Drug Discovery Today • Volume 15, Numbers 19/20 • October 2010

Cancer nanotechnology: application of nanotechnology in cancer therapy

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The application of nanotechnology for cancer therapy has received considerable attention in recent years. Cancer nanotechnology (an interdisciplinary area of research in science, engineering and medicine) is an upcoming field with extensive applications. It provides a unique approach and comprehensive technology against cancer through early diagnosis, prediction, prevention, personalized therapy and medicine. Target-specific drug therapy and methods for early diagnosis of pathologies are the priority research areas in which nanotechnology would play a vital part. This review focuses on the approaches of cancer nanotechnology in the advancement of cancer therapy.

Cancer is a major cause of mortality: more than ten million people are diagnosed with the disease annually. Cancer is known to develop via a multistep carcinogenesis process entailing numerous cellular physiological systems such as cell signaling and apoptosis, making it a highly incomprehensible and complex disease [1,2]. Initially, cancers start as localized diseases, but they are prone to spread to distant sites within the body, which makes cancer incurable. To date, cancer treatments have been performed on the basis of clinical and pathologic staging that is determined using morphologic diagnostic tools, such as conventional radiological and histopathological examinations. The most common cancer treatments are restricted to chemotherapy, radiation and surgery [3]. At present, however, the early recognition and treatment of cancer remain a technological bottleneck. Despite many advances in conventional treatment options such as chemotherapy and radiation, cancer therapy is still far from optimal because it is plagued by some drawbacks. Frequent challenges encountered by current cancer therapies include nonspecific systemic distribution of antitumor agents, inadequate drug concentrations reaching the tumor site, intolerable cytotoxicity, limited ability to monitor therapeutic responses and development of multiple drug resistance [4–6]. Current diagnostic and prognostic classifications are insufficient to make predictions for successful treatment and patient outcome [7]. Thus, there is an urgent need and major opportunities to develop new and innovative technologies that could help to delineate tumor margins, identify residual tumor cells and micrometastases, and determine whether a tumor has been completely removed.

Cancer nanotechnology: a new revolution for cancer therapy

As with any cancer therapy, the key issue is to achieve the desired concentration of therapeutic agent in tumor sites, thereby destroying cancerous cells while minimizing damage to normal cells. With this vision, it is imperative to create single agents with tremendous potential to make an important contribution in cancer prevention, detection and treatment. In this regard, several ligand-targeted therapeutic strategies, including immunotoxins, radioimmunotherapeutics and drug immunoconjugates, are being developed to overcome the problems associated with conventional chemotherapeutic drugs, thereby providing additional tools in the arsenal of cancer therapy [8]. Although these conjugated agents have shown promising efficacy compared with conventional chemotherapy drugs, limitations in their delivery still remains a major problem. Recent advances suggest that nanotechnology (which involves the creation and manipulation of materials at nanoscale levels to create products that exhibit novel properties) will have a profound impact on disease prevention, diagnosis and treatment. Cancer nanotechnology is emerging as a new field of interdisciplinary research – cutting across the disciplines of biology, chemistry, engineering and medicine – and is expected to lead to major advances in cancer detection, diagnosis

