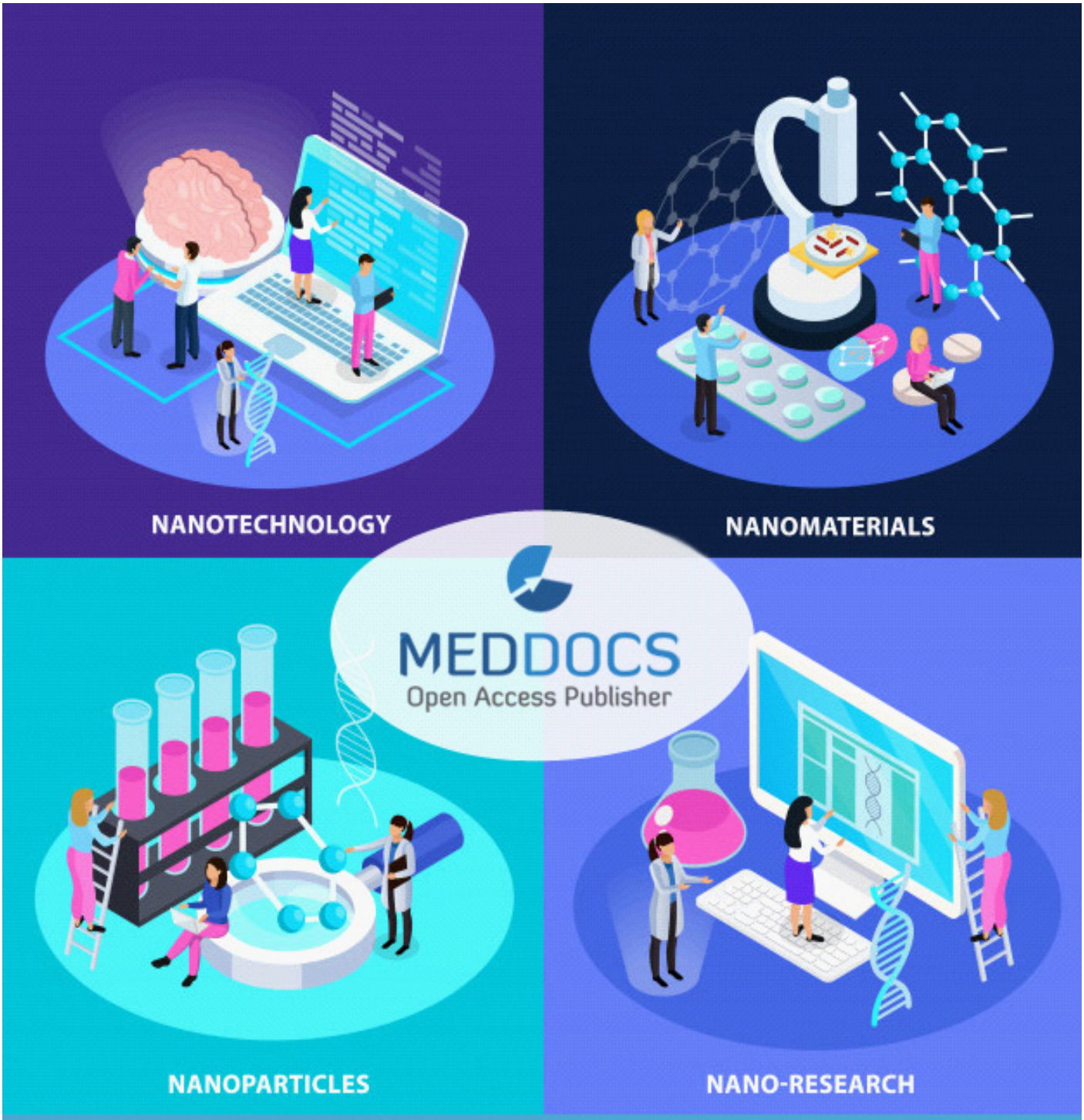

IMPORTANCE & APPLICATIONS OF NANOTECHNOLOGY

Role of Nanotechnology in Cancer Treatment

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Abstract

Everyone is living in a fat city, with the advancement of luxuries in lives; there is also an elevation in lifestyle-related disorders. Cancer is one of the leading causes of mortality which is the result of unhealthy practices in daily lifestyle. Although extensive techniques are in use for diagnosis as well as treatment with intention of reduction in death rate, chronic pain, and improvement in the life of riley. An amalgamation of cancer therapy with nanotechnology proves to be an effective solution for this dire situation. Nanotechnology along with the diverse conventional therapeutic techniques imparts eminent outcomes. Alteration with diverse varieties of nanoparticles like gold nanoparticle, quantum dots, nano biochips, etc. in the drug delivery process, chemotherapy, and photo imaging techniques are either completed or going through clinical trials and their preliminary results are quite promising. Besides the considerate impact of nanotechnology in treatment, it manifests efficacious in initial stage screening as well as in diagnostic therapies. This chapter intends to highlight the emerging beneficial impact of nanotechnology in cancer research. While elevation in success rate, as well as abating the repercussion of diagnosis and treatment, will remain the main objective of the merger of nanotechnology with cancer.

