed excellent cellular uptakes [72]. NPs have some unique properties in biological and non-biological systems, and the alteration of some physical and chemical properties of materials, such as their toxicity, has put nanomaterials in the focus of researchers [29]. In addition to its main properties, shredded NPs and their effects on surface properties can be formed into materials with important and sometimes different biological activities. These particles also have properties of the surface causing them biological responses such as inflammatory effects, DNA damage, cytotoxicity, hormonal changes, and so on [73]. Changes in the biological effects of particles are due to closely link to the biological system and facilitated entrance into the cells biological system, and structural properties, which rapidly change when NPs lose their capacity. These traits have caused their various potential effects on biological systems and thus, have different biological uses such as cancer therapy, plant hormone operation, gene transfer, cell labeling, organic absorption, imaging, and so on [74,98].

Cancer Treatment

NPs have gained wide attention as gene delivery systems Fig. 9, especially for transfection with

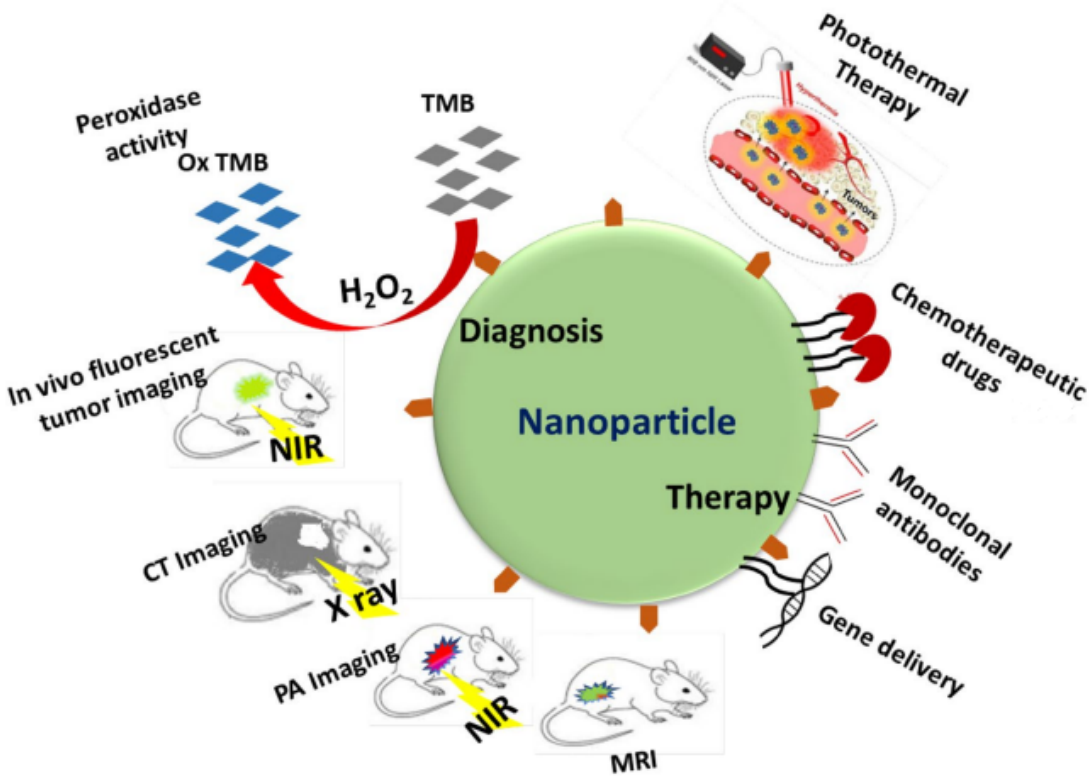

Fig. 9. Various applications of nanoparticles in diagnosis and therapy of cancer [80].