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.08.006

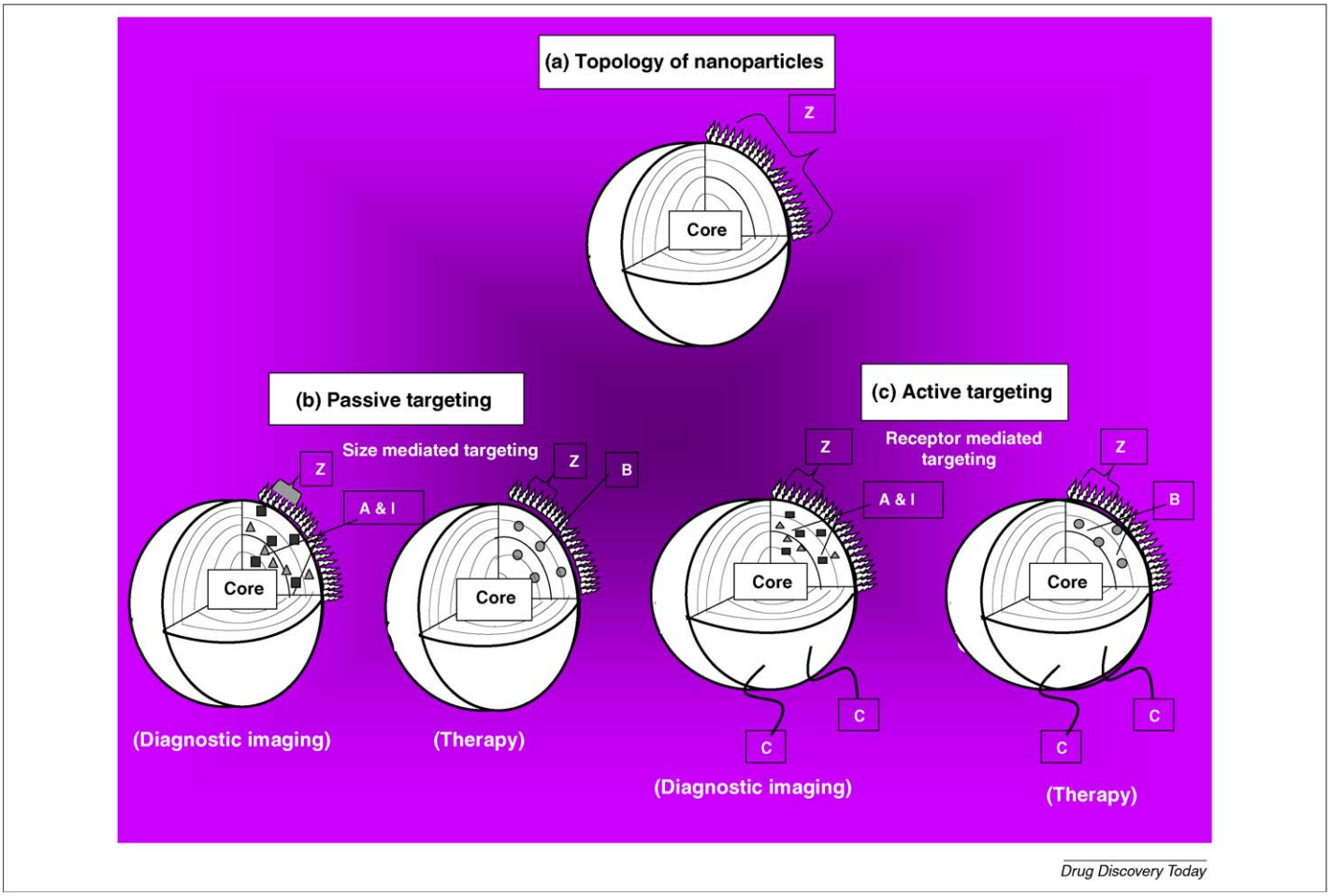

FIGURE 1

Cancer therapy. Nanoparticulate architecture and drug delivery modalities. **(a)** Universal structural topology of nanoparticles illustrating core compartment with terminal surface groups (*Z*). **(b)** Size-mediated passive targeting of multifunctional nanoparticles carrying diagnostic and imaging agents (A and I) and therapeutic drugs for cancer therapy. **(c)** Active receptor-mediated targeting of multifunctional nanoparticles by different homing agents (C).

and treatment [9] (Fig. 1). The idea of crafting more effective cancer treatments by engineering matter at the nanoscale provides a compelling panacea for preferential elimination of cancer cells without serious damage to normal cells.

Nanotechnology is a multidisciplinary field that has emerged recently as one of the most propitious fields in cancer treatment [10]. Nanomedicine (the medical application of nanotechnology) has incredible potential for revolutionizing cancer therapeutics and diagnostics by developing ingenious biocompatible nanocomposites for drug delivery purposes, which represent the most pertinent application of nanoparticles [6]. Recent years have witnessed unprecedented use of nanocarriers (particularly in the size range from 10 nm to 100 nm) as an emerging class of therapeutics for cancer treatment. Two therapeutic nanocarrier-liposomes and albumin nanoparticles have been approved by the US FDA for clinical practices. In addition, liposomal doxorubicin, albumin-bound paclitaxel (Abraxane®) is another example of an enhanced permeability and retention (EPR)-based nanovector application for breast cancer chemotherapy [11,12]. These nanosystems have four unique properties that distinguish them from other cancer therapeutics: (i) the nanosystems can themselves have therapeutic or diagnostic properties and can be designed to carry a large therapeutic 'payload'; (ii) nanosystems can be attached to multivalent targeting ligands, which yield high affinity and specificity for target cells; (iii) nanosystems can be made to accommodate multiple drug molecules that simultaneously enable combinatorial cancer therapy and (iv) nanosystems can bypass traditional drug resistance mechanisms. By using both passive and active targeting strategies, the nanocarriers can achieve increased intracellular concentration of drugs in cancer cells while minimizing toxicity in normal cells, simultaneously enhancing anticancer effects and reducing systemic toxicity [13].

Tools of nanotechnology for cancer therapy

The tools of nanotechnology with applications in early cancer detection and treatment include the following (Box 1 and Fig. 2).

Liposomes

Liposomes have become very versatile tools in biology, biochemistry and medicine because of their enormous diversity of structure and compositions [7,8,14–16]. Examples of liposome-mediated drug delivery are doxorubicin (Doxil) and daunorubicin (Daunoxome), which are currently being marketed as liposome delivery systems. Polyethylene glycol (PEG)ylated liposomal doxorubicin

BOX 1

Tools of nanotechnology

- Liposomes
- Nanoparticles
- Polymeric micelles
- Dendrimers
- Nanocantilever
- Carbon nanotubes
- Quantum dots

(Doxil®, Caelyx®; Alza Pharmaceuticals, San Bruno, CA, USA) has achieved the most prolonged circulation to date, with a terminal half-life of 55 hours in humans [7,9,17]. These PEGylated (also referred to as sterically stabilized, or 'Stealth') liposomes display inhibited interaction with plasma proteins and mononuclear phagocytes and, consequently, display greatly prolonged circulation time. A similar approach was utilized by packaging therapeutic molecules inside a liposome and decorating the surface of liposome using molecular 'Trojan Horse' technology [8,18,19]. Zhang *et al.* [20] prepared OX-26-transferrin-targeted PEGylated