Introduction

Any technology contrived at the nanoscale and evinces relevance in today's scenario referred to as nanotechnology. It entails reshuffling and reorganization of matter in size extending up to 1 to 100 nm [1]. Divergence in properties of matter was perceived at the nanoscale and the larger scale. At the preliminary stage, properties remain unvarying, but as the size descends below 100 nm, dire repercussions in properties were noticed. Novel and commercial applications of physical and chemical properties of nanoparticles can be maneuvered for the welfare of society [2,3]. Nanotechnology comprehends two foremost overtures: Top-down and bottom-up. The top-down approach incorporates the diminution of larger structures into smaller parts in absence of atomic-level control. It avails lithographic and non-lithographic technologies which are used to formulate components ranging from micro to nanometer. The bottom-up approach encompasses materials fabricated by molecular and atomic elements through self-assembly, roll to roll processing, chemical synthesis, etc. [4].

Nanotechnology is a multifaceted field that collaborates with other discrete fields like material sciences, pharmaceutical sciences, mechanical and electrical engineering, colloidal sciences, applied physics, supramolecular chemistry, etc. Nanotechnology is the augmentation of contemporary sciences into the nanoscale [5].The eminence of nanotechnology in biology is attributable to its minuteness and targeted results. Nanoscale devices are much smaller than human cells. The smaller size and relatively larger surface area than volume give an edge to nanoparticles to correspond to receptors and enzymes on the inside as well as outside of the cell surface. Nanoparticles easily anticipate diseases and dispense treatment at the micro-level. Nanoparticles are formulated from enormous materials like gold, silver, Silicon Dioxide (SiO_2), Titanium Dioxide (TiO_2), lipids, carbon nanotubes, etc. Nanowires and nanoshells are some other tools used as biomarkers [6].

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Cancer is one of the primes beget of mortality, yearly around 10 million people are affected by this disease. Cancer is a highly convoluted and incomprehensible disease. The most familiar cancer ministrations are confined to radiation, chemotherapy, and surgery [7-9]. A crucial issue with cancer therapy is the obliteration of cancer cells, with minimum damage to normal cells. Cancer nanotechnology is emanating as a futuristic and propitious field of multidisciplinary research, which leads to vital proceedings in cancer revelation, diagnosis, and treatment [10] (Figure 1).

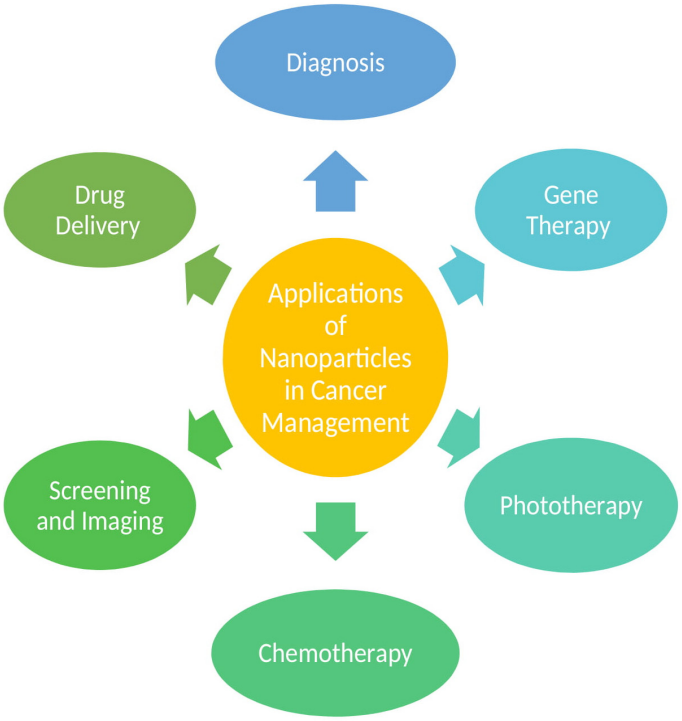

Figure 1: Applications of nanoparticles in cancer management.