additional breast cancer-associated genes. These NPs have demonstrated proper efficiency and low toxicity profiles [54]. Recently, Tyrosine kinases are molecular targets for the treatment of lung cancer, non small cell lung cancer, ovarian cancer, as well as squamous cell carcinoma and adenosquamous carcinoma of pancreas, which are prensently under active investigation and phase III in many clinical trials for solid tumors and acute myeloid leukemia [75]. The choice of targeting against the EGF R is due to the fact that its activation along with activated RAS signal transduction is an important feature of the pathology of pancreas cancer. It is clear that by using a vector which can deliver therapeutic genes to the most cancerous cell and consequently can induce suitable pattern of chemotherapy, the selection of an antimalignancy strategy with minimal adverse effects will be possible. These works open up much brighter perspectives for tumor control and higher quality of life in patients with pancreatic cancer [76].

Recently, gene therapy has shown the potential to target undruggable genes, providing an effective alternative strategy to conventional drug treatments in cancer. The gene therapy can achieve tumor-killing efficiencies by modulating the expression of proapoptotic, antiangiogenic, and tumor suppressor genes while also modulating the expression of oncogenes and drug resistance-related genes [77,78]. However, gene therapy has challenges attributed to the characteristics of nucleic acids such as stability, immunogenicity, poor intracellular performance, and nontargeted nature. To overcome these, the effcient transfer of chosen genetic materials to target cells and the achievement of adequate gene expression levels without causing adverse effects on the hosts must be translated. Currently, various nonviral vectors have been utilized in gene therapy to target cancer cells by encapsulating or conjugating the genetic materials of interest, effciently introducing them to target cells, and subsequently inducing high level of gene expression [79].

Genetic Disorders

Despite the fact that only a few nanomedicines have ultimately demonstrated significant clinical efficacy, advantages of non-viral nanosystems make them attractive tools in cell and gene therapy [81]. Gene therapy may have therapeutic potential for various chronic disease states, particularly genetic disorders [37]. Genetic diseases involve the addition or deletion of small areas of the genome, or point mutations that can result in non-functioning proteins and lead to abnormal gene expression, which often have serious consequences for the afflicted person. These diseases can be caused by single mutations in a single gene, though complex genetic disorders can also occur as a result of altered expression in a combination of genes; this makes development of simple gene therapy strategies more difficult [82,83]. Nanotechnology can provide solutions to such complex therapeutic challenges in the context of genetics and gene therapy treatments.

RAPD Fingerprinting

RAPD (Random Amplified Polymorphic DNA) fingerprinting is a PCR-based technique in molecular biology that identifies and estimates the genetic relationship of closely related organisms . The use of fingerprints in general to identify bacteria has a promising future [84]. Most of the properties of different types of nanoparticles (NPs) depend upon changes in nanoparticulate size with respect to the bulk. Evaluating the properties of NPs is more difficult compared to bulk, locations, and aggregation. Thus, it is difficult to measure the properties of these NPs and their reactivity with biomolecules, specifically ligands mainly in organ targeting, drug delivery, and gene transfer functions. Basically, the methods used for the assessment of the characteristics of NPs are microscopic, diffraction, and light scattering methods, as well as small angle scattering, such as X-ray diffraction, Fourier transform infrared spectroscopy, transmission electron microscopy, Brioux Scattering, and dynamic light scattering methods. These methods are also used for the measurement of crystal structures of single-layer molecules and ion trafficking (usually as glycoprotein channels in the bulk and specifically those incorporated in the tethered lipid membrane or in the lipid glyco-coated vesicle). The above methods have been studied, but the need for their application was repeatability and ability for less meticulous applications. Thus, the above methods are not so useful for the assessment of free ligands for evaluating their properties [85]. Therefore, the aforementioned techniques are required for nanoparticle (free ligand) characteristics and also used for receptor or membrane characterization. So, the amplification of random polymorphic DNA/polymerase chain reaction is one of these

techniques that can be used for these applications. In biological systems, random amplification of polymorphic DNA (RAPD) fingerprinting can be used as a PCR-based marker for gene therapy studies [86].