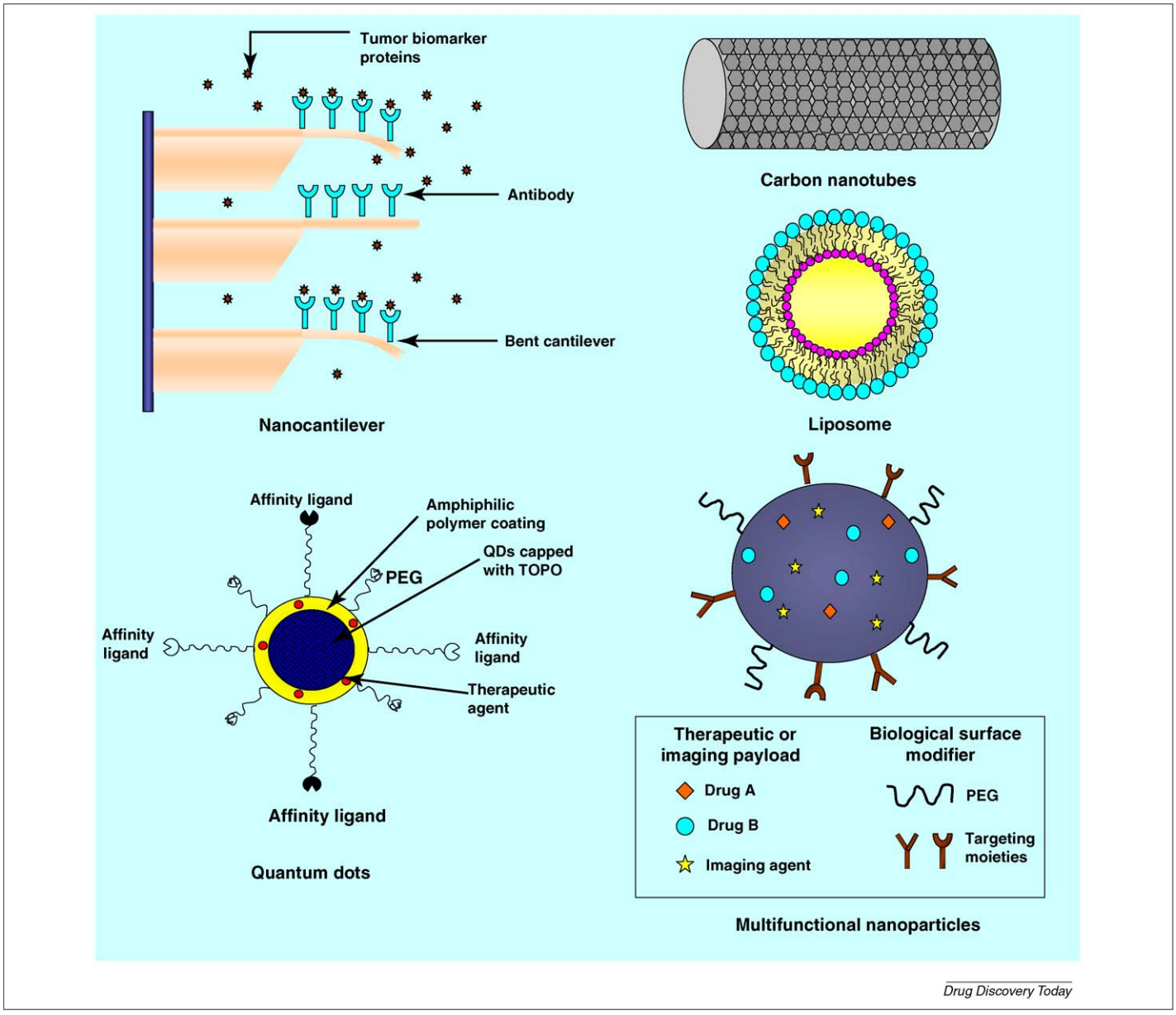

FIGURE 2

Tools of nanotechnology. Schematics of different nanotechnology-based tools used for cancer therapy. Liposomes are made up of lipid structures that can be made stealth by PEGylation and encapsulating different therapeutic agents; these are used as a potential nanocarrier for cancer therapy. Nanocantilevers are array-like structures in which engineered tiny bars anchored at one end help in the detection of altered proteins present in certain types of cancers. During the detection procedure, on one side the cantilever bends, which is detected optically. Quantum dots are fluorescent nanocrystals that can be conjugated to a ligand by coating a polymeric layer onto it; therapeutic agents are encapsulated and used for cancer therapy. New synthetic methods have been developed to design multifunctional nanoparticles, in which we can encapsulate both therapeutic and imaging agents in a single nanocarrier system that will conjugate with more than one ligand on the surface; thus, it will act as a novel multifunctional nanocarrier system with the capacity of targeted tumor imaging and the delivery of therapeutic agents.

immunoliposomes carrying expression plasmids of gene encoding tyrosine hydroxylase, and promising results were obtained in a rat model for Parkinson's disease. Leamon *et al.* [21] have recently evaluated the *in vitro* and *in vivo* status of the delivery of oligonucleotides encapsulated in folate-coated liposomes. Moreover, folate-receptor-targeted liposomes have proven effective in delivering doxorubicin *in vivo* and have been found to bypass multidrug resistance in cultured tumor cells [22].