Nanotechnology-based cancer theragnosis

Combining diagnosis and therapy in one process is an emerging biomedical method referred to as theragnostic. The primary goal of theragnostic is to selectively target-specific (diseased) tissues or cells to increase diagnostic and therapeutic accuracy [11]. With the help of theragnosis, we can bring together key stages of medical procedures, such as diagnosis and therapy, and make treatment shorter, safer, and more efficient. Several theragnostic methods have employed nanoparticles as the carriers of diagnostic agents and drugs [12]. With the upcoming researches, biocompatible nanoparticles have emerged as a better option for theragnostic treatment, due to its noninvasive diagnostic properties as well as it evinces as faithful cancer therapy. Additionally, nanoparticle-mediated combinatorial strategies also promise faster treatment meanwhile the side effects of treatment were also diminished and further results in improved cancer cure rates. Lukianova-Hleb et al., [13] (2010), have studied the optical generation and detection of plasmonic nanobubbles (PNBs) around gold nanoparticles in individual living cells, with the focus on tuning the PNB properties in one cell and evaluating the multifunctionality of the PNB. Several reviews have discussed engineering designs, physicochemical characteristics, and biomedical applications of magnetic nanoparticles and aided that magnetic nanoparticles can simultaneously act as diagnostic molecular imaging agents as well as a drug carrier [14]. Shim et al., [15] (2010) used gold nanoparticles coated small-interfering-RNA-encapsulating polyplexes covalently by acid-cleavable linkages for diagnosis and therapy of cancer. They studied combined stimuli-responsive multimodal optical imaging and stimuli-enhanced gene silencing. Thus, these theragnostic techniques seem to provide propitious results and can solve various muddle problems for an oncologist [16].

Nanotechnology-based cancer diagnosis

For any diagnosis process, screening is one of the most crucial steps. An effective screening at the initial stage can lead to lessen the ill effect of that disease. Cancer is a set of diseases formed by abnormal growth of cells which leads to the formation of the tumor. During metastasis, the development of secondary malignant growths occurs at a distance site apart from the primary site of origin of cancer. This becomes one of the main reasons for the late detection of disease and at later stages cancer becomes incurable or the success rate for cancer cure becomes poorer [17]. Therefore, screening and early diagnosis play a significant role in effective treatment and lowering of cancer mortality rate. The conventional method for diagnosis of cancer utilizes various scanning techniques which usually provide signified results after the substantial growth level of the tumor and consequences of metastasis were analyzed [18]. Consequently, early detection of cancer should be the priority. And for this purpose, we can take advantage of the unique property of nanoparticles. Due to their minute size, they can enter the cell and assess various working mechanism at molecular as well as genetic levels and that will help in early diagnosis of any kind of defects in functioning moreover which is possible both *in vitro* as well as *in vivo* [19]. For detection of cancer, various imaging techniques are manipulated using nanoparticles which can provide information at the molecular and subcellular levels and hence, helpful in tracking diverse biological pathways. The deviation of these biological pathways from their normal mechanism could help in discovery of several initial features of cancer establishment and for various disorder detections. The established imaging techniques like Computed Tomography (CT) scan, photoacoustic imaging, and various biomarkers which can be further helpful for diagnosis of cancer, are manipulated with the help of nanotechnology. The CT scan is used for early-stage cancer detection and it helps accomplish sensitive result and also the accuracy of these techniques is commendable [20]. Although CT scan contrast agents such as small iodinated molecules are effective in absorbing X-rays, non-specific distribution and rapid pharmacokinetics have rather limited their micro-vascular and targeting performance. Therefore, for diagnosis and treatment, more emphasis is provided to non-invasive techniques because with them there are lesser chances of any kind of harm to the normal body functioning [21]. The various photo imaging techniques are used as these imaging techniques are substantially non-invasive in nature as well as these provide high contrast image for cancer diagnosis, besides possessing properties for optical imaging and the penetrability of ultrasound imaging. Zhang et al., [22] (2018) diagnose significant antitumor application of gold nanoparticle containing three functional components that are gold nanoparticle with photoacoustic effect and which can be used in the drug delivery platform, DNA to load Doxorubicin (DOX) and folate functionalize. These properties of nanoparticle are availed as the appropriate wavelength is used to enhance the photoacoustic imaging as well as to determine the different expression levels of various cancer cells using gold nanoparticles which are further detected by real-time photoacoustic flow cytometry. An evaluation of these circulating cells labeled with gold nanoparticle is

done together with threshold sensitivity [23,24].

Artificial intelligence is an emerging field that can solve various problems in a diverse field of medicine. Artificial intelligence and nanotechnology together provide one of the prime leading techniques that have remedial aspects for cancer. By using biomarkers we can draw a rough route map of functional proteins by which we can determine the various activities occurring in a cell. When these biomarkers are attached with some nanoparticles like nano-wire or nano-biochip proceed as a promising developmental technique that can be used for the early diagnosis and treatment purpose of cancer. These particles are supremely sensitive as well as selective in their functioning and hence, provide an accurate result of diagnosis and solve the sole purpose of using nano techniques for the diagnosis of cancer at an early stage which can be applicable in eradicating this disease on time [25].