Challenges and Future Directions

In real clinical trials, researchers have realized that few nanotherapeutics are available in the market due to numerous traps toward their development in the clinical phase. The difficulties include, but are not limited to, synthesis issues, amplification of the NPs, difficulty in achieving the scale-up process, toxicological assessments, immunological concerns, biodegradability of NPs and their by-products, excessive costs, ethical issues regarding the use of nanoparticle-based investigational new drugs (INDs) in clinical trials, and the immense work related to undergoing different phases of the trial [87]. In addition, incorporating different multiple identities of the NPs functionalized with diverse protein ligands might trigger a cytotoxic reaction. It is also essential to notice the stability problems linked to the physiological liquid medium, cells, and nanotherapeutic agents within the biological system [88]. Irrespective of these difficulties, the wheel of clinical trials is actively revolving. Also, the present storages to induce mechanisms that can accomplish the block of metabolic pathways, defy drug resistance, continuous drug release, deliver anticancer agents, and offer cheap strategies are needed on an urgent basis [89-91]. Before considering the potential clinical trials and nanomedicines, plenty of challenges have to be overcome [1].

Current Challenges in Nanoparticle-Based Gene Therapy

Regarding the gene therapy, an ideal vector should possess the following properties: availability of optimal gene expression for an extended period; ability to maintain and deliver an integrated transgene in every cell, including mitotically inactive cells, such as neurons; minimal or no interference with endogenous gene expression; targetable and nontoxic; and safe from inducing an immune or inflammatory response. In the future, efforts to modify and incorporate novel biomaterials may be helpful to develop multifunctional vectors for delivering genes. So, efforts should be taken to concentrate on the suitability of NPs or engineered systems by identifying specific NPs for a disease, knowing the gene expression, stability to genes and NPs, biocompatibility and clearance from the system of what will be the key for improve gene delivery to cancerous and noncancerous tissue also. Despite the several exosome-based delivery systems available, one of which is nanoparticle based and efficient to deliver the cancer gene therapy. Even if the technology used here on is not quite established, followed by the cell type and bioengineering requirements, the promotional materials used still have extrusive practices on what has been reported. The crepes will improve incrementally. Such cooperation is also vital so that in a short while, these therapies might be firmly grounded in cancer control and prevention [1].

Gene therapy holds promise for treating genetic diseases, cancer, and certain viral and fungal infections, but highly efficient and noninvasive transfer techniques are essential. Nonviral gene transfer systems based on various types of NPs (NPs) are suitable for gene delivery. Despite their ability to effectively transfer genes into cells, using NPs for effective gene delivery in clinic is still challenging and many potential artists remain to be addressed before the technology is ready for widespread medical use [4]. The size, composition and structure of NPs affect their functionality and efficiency for gene delivery. Therefore, developing improved particles for better gene therapy is vital. The characteristics that are taken into consideration for an NPs for developing exceptional NP for gene delivery are ability to protect the genetic material from nuclease and clearance from the body's system, cellular internalization, being able to cross vessel barriers (Fig. 10), and a large production and scale able to production for GMP condition at a low cost. Several challenges still in order to optimize the nanoparticle and increase its banker for clinical trial a few are stability, polydispersity and particle pollution. The key to overcome these challenges are in the synthesis of the particle itself where we should keep its important structural conformation and not changing the genes replication capacity or a structure itself to maintain the mass.

Future Prospects and Innovations

Gene therapy is a permanent treatment target but still, its clinical success is limited due