Nanoparticles

These are submicron-sized colloidal particles with a therapeutic agent of interest encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface [15]. Nanoparticles are targeted to specific sites by surface modifications, which provide specific biochemical interactions with the receptors expressed on target cells [6,23]. Another important function of nanoparticles is their ability to deliver drugs to the target site, crossing several biological barriers such as the blood–brain barrier. By coating the nanoparticles with polysorbates, the drug-loaded nanoparticles can be transported across the blood–brain barrier, enabling brain targeting after an intravenous injection [7,24–27]. Recently, our group has developed several different potential nanocarrier systems for the treatment of cancer. Acharya *et al.* [13] have designed epithelial growth factor antibody-conjugated rapamycin-loaded nanoparticles and showed the enhanced efficacy of these formulated immunonanoparticles in MCF 7 breast cancer-cell line. Misra *et al.* [23] have improved the therapeutic efficacy of the potent anticancer drug doxorubicin by directly targeting the drug to the nucleus of breast cancer cells by conjugating a nuclear localization sequence to the surface of the nanoparticles. Mohanty and Sahoo [28] have formulated a nanoparticulate delivery system through the use of glycerol monooleate and pluronic F-127 that can solubilize curcumin in aqueous media at clinically relevant concentrations, protect it from hydrolytic degradation and *in vivo* biotransformation, and deliver curcumin in a controlled manner. It is well recognized that the development of novel approaches for early cancer detection and effective therapy will contribute notably to improving patient survival. New synthetic methods have been developed to control precisely the size and shape of nanoparticles as a means to tune absorption and emission properties [29]. The development of nanoparticles as imaging contrast agents also makes possible the production of multifunctional nanoparticles with a capacity for targeted tumor imaging and delivery of therapeutic agents [30].

Polymeric micelles

A micelle is defined as a collection of amphiphilic surfactant molecules; micelles are turning out to be a keystone in the future of therapeutics [31]. The first polymeric micelle formulation of paclitaxel, Genexol-PM (PEG-poly (D,L-lactide)-paclitaxel), is a cremophor-EL-free polymeric micelle-formulated paclitaxel [32,33]. A phase I and pharmacokinetic study has been conducted in patients with advanced refractory malignancies. Several polymeric PEG-micelle formulations have entered clinical trials; for example, doxorubicin-loaded polymeric micelle has gone through a phase I clinical trial for solid tumors and shown encouraging results in treating restenosis by encouraging accumulation in vascular lesions [34,35]. Torchilin *et al.* [36] have formulated antitumor antibody-conjugated polymeric micelles (immunomicelles), encapsulating the water-insoluble drug Taxol, that effectively recognize and bind to various cancer cells *in vitro*. Mohanty *et al.* [37] have developed curcumin-loaded methoxy poly ethylene glycol/poly-ε-caprolactone diblock copolymeric micelles and have shown the improved efficacy of the micellar system over the native drug using pancreatic cell lines.

Dendrimers

Dendrimers are macromolecular compounds that comprise a series of branches around an inner core, the size and shape of which can be altered as desired, and hence serve as an attractive modality for drug delivery [38–41]. In a recent work by Choi *et al.* [42], DNA-assembled polyamidoamine dendrimer clusters were prepared for cancer-cell-specific targeting. They have prepared dendrimer-5FU conjugates by acetylation, which – upon hydrolysis – release free 5FU, thus minimizing the toxicity of 5FU [31,42]. The unique architecture of dendrimers enables for multivalent attachment of imaging probes, as well as targeting moieties; thus, it can be also used as a highly efficient diagnostic tool for cancer imaging. Gadolinium-based magnetic resonance imaging contrast agents can operate at an approximately 100-fold less concentration than iodine atoms required for computed tomography imaging. They can be targeted to a single site, which improves the sensitivity of imaging [43,44]. Phase I clinical trials of Starpharma's dendrimer-based microbicide (VivaGel) are also the first human dendrimer pharmaceutical clinical trials [45].

Nanocantilever

Microarray methods employing the detection of specific biomolecular interactions are now an indispensable tool for disease diagnosis, genome research and drug discovery. Tiny bars anchored at one end can be engineered to bind to molecules associated with cancer. These molecules can bind to altered DNA proteins that are present in certain types of cancer. During detection procedures, when biospecific interactions occur between a receptor immobilized on one side of a cantilever and a ligand in solution, the cantilever bends; if detected optically, it is possible to tell whether cancer molecules are present and, hence, detect early molecular events in the development of cancer. The deflection of silicon beams depends on the amount of DNA or protein bound to the cantilever surface. The deflection can be observed directly, using laser light, or by measurement of perturbations in their resonant vibration frequency. Arun Majumdar and colleagues used microcantilevers to detect single-nucleotide polymorphisms in a 10-mer DNA target oligonucleotide without the use of extrinsic fluorescent or radioactive labeling. They also demonstrated the applicability of microcantilevers for the quantitation of PSA at clinically considerable concentrations. The breakthrough potential afforded by nanocantilevers resides in their extraordinary multiplexing capability [46].