Hence, early detection is very crucial for the further processing of treatment of cancer as this will help the oncologist in selecting the suitable therapy for a particular patient according to the stage, category, and criteria of cancerous infection in that patient. Correspondently, with early detection, we will be able to get real-time information about the effectiveness, sensitivity, and specificity of the ongoing therapeutic techniques. Thereby nanotechnology proves to be effectual in cancer diagnosis and which forecasts promising results. And further assessment of potency of technique for the patient or there is a need to switch to some other technique which can provide better and immediate effects is evaluated [26,27].

Nanotechnology-based cancer treatment

Conventional cancer treatment is surgery by which we remove the cancerous part. However, cancer may appear again, also surgery is not possible for all types of cases of cancer. Other options to relay are radiation therapy, drug therapy, and chemotherapy, but these therapies came along with extensive side effects with which patient has to suffer for long period and these approaches also affect healthy cells.

However Nano-techniques are designed in which certain Nanoparticles can preferentially absorb a definite range of wavelength of radiation, which aims to be heated eventually and hence when such Nanoparticle enters in the cancerous cell, it will burn. Various therapeutic agents are in use by which we can target and toxicate cancerous cells [28]. However, there are certain NPs which circulate through the body and detect cancer-associated molecular changes and further assists with imaging release of a therapeutic agent, and then monitor the effectiveness of the intervention. The demand for techniques which provide minimal side effect and with higher specificity led to move toward Nanotechnology-based therapies. Still, certain problems need solutions, like improvements in molecular therapy so that nanoparticle can circulate in the bloodstream and reach the desirable cells without being detected by the immune system [29].

Nano-technology based drug delivery in cancer

Nanotechnologies, mostly based on nanoparticles, can facilitate drug delivery in cancer. Nanoparticle mediated delivery of conventional cytotoxic drugs allows control over drug cytotoxicity based upon the bio-distribution profile for the nanoparticle rather than for the free drug [30,31]. NPs based Drug delivery system also increases the half-life of vulnerable drugs and proteins and improve the solubility of hydrophobic drugs that proves to be effective in drug bases therapy also [32]. For more effective drug delivery various aspects of science and technology implies association of drug delivery with nanoparticles, some of them are mentioned in Figure 2.

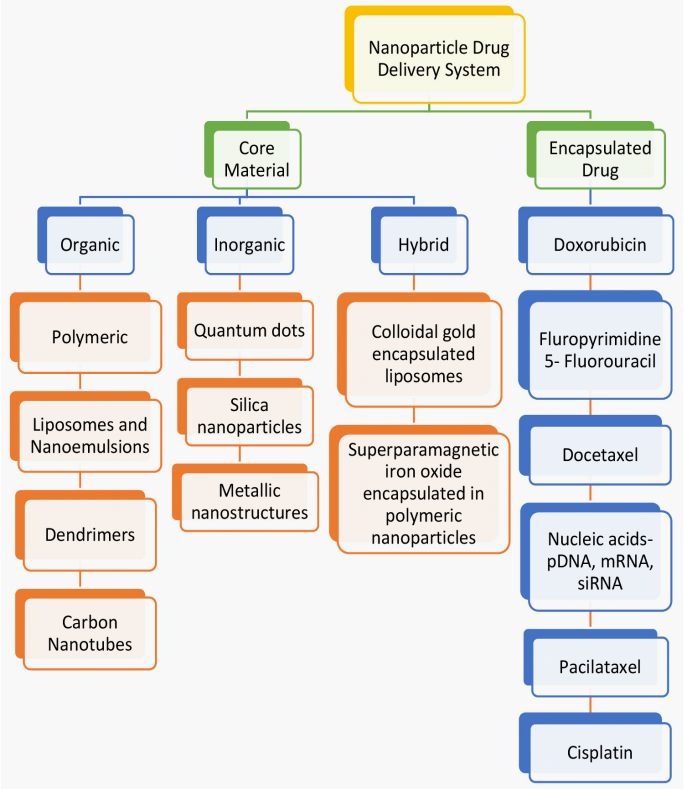

Figure 2: Various nanoparticles based drug delivery systems.

Drugs in hydrogel nanoparticle are based upon proprietary hydrophobic polysaccharides for drug delivery in which proteins and/or antibodies can be encapsulated. NanoGels belongs to nanoparticulate hydrogels that can encapsulate magnetic material within to create a particle ~25 nm in diameter to which 5 to 100 ligands can be attached. Whereas magnetic nanogel, have an iron oxide core ~10 nm in diameter with a polymer coating and can be loaded with up to 1000 anticancer drug molecules. These particles can be tracked by MRI as they accumulate in tumors [33,34]. But systemic administration of chemotherapeutic agents causes severe toxicity. To overcome this problem several nanotechniques are used, by which encapsulation and cancer cell-specific targeting of chemotherapeutics are done in 400 nm nano cells, and the packaging of chemotherapeutics is done while keeping in mind the specific criteria of charge, hydrophobicity, and solubility which can be further altered by changing minute concentrations. Effective targeting of nano cells on cancerous cell must upshot into endocytosis, then either intracellular drug release or degradation of drug is possible but bio-specific antibodies receptor must be present on cancerous cell membrane [35]. For tumor –targeted drug delivery, assorted nano-systems are serviceable, even so for this purpose, structural and analytical properties of novel nanoparticles are preprogrammed which will be effective for both extra- and intracellular delivery.