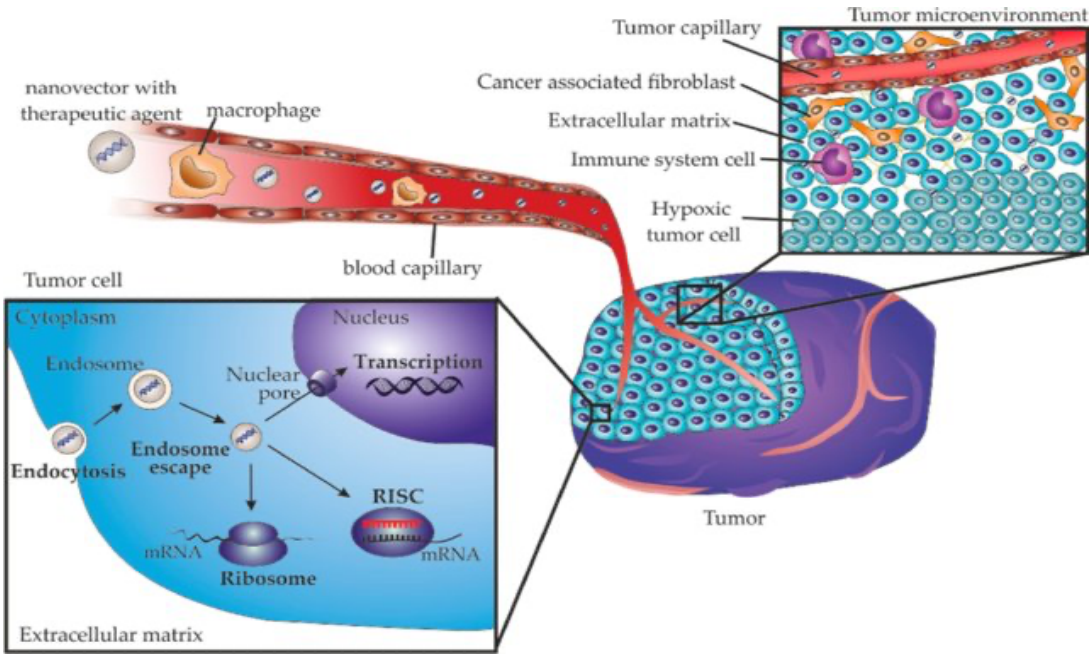

Fig. 10. Barriers that nanoparticles must overcome for effective cancer gene delivery [92].

to uncontrolled gene editing with relatively low transfection efficiency and off-target effects [93]. NPs (NPs) offer solution that effectively transfect therapeutic genes into targeted cells with minimal toxic effects of transfection [12]. NPs are made up of polymeric, lipidic, metallic, and hybrid particles that have been successively used in various applications including imaging, diagnosis, treatment, stem cell, and gene therapy [94]. Developing NPs-based gene delivery systems, could be the promise treatment of neurological diseases, a new way to treat patulous Eustachian tube, phenotype generation of disease resistant goose, treatment of osteochondritis dissecans, and many more [95].

CONCLUSION

Effective gene delivery, cellular uptake and induced endosomal escape have long been identified as the three major barriers to safe and effective gene therapy, particularly for the complexities of solid tumors. In addition, effective deliverance of genes into solid tumors needs to overcome, such as stimuli-secure, controlled gene release from the vehicle, biological compatibility, blood clearance, and accumulation at the target sites sufficiently, and fast internalization. So to improve cancer cell anticancer effect of NPs, strategies such as multistage activated NPs, tumor targeted NPs, combination or even alternation chemotherapy, and gene therapy are frequently used, and the same time cancer cell survival apoptosis, tumor metastasis, and crosstalk silence have not detoured from the aim of achieving successful cancer therapy. The mechanism of NPs as effective gene carriers and cancer therapy has been discussed based on gene therapy.

Combining disease diagnosis and therapy through genetic engineering of immune cells designed to attack malignant cells — or so-called T cell engineering — appears to be a more effective treatment in cancer research compared to more traditional surgery, radiotherapy, or chemotherapy [96]. Given the high toxicity of the aforementioned treatment options and the development of resistance, especially in cancer, this treatment strategy lead to revolutionary advances in dealing with clinical problems and patient prognosis. In fact, engineered T cells have been unitized to better manage diseases, from the treatment of autoimmune disease to the cultivation of solid tumor focus. T cell engineering is already ongoing to target tumor marks generated from the generation of diverse products in short-lived cells, particularly active molecules or so-called CAR-T cell therapy. In our review, the roles of NPs

in packaging and transferring genes for cancers.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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