Carbon nanotubes

Another type of nanodevice for biomarker detection is the carbon nanotube [47]. Carbon nanotubes are carbon cylinders composed of benzene rings that have been applied in biology as sensors for detecting DNA and protein, as diagnostic devices for the discri-

mination of different proteins from serum samples and as carriers to deliver drug, vaccine or protein [48]. An emerging field in nanotechnology is the exploration of interesting structural, mechanical, electrical and optical properties of single-walled carbon nanotubes (SWNTs) for biological applications including biosensors, molecular transporters for drug delivery and potential new therapies [9]. The high optical absorbance of SWNTs in the near-infrared regime causes heating under laser irradiation, which is useful for destroying cancer cells that are selectively internalized with nanotubes. Current trends in biomedical imaging have focused on the Near Infrared fluorescence properties of SWNTs and on surface functionalization. NIR fluorescence lies in the biologically transparent region (700–1300 nm) where autofluorescence, absorption and scattering by blood and tissue are minimized. Surface-functionalized multiwalled carbon nanotubes have also been used successfully for bioimaging purposes [49–51]. In an *in vitro* study, drugs bound to carbon nanotubes were shown to be more effectively internalized into cells than free drug alone.

Quantum dots

In recent years, semiconductor quantum dots (QDs) have attracted the attention of many research groups because of their scientific and technological significance in microelectronics, optoelectronics and cellular imaging [9,47,48]. Semiconductor QDs are emerging as a new class of fluorescent labels for biology and medicine. The broad absorption and narrow emission characteristics of the QDs make it possible to perform multicolor imaging with a single excitation source. The high fluorescence quantum yield of the QDs, their resistance to photobleaching and their unique physical, chemical and optical properties make them good candidates for fluorescent tagging for *in vivo* molecular and cellular imaging [52–55]. QDs also provide a versatile nanoscale scaffold for designing multifunctional nanoparticles with both imaging and therapeutic functions. For *in vivo* and intraoperative tumor imaging, QDs hold great promise, mainly because of their intense fluorescent signals and multiplexing capabilities, which could enable a high degree of sensitivity and selectivity. QDs have been the subject of toxicological scrutiny because of their material formulations; however, several groups have reported that with biocompatible surface coatings, such as PEG-silica, QDs can be well tolerated by cells *in vitro* [56]. Nie *et al.* [47] first reported that it is feasible to simultaneously target and image prostate tumors in living animal models using bioconjugated, prostate membrane antigen-targeted QDs. The surface of QDs can be engineered or modified to improve QD solubility, sensitivity, specificity and visualization in target tissue.

Aspects of targeted cancer therapy

Ideally, for anticancer drugs to be effective in cancer treatment, they should first (after administration) be able to reach the desired tumor tissues through the penetration of barriers in the body with minimal loss of volume or activity in the blood circulation. Second, after reaching the tumor tissue, drugs should have the ability to selectively kill tumor cells without affecting normal cells with a controlled release mechanism of the active form. These two basic strategies are also associated with improvements in patient survival and quality of life, by simultaneously increasing the intracellular concentration of drugs and reducing dose-limiting toxicities. In principle, nanoparticle delivery of anticancer drugs to tumor tissues can be achieved by either passive or active targeting (Fig. 3).

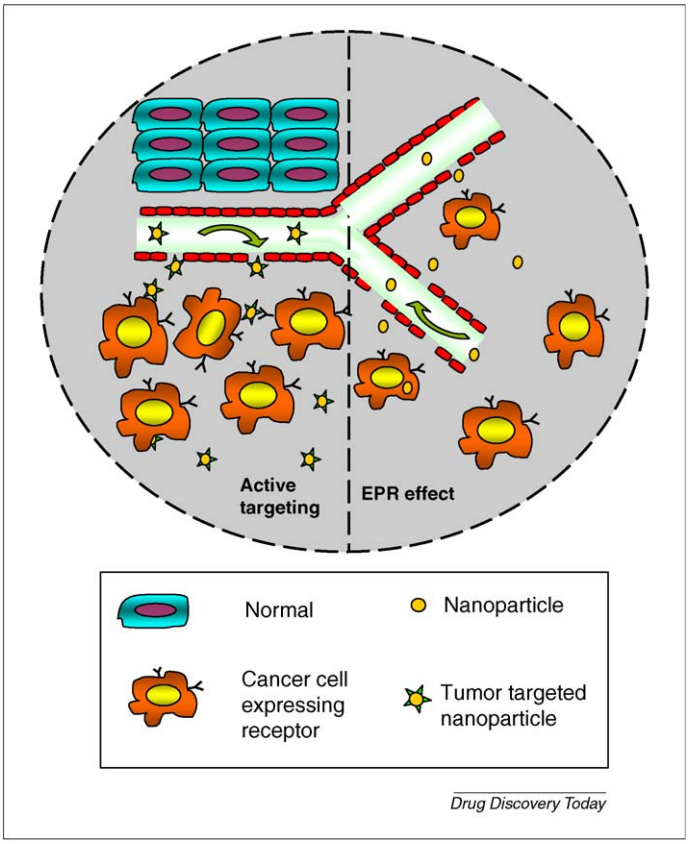

FIGURE 3

Tumor targeting. The right-hand part of the figure depicts the increased accumulation of nanoparticles in tumor owing to leaky tumor vasculature, leading to the enhanced permeability and retention effect. The left-hand part of the figure shows active targeting mediated by targeted nanoparticles.