Injection of quantum dots conjugated with a tumor-targeting MAb (anti-HER2), six distinct 'stop-and-go' steps were identified in the process involved as the particles traveled from the injection site to the cell where they bind HER2: Within a blood vessel in the circulation, during extravasation, in the extracel-

lular region, binding HER2 on the cell membrane, moving into and within the perinuclear region. *In vivo*, image analysis of the delivery process for single particles provides valuable information on antibody conjugated therapeutic nanoparticles, which will be further utilized in increasing their anticancer therapeutic efficacy using a high-speed confocal microscope with a high-sensitivity camera [36–39].Tumor Necrosis Factor (TNF) can be bound to gold nanocrystals and delivered safely and effectively to tumor-burdened mice and dogs. An effective example of nanotechnology- mediated drug delivery is the liposome-mediated delivery of DOX (e.g., Doxil) that have substantially reduced cardiotoxicity relative to free DOX [40,41].

Nano-techniques manipulated for different cancer therapies

In the new age of treatment of cancer, preference is given to reduce the injurious effect on normal cells as well as effectively target cancer cells only. The introduction of nanotechnology has brought new materials and pathways for the targeted treatment of cancer. Diverse unique properties of nanoparticles are utilized for noninvasive cancerous therapy, which was not previously possible but with the advancement in the nanotechnological techniques, it become more reliable treatment for cancer.

Nanotechnology-based gene therapy

Nanotechnology is now discovering many more hidden potentials of DNA, by exploiting its amphipathic property; single-stranded DNA (ssDNA) sequences could be used to solubilize hydrophobic nanoparticles like Carbon Nanotubes (cNTs) to make it suitable for *in vivo* use. Using gene therapy tumoricidal effect is achieved, by incorporating specific exogenous genes into the genome of the tumor cells. DNA sequences can process information in biochemical assays, whereas its structure and self-assembling property made it an ideal scaffolding material to arrange nanoparticle in biochip and biosensor production [42]. Although for the alteration of the damaged or dysfunctional cells, viral vectors have traditionally been the primary agents used to deliver genes to targeted cells. However, the problem associated with the viral vector is the toxicity, immune and inflammatory responses, gene control, and targeting issue; also, there is always a fear of the virus recovering and causing disease. To conquer this, non-viral mediated gene transfer techniques are preferred. The most widely used nonviral vectors combined along with nanoparticles are polymers, cell-penetrating peptides, dendrimers, liposome-mediated cationic polymers, and gold nanoparticles. The physical properties of nanoparticles, including their morphology, size, charge density, and colloidal stability, which are important parameters for determining the overall efficacy of nanoparticles to act as potential nonviral gene delivery vehicles [43].

Studies of gene therapy by Jere et al., [44] (2009), they efficiently delivered Akt1 small interference- RNA-loaded biodegradable Nano-polymeric carrier, leading to silencing of Akt1 protein and reduced cancer cell survival, proliferation, malignancy, and metastasis. Similarly, nanoparticles for gene therapy of p53 gene with sustained expression of the p53 protein in the target cells were a well-recognized approach in cancer gene therapy. A single-dose regimen results in only weak and transient inhibition of cell proliferation. Gene delivery with nanoparticles usually requires direct intratumoral injection but tumor targeting via intravascular administration is possible if the nanoparticle surface is modified to avoid trapping of the nanoparticles by the reticuloendothelial system. Another approach is the use of poly (D, L-lactide-co-glycolide) nanoparticles loaded with wild type (wt) p53 DNA, which has demonstrated a sustained antiproliferative effect in a breast cancer cell line following slow intracellular release of the encapsulated DNA from nanoparticles. The results of the study suggest that wt-p53 DNA-loaded nanoparticles have potential use in the therapy of breast and other cancers associated with mutations in the p53 gene [45,46].

In the last few years, several researchers demonstrated the potential of augmenting gene therapy with the help of nanotechnology addressing a majority of these issues and successfully translated into clinical trials [17].

Nanotechnology-based chemotherapy

Nanotechnology associated with chemotherapy is an effective way of solving many problems related to drug delivery as well as targeting cancerous cells. For fruitful results of chemotherapy, target based drug delivery is foremost requirement, at the same time effectiveness of drug for the cancer is also necessary. And for both the process, nanotechnology plays a crucial role. Some of the combinational studies of nanotechnologies with chemotherapies are listed below:

Chemotherapy with drugs such as dacarbazine, temozolomide, nitrosoureas, vinca alkaloids, taxanes, and cisplatin has been used for cases of advanced melanoma skin cancer. 5-FU is an actively and widely used drug for the treatment of cancers, such as actinic keratosis and basal cell carcinomas. However, 5-FU is highly hydrophilic, which limits it to ability to reach tumor tissues through Skin cancer [47–49]. Dacarbazine has a short half-life and is a poorly soluble active drug, it is used as a single-agent FDA-approved anticancer drug and is the drug of choice for use in chemotherapy against melanoma skin cancer [50,51]. This drug has been encapsulated in lipid nanoparticles for topical delivery in melanoma skin cancer treatment [52]. More complex nanoparticles were developed by Liu et al., [51] (2017), who rationally designed a nanocarrier based on hollow mesoporous silica nanoparticles enveloped with folic acid-grafted liposomes. Carboplatin, a second-generation platinum compound also recommended by the FDA for the treatment of melanoma, was loaded into poly (ε-caprolactone) NPs with a chitosan-β-glycerophosphate gel for intratumoral administration [53]. Additionally, an antitumor effect *in vitro* and in a xenograft tumor model *in vivo* was evaluated by Su et al., [54] (2017), who produced paclitaxel-loaded copolymer NPs. The antitumor doxorubicin was encapsulated into polymeric NPs, and via self-assembly induced with polyphosphazenes, generated a pH-responsive amphiphilic polymer. Solid lipid NPs were used as a delivery system for temozolomide, which was preliminarily investigated for mesenchymal Stem Cell treatment [55]. In studies of Jiang et al., [56] (2017), a temozolomide-loaded polyamide-amine dendrimer in a PAMAM delivery system was explored for *in vitro* targeting of human melanoma cells. Table 1 comprises some of the FDA approved nanoparticle related drugs currently in use for cancer treatment.

Table 1: List of US Food and Drug Administration (FDA)–Approved Nanoparticle Related for Cancer Treatment.

Carrier	Nanoparticle advantage	Trade name	Year(s) approved	Ref
Liposomal doxorubicin	Decrease in systemic toxicity of free drug and improved delivery to site of disease	Doxil	1995	[81]
Liposomal cytarabine	Lower systemic toxicity arising from side effects and increased delivery to tumor site	DepoCyt	1996	[82]
Liposomal daunorubicin	Lower systemic toxicity arising from side effects and increased delivery to tumor site	DaunoXome	1996	[83]
Leuprolide acetate and polymer; PLGH (poly (DL-Lactide-co-glycolide)	Controlled delivery of payload with longer circulation time	Eligard	2002	[84]
Albumin-bound paclitaxel nanoparticles	Improved solubility; improved delivery to tumor	Abraxane	2005	[85]
Liposomal doxorubicin	Decrease in systemic toxicity of free drug and improved delivery to site of disease	Myocet	2005	[86]
Liposomal Vincristine	Lower systemic toxicity arising from side effects and increased delivery to tumor site	Marqibo	2012	[87]
Liposomal Irinotecan	Lower systemic toxicity arising from side effects and increased delivery to tumor site	Onivyde	2015	[88]

A drug delivery system by Huang et al., [57] (2006), uses ultrasound for imaging of tumor as well as release of drug from nanobubbles into the tumor. Mixtures of drug-loaded polymeric micelles and Perfluoropentane (PFP) nanobubbles stabilized by the same biodegradable block copolymer were prepared. The size distribution of nanoparticles was measured by dynamic light scattering. Cavitation activity (oscillation, growth, and collapse of microbubbles) under ultrasound was assessed based on the changes in micelle/nanobubble volume ratios. The effect of the Nanobubbles on the ultrasound-mediated cellular uptake of doxorubicin (Dox) in MDA MB231 breast tumors *in vitro* and *in vivo* (in mice bearing xenograft tumors) was determined by flow cytometry. It was noted that the volume ratio of copolymer/perfluorocarbon is an important factor for the sensitizing phase state and nanoparticle sizes. At physiologic temperatures, nanodroplets are converted into nanobubbles. Nanobubble wall was formed by block copolymer that incorporates doxorubicin. The Dox-loaded micelles and nanobubbles injected intravenously into mice, and they extravasated selectively into the tumor interstitium where microbubbles formed by nanobubbles aggregation. For cancer therapy, various enduring ultrasound contrast agents and intensified ultrasound mediated drug delivery system that contain multifunctional tumor – targeted drug carrier nanoparticles were explored [58,59].