Passive targeting

Passive targeting refers to the accumulation of a drug or drug carrier system at a desired site owing to physico-chemical or pharmacological factors. It takes advantage of the inherent size of nanoparticles and the unique properties of tumor vasculature, such as the EPR effect and the tumor microenvironment. This approach can effectively enhance drug bioavailability and efficacy: it makes use of the anatomical and functional differences between normal and tumor vasculature to deliver the drug to a targeted site or might include localized delivery. Tumor vasculature is very different to normal tissue. Angiogenic blood vessels in tumor tissues, unlike those in normal tissues, have gaps as large as 600–800 nm between adjacent endothelial cells. The leaky and defective architecture of tumor vasculature might be due to elevated levels of vascular mediators such as bradykinins, nitric oxide, vascular endothelial growth factor, basic fibroblast growth factor, prostaglandins and so on. The unique pathophysiologic characteristics of tumor vessels coupled with poor lymphatic drainage induces the EPR effect, which enables macromolecules, including nanoparticles, to extravasate through these gaps into extravascular spaces and accumulate inside tumor tissues [57]. Dramatic increases in tumor drug accumulation, usually tenfold or greater, can be achieved when a drug is delivered by a nanoparticle rather

than as a free drug. Another contributor to passive targeting is the unique microenvironment surrounding tumor cells, which is different to that of normal cells. Fast-growing, hyperproliferative cancer cells have a high metabolic rate, and the supply of oxygen and nutrients is usually not sufficient for them to maintain this. Therefore, tumor cells use glycolysis to obtain extra energy, resulting in an acidic environment. The pH-sensitive liposomes are designed to be stable at a physiologic pH of 7.4 but degraded to release active drug in target tissues in which the pH is less than physiologic values, such as in the acidic environment of tumor cells. In addition, cancer cells express and release unique enzymes, such as matrix metalloproteinases, which are implicated in their movement and survival mechanisms. An albumin-bound form of doxorubicin incorporating a matrix-metalloproteinase-2-specific octapeptide sequence between the drug and the carrier was observed to be efficiently and specifically cleaved by matrix metalloproteinase in an *in vitro* study [58].

Active targeting

The polymeric nanoparticles that have been tested clinically so far have mostly lacked a targeting moiety and instead rely mainly on the EPR effect of tumors, the tumor microenvironment and tumor angiogenesis to promote some tumor-selective delivery of nanoparticles to tumor tissues. However, these drug delivery systems using a binary structure conjugate inevitably have intrinsic limitations to the degree of targeting specificity they can achieve. One suggested approach to overcoming these limitations is known as active targeting. It involves the attachment of a homing moiety, such as a monoclonal antibody or a ligand, to deliver a drug to pathological sites or to cross biological barriers based on molecular recognition processes [59–61]. When constructing ternary-structured nanoparticles (consisting of drugs and targeting moiety), some factors must be considered to create more efficient delivery systems. First, the antigen or receptor should be expressed exclusively on tumor cells and not expressed on normal cells. Second, they should be expressed homogeneously on all targeted tumor cells. Finally, cell-surface antigens and receptors should not be shed into the blood circulation. Internalization of targeted conjugates after binding to target cells is an important criterion in the selection of proper targeting ligands. Internalization usually occurs via receptor-mediated endocytosis. For example, when a folate-targeted conjugate binds with folate receptor on the cell surface, the invaginating plasma membrane envelopes the complex of the receptor and ligand to form an endosome. Newly formed endosomes are transferred to target organelles. As the pH value in the interior of the endosome becomes acidic and lysozymes are activated, the drug is released from the conjugate and enters the cytoplasm, if the drug has the proper physico-chemical properties to cross the endosomal membrane. Released drugs are then trafficked by their target organelle, depending on the drug. Meanwhile, the folate receptor released from the conjugate returns to the cell membrane to start a second round of transport by binding with new folate-targeted conjugates. Ligands targeting cell-surface receptors can be natural materials, such as folate and growth factors, which have the advantages of lower molecular weight and lower immunogenicity than antibodies. Some ligands, however, such as folate that is supplied by food, show naturally high concentrations in the human body and might compete with the nanoparticle-conjugated ligand for binding to the receptor, effectively reducing the intracellular concentration of delivered drug.

BOX 2

Nanotechnology-based novel cancer therapy

- Nanotechnology-based gene therapy
- Nanotechnology-based photodynamic therapy
- Nanotechnology-based radiotherapy and radiofrequency therapy
- Nanotechnology-based cancer theragnostics

Nanotechnology-mediated novel cancer therapy

In the treatment of cancer, targeted treatment – in which only cancer cells are killed and normal cells are not harmed – has become increasingly desirable. The introduction of nanotechnology has brought new materials and pathways for the targeted treatment of cancer. Engineered properties of nanoparticles are opening the door to new, noninvasive strategies for cancer therapy that were not previously possible, including nanotechnology-based advance cancer therapy strategies such as photodynamic therapy (PDT), radiotherapy and radiofrequency therapy, and theragnostics (Box 2 and Fig. 4).

Nanotechnology-based gene therapy

Gene therapy is based on the concept that specific exogenous genes can be incorporated into the tumor cell genome to produce a tumoricidal effect. It represents one of the most rapidly developing areas in preclinical and clinical cancer research. Although viral vectors have traditionally been the primary agents used to deliver genes to target cells, they carry the risk of serious immune and inflammatory responses in the host. The problem associated with the viral vector is the toxicity, immune and inflammatory responses, gene control and targeting issue; in addition, there is always a fear of the virus recovering and causing disease. To overcome this, much interest has been shown in nonviral-mediated gene transfer techniques. The advantage of using nonviral vectors is repeated administration at a very low cost and less immune reaction, owing to their nontoxicity. The most widely used nonviral vectors are liposome-mediated cationic polymers and nanoparticles. The physical properties of nanoparticles, including their morphology, size, charge density and colloidal stability, are important parameters for determining the overall efficacy of nanoparticles to act as potential nonviral gene delivery vehicles. Jere *et al.* [62] have 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.