Nanotechnology-based phototherapy

Phototherapy includes conversion of light energy into either chemical energy or heat energy, which further results in chemical reaction and create diverse therapeutic effect in body. For eradication of malignant cells, photoreactive agents are provided to patients and light is applied to affected area to initiate photoreaction that generate Reactive Oxygen Species (ROS). Various combinational effects of phototherapy were assed and auspicious tumor ablation and reduced invasive treatment, makes it more convenient technique for treatment of cancer. The phototherapies are categorized as either oxidative stress inducing photodynamic therapy or thermal stress inducing photothermal therapy [60].

Nanotechnology based photodynamic therapy

Photodynamic Therapy (PDT) uses light-activated drugs called Photosensitizers (PS) to treat a range of diseases characterized by rapidly growing tissue, including the formation of abnormal blood vessels, such as cancer. Treatment with PDT depends on three non-toxic components: Photosensitizer, light and oxygen. It further consists of a two-step process that starts with the administration of the drug, or photosensitizer, by intravenous injection. Once the drug enters the bloodstream, it attaches itself to low-density lipoproteins that are already circulating. Since the rapidly growing cells need an elevated supply of lipoproteins, this distinctive feature is utilized to reach affected cells more quickly and also in higher concentrations. Once the necessary level of concentration is attained, the second step is to activate the drug with a specific dose of light of a particular wavelength. This causes the conversion of normal oxygen found in tissue to a highly energized form called singlet oxygen, which in turn, disrupts normal cellular functions. Neither the drug nor the light exerts any effect until combined [61]. Some of the photosensitizer used in anti-tumoral application are photofrinV, methylene blue, 5- aminolaevulininc, and chlorin e6 [62]. Numerous studies have used liposomes, oils, and polymeric micelles as encapsulation methods, with some success. However, all of these techniques suffer from one unpleasant side effect: After controlled release and photosensitization, the drug is free to circulate the body, accumulating in the eyes and skin. This leads to phototoxic side effects, rendering the patient highly sensitive to light. A further disadvantage is that liposomes can be engulfed and destroyed by cells of the Reticuloendothelial system [29]. Such problems have limited the emerging field of PDT, but the combination of this technique with nanotechnology is promising [63].

The possibility of improving dendrimers through appropriate functionalization of their periphery makes them promising carriers of PDT. Some new developments in the use of nanoparticles in PDT are described in this section.

Ohulchanskyy et al., [64] (2007) reported covalent incorporation of Photosensitizer (PS) into Organically Modified Silica (ORMOSIL) nanoparticles. They found that it helps PS to retain their spectroscopic and functional properties with enhanced capability to generate cytotoxic singlet oxygen molecules upon photoirradiation. The synthesized nanoparticles had average size of 20 nm and are highly monodispersed and stable in aqueous suspension. They suggested that due to covalent linkage the drug is not released during systemic circulation, which is often a problem with physical encapsulation. Moreover, the *in vitro* studies showed their phototoxicity and preferred uptake by tumor cells, thereby highlighting their potential in diagnosis

and PDT of cancer.

The use of 5-Aminolevulinic Acid (ALA) is one approach to PDT based on dendrimers. ALA is a natural precursor of the photosensitizer Protoporphyrin IX (PIX) and its administration increases the cellular concentrations of PIX. An approach to deep tissue penetration is based on two-photon excitation with near-infrared lasers [65]. Multivalent aspects of the dendrimer scaffold have been used to conjugate several two-photon absorbing chromophores to the porphyrin core. This system has been shown to generate singlet oxygen efficiently on light irradiation at 780 nm wavelength [66]. Dynamic ceramics is a new development that addresses the various problems of PDT for cancer. An adjunct anticancer drug, 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide (HPPH), was encapsulated within a ceramic-based nanoparticle, which is 35 nm in diameter and is made from silica. They are stable to fluctuations in temperature and pH and small enough to evade the reticuloendothelial system (RES). The success of the technique relies upon the tiny pores in the ceramic particle, which range from 0.5-1.0 nm [67,68].

The magnetic Fe_3O_4 nanoparticle and the photosensitizer drug 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide- a (HPPH) co-loaded in polymeric micelles of diacylphospholipid-poly (ethylene glycol) (PE-PEG), has been used for guided drug delivery with light-activated photodynamic therapy for cancer. The nanocarrier shows excellent stability and activity over several weeks. The loading efficiency of HPPH is practically unaffected upon co-loading with the magnetic nanoparticles, and its phototoxicity is retained. The magnetic response of the nanocarriers was demonstrated by their magnetically directed delivery to tumor cells *in vitro*. Controlled magnetophoretic uptake at cellular level improves imaging as well as phototoxicity. Multifunctional nanocarriers put forward diverse aspect of nanochemistry for targeting photodynamic cancer therapy [69,70].