Nanotechnology-based photodynamic therapy

PDT is an alternative to current adjuvant therapy that carries little local or systemic treatment-associated morbidity and is not susceptible to the development of resistance. It involves the administration of a photosensitizing drug. PDT relies on activation of a photosensitizer, which – when activated by a specific wavelength of light – induces the release of reactive oxygen species that can kill tumor cells directly, as well as the tumor-associated vasculature, leading to tumor infraction. Targeting is essential in PDT because

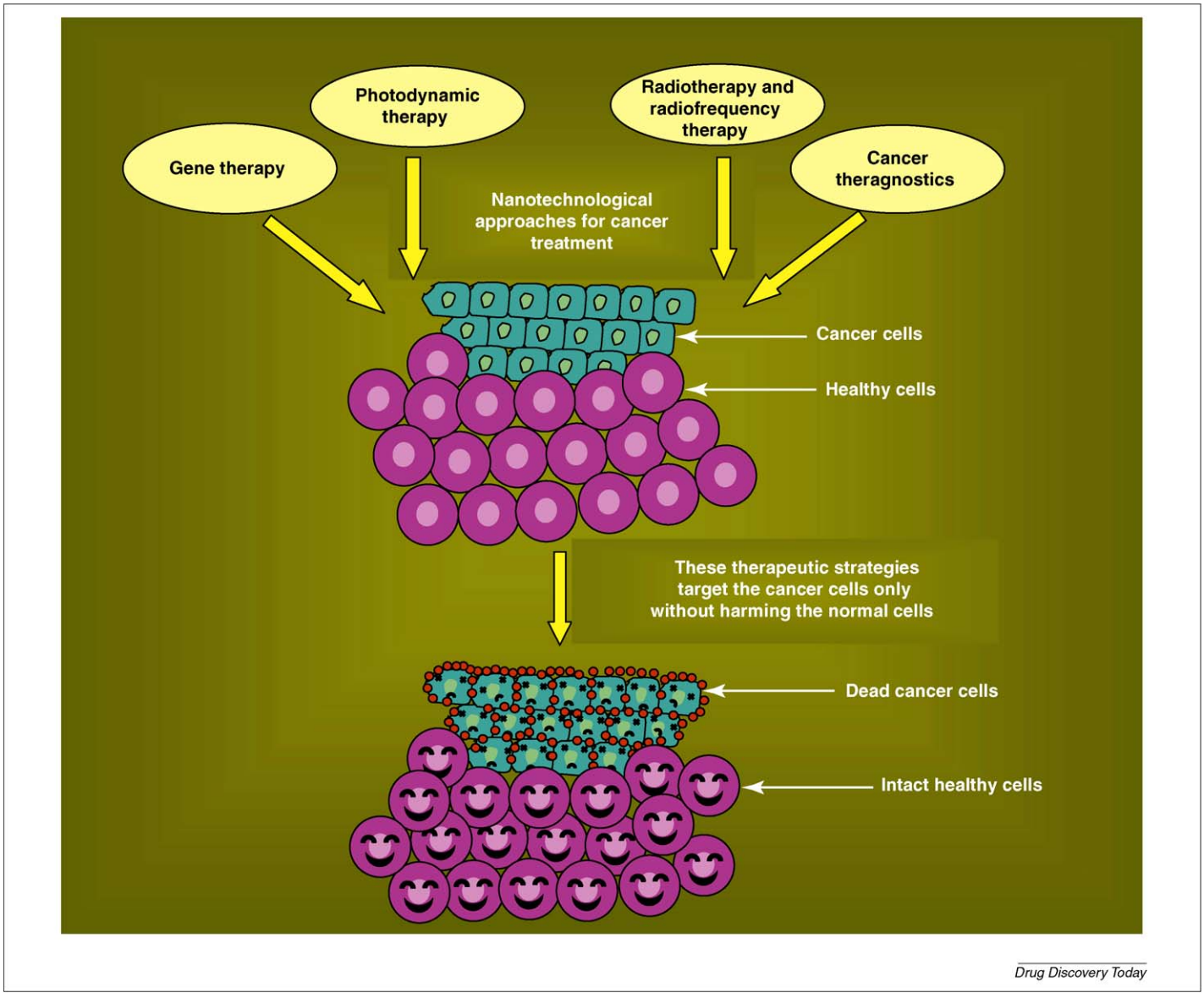

FIGURE 4

Different approaches of nanotechnology such as gene therapy, photodynamic therapy, radio therapy, radiofrequency therapy and cancer theragnostics are being applied for the treatment of cancer. These advanced technologies help target cancer cells only, without affecting normal cells. Ultimately, this leads to death of the cancer cells while the normal, healthy cells survive.

singlet oxygen is highly reactive. Polymeric nanoparticles offer a solution to this problem by enabling the delivery of a high quantity of photosensitizers to tumor cells via tumor-specific ligands. 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.* [63] have developed pH-sensitive nanoparticles as potential carriers for tumor targeting and PDT.

Nanotechnology-based radiotherapy and radiofrequency therapy

Enhancement of radiation dose by high atomic number (Z) materials has long been of interest. It has been reported that loading high Z materials into the tumor could result in greater photoelectric absorption within the tumor than in surrounding tissues, and thereby enhance the dose delivered to a tumor during radiation therapy. To be clinically useful, a radiosensitizer and/or dose enhancer should notably increase the therapeutic ratio and should be readily available, easily utilized and nontoxic. Gold (Au; $Z = 79$) or nanogold (gold nanoparticles) showed dose-enhancing effects in cell experiments and in a murine model. Gold nanoparticles have been actively investigated in a wide variety of biomedical applications because of their biocompatibility and ease of conjugation to biomolecules. Chang *et al.* [64] have 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. Unresectable malignant hepatic lesions are the most common tumor treated with this procedure.

Radiofrequency ablation is an established approach to destroying tumors that has traditionally involved the insertion of probes into tumors; however, nanotechnology is enabling the development of noninvasive radiofrequency ablation of tumors. Gold nanoparticles have been demonstrated *in vitro* and *in vivo* to enhance cancer-cell destruction in a noninvasive radiofrequency field. Cardinal *et al.* [65] have highlighted the potential use of gold nanoparticles for the specific targeting of cancer cells. They have used a novel, noninvasive radiowave machine coupled with gold nanoparticle enhancer solutions to thermally ablate tissue and cancer cells in both *in vitro* and *in vivo* systems.

Nanotechnology-based cancer theragnostics

Combining diagnosis and therapy in one process is an emerging biomedical method referred to as theragnostics. The primary goal of theragnostics is to selectively target-specific (diseased) tissues or cells to increase diagnostic and therapeutic accuracy. With the help of theragnostics, we can bring together key stages of a medical treatment, such as diagnosis and therapy, and make a treatment shorter, safer and more efficient. Several theragnostic methods have employed nanoparticles as the carriers of diagnostic agents and drugs. Biocompatible nanoparticles are currently under development as cancer theragnostic agents that would enable noninvasive diagnosis and precise cancer therapy. Such nanoparticle-mediated combinatorial strategies offer promise for accelerating treatment, reducing side-effects of treatment and improving cancer cure rates. Lukianova-Hleb *et al.* [66] 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 recent reviews have discussed engineering designs, physiochemical characteristics and biomedical applications of magnetic nanoparticles and have mentioned that magnetic nanoparticles can simultaneously act as diagnostic molecular imaging agents and as drug carriers [67]. Shim *et al.* [68] have achieved combined diagnosis and therapy for cancer (theragnostics). In their study, they coated small-interfering-RNA-encapsulating polyplexes covalently with small gold nanoparticles via acid-cleavable linkages to explore the possibility of achieving combined stimuli-responsive multimodal optical imaging and stimuli-enhanced gene silencing.

Future directions

Nanotechnology has become an enabling technology for personalized oncology, in which cancer detection, diagnosis and therapy are tailored to each individual's tumor molecular profile, and for predictive oncology, in which genetic and/or molecular markers are used to predict disease development, progression and clinical outcomes. In recognition of its potential impact in cancer research, the US National Cancer Institute has recently funded eight national Centers of Cancer Nanotechnology Excellence. Looking into the future, there are several research themes or directions that are particularly promising but require concerted effort for success. The first is the design and development of nanoparticles with monofunctions or multiple functions. For cancer and other medical applications, important functions include imaging (single or dual modality), therapy (a single drug or a combination of two or more drugs) and targeting (one or more ligands). Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs and have shown they have a bright future as a new generation of cancer therapeutics. Furthermore, the development of multifunctional nanoparticles might eventually render nanoparticles able to detect and kill cancer cells simultaneously. Although there are certain crucial questions and many challenges remaining for the clinical development of nanoparticles, as more clinical data are available, further understanding in nanotechnology will certainly lead to the more rational design of optimized nanoparticles with improved selectivity, efficacy and safety. Current knowledge regarding the safety of nanocarriers, however, is insufficient. The pharmacokinetic behavior of different types of nanoparticles requires detailed investigation, and a database of health risks associated with different nanoparticles should be created. Preliminary and complementary animal studies should be carried out to identify the risks associated with nanoparticle use, with particular attention paid to elimination processes. Furthermore, very little attention has been paid to environmental effects and the potential effects on the health of those manufacturing these particles. Considering the countless potential applications of nanoparticles in the health sector, particularly in cancer research, there is an urgent need for the development of safety guidelines by the government. The emergence of Nanotechnology Research Centers, established in recent years (some of which are funded through the National Institutes of Health and the National Science Foundation), demonstrate the enthusiasm of investigators and granting agencies for the technology. In the next few years, many applications of nanotechnology will become commonplace within medical practice. Because these advancements will be incremental and will be initially derived from ongoing 'wet science' instead of scaled-down machining and computing, they might, ironically, sometimes be too small to be noticed.

Concluding remarks

The application of nanotechnology in the field of cancer nanotechnology has experienced exponential growth in the past few years. Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs and have shown they have a bright future as a new generation of cancer therapeutics. The multidisciplinary field of nanotechnology holds the promise of delivering a technological breakthrough and is moving very fast from concept to reality.

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