Additional advantages of PDT are that it can be used repeatedly without producing immunosuppressive and myelosuppressive effects and can be administered even after surgery, chemotherapy, or radiotherapy. Peng et al., [71] 2010 have developed pH-sensitive nanoparticles as potential carriers for tumor targeting and PDT. Another researcher, Chang et al., [72] 2008 has investigated the dose-enhancing effect and apoptotic potential of gold nanoparticles in combination with single-dose clinical electron beams on B16F10 melanoma tumor-bearing mice. Although radiofrequency ablation has been used in the treatment of cancer, cardiac conduction abnormalities, and neurological lesions, it is most commonly used in cancer therapies. Gold nanoparticles have been demonstrated in vitro and in vivo to enhance cancer cell destruction in a noninvasive radiofrequency field. Cardinal et al., [73] 2008 have highlighted the potential use of gold nanoparticles for the specific targeting of cancer cells. They used noninvasive radio wave machine coupled with gold nanoparticle enhancer solutions to thermally ablate tissue and cancer cells in both *in vitro* and *in vivo* systems.

Nanoparticle-based photothermal therapy

Photothermal therapy (PTT) is another promising phototherapy, and its precedence includes non-invasive nature, harmlessness and high selectivity. This technique is actually an extension of PDT, which includes excitation of photosensitizer with light of specific band only. And hence vibrational energy in the form of heat is released by sensitizer after it reaches its excitation stage and this activated energy is used to kill targeted cells. PTT is safer option as it used light of longer wavelength, which is less energetic and consequently lesser harmful for other non-targeted cells or tissue [74].

Unique optical properties of gold nanoparticles have been utilized in surface Plasmon resonance and also possess Photothermal characteristics and qualified for imaging applications as well as induce Photothermal effects [75,76]. *In vitro* studies have demonstrated that gold nanorods are novel contrast agents for both molecular imaging and photothermal cancer therapy [57]. Cellular uptake of nano-carrier was enhanced by hyperthermal effect caused by PTT agents. Which further improve the membrane penetrability and intracellular delivery of drugs that results in photothermally enhanced chemotherapy [77].

Nanorods are synthesized and conjugated to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies (MAbs) and incubated in cancer cell cultures. Due to the over-expressed EGFR on the cytoplasmic membrane of the malignant cells, their binding affinity for the anti-EGFR antibody-conjugated nanorods increases. As a result, strongly scattered red light from gold nanorods in the dark field, when observed using a laboratory microscope, anticipate the malignant cells and distinguished from the nonmalignant cells. Results depict that when continuous exposure of red laser at 800nm was provided, then malignant cells require about half the laser energy to be photothermally destroyed than the nonmalignant cells. Hence realization of coherent cancer cell diagnostics, as well as selective photothermal therapy, can occur simultaneously. To ensure the accumulation of nanoparticles in neoplastic tissue, targeting ligands, such as antibodies and targeted gene therapy vectors, are being incorporated into the nanoparticles, which act as thermal scalpels upon laser irradiation and destroy tumor tissue [78). “Magnetic thermal ablation” a treatment for breast cancer has been examined under *in vivo* animal conditions. The method consists of the intratumoral application of iron nanoparticles and the exposure of the breast to an alternating magnetic field, whereby the tumor is eliminated by the heat [79,80].

Conclusion and future perspective

In cancer therapeutic applications there is advancement day-by-day. Multifunctional nanoparticles used for cancer therapeutic and diagnostic are blooming areas as these provide an edge over traditional approaches with more efficacy and safety. Besides cancer therapy, NPs contribute in many cancer management functions including diagnosis, imaging, and theragnostic.

But there are certain disadvantages of NPs that show the dire need to optimize some of their characteristics. To overcome the associated challenges and obstacles, a thorough understanding of cancer biology is required that could concurrently hinder clinical translation and commercialization. The toxicity, biodistribution, and physicochemical characteristics of the used NPs such as size, shape, surface charge, internal nanostructure, and surface characteristics are an important consideration that affects the therapeutic outcomes. The NPs administrated must be efficient and safe *in vivo* as it *in vitro*. In the human body, nanoparticles are a foreign substance that affects their acceptance by the body’s immune system and due to small size; it is easy to eliminate them by the reticuloendothelial system from blood circulation, despite their beneficial application. There is a need to overcome these limitations such as bio-adhesion, non-specific NPs uptake, low circulation time, and improvement in specific targeting mechanisms with preferred accumulation at the site of interest. Similarly, nanoparticles in the drug delivery

system come with many advantages, but low circulation time, as well as poor controlled drug loading and release, are the main challenges to overcome.

The present production methods for NPs are mostly suitable for lab-scale synthesis with expensive and lengthy research and development process for large scale production. There should be efficient, low energy input and commercial capable methods for large scale production and clinical translation of NPs. Most of the research investigations are being focused on *in vitro* or *in vivo* studies and only a few systems have been implemented clinically. With the advancement of nanotechnology, the NPs can establish a new era in screening, treatment, and prevention of cancer diseases.

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