Chapter 8

Nanotherapeutics in Cancer Prevention, Diagnosis and Treatment

Samaya R Krishnan and Suraj K George

Additional information is available at the end of the chapter

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1. Introduction

Definitions of nanotechnology vary widely. Some scientists restrict the definition to work with molecules and devices between 1 and 100nm, while others widen these parameters to 1-1000nm. Kostoff believes that nanotechnology is best defined by the capacity to artificially construct and manipulate structures at nanoscale, and nanoscale's novel properties [1].

Drug loaded nanoparticles are widely utilized in the treatment of a number of diseases, such as metabolic disorders, autoimmune diseases, inflammatory disorders, neurodegenerative diseases and cancer. For instance, nanomedicines have been extremely useful in improving the efficacy of small molecule drug delivery across the blood-brain barrier for the treatment of CNS diseases [2]. In addition, nanoparticles serve as artificial oxygen carriers that can act as a substitute for blood, saving the lives of those in dire need of transfusion [3]. Although liposome-encapsulated formulations of Doxorubicin were being widely administered as early as the 1990's, nanotherapeutics is still viewed as a new and emerging field. The current chapter will focus on the progress made using nanoparticles in cancer prevention, diagnosis and treatment. This is certainly an area of rapid progression, with current nanotherapeutics for cancer encompassing a vast array of nanomaterials and nanodevices [4, 5]. But some critics believe that nanotechnology has not fulfilled its early promise and have expressed concern that progress and investment in the laboratory has not been mirrored by comparable progress or significant clinical success in cancer treatment [5, 6], a concern echoed in the title of Vendito and Szoka Jr's 2013 review: 'Cancer nanomedicines: So many papers and so few drugs!' [7]

However, much investment, research and development into nanotechnology diagnostics, therapies, devices, biosensors, and microfluidics continues to provide advances in the prevention, diagnosis and treatment of cancer [4]. Many scientists believe that nanoparticles

are the future of diagnosis and drug delivery [8] with the potential to overcome many of the obstacles that cancer presents.

2. Obstacles in cancer diagnosis and treatment

2.1. Late stage diagnosis

Late detection and diagnosis of cancer remains one of the fundamental causes of low survival rates [9, 10], so developing a test that detects clinically apparent cancer before symptoms appear is obviously an important goal [9]. The traditional biomedical imaging tools of magnetic resonance imaging, ultrasound and positron emission tomography have several limitations in the diagnosis of cancer, including an inadequate imaging period, a risk of renal toxicity and an inability to detect tumor cells smaller than 1cm [6, 11]. Improvements in PET, CT and MRI, through the use of small molecule imaging agents, such as 2-deoxy-2-(^{18}F) fluoro-D-glucose [FDG], iodinated small molecules and chelated gadolinium respectively, are routinely used in the diagnosis of cancer. However, poor stability, rapid clearance and low signal intensity have limited the use of these techniques and prompted more research into the use of nanoparticles as a diagnostic tool [12].

2.2. Challenges in targeting, transport and delivery of treatment

Chemotherapy's perennial problem has always been that, due to challenges presented by its targeting, transport and delivery, a pharmacologically active concentration in tumor cells is often only achieved at the expense of what Couvrer terms 'massive contamination of the rest of the body' [13]. This toxicity can result in the use of suboptimal and/or intermittent dosing, to allow the body to rest, or in some cases to forgo chemotherapy altogether [14].

Many traditional chemotherapeutics have poor stability and aqueous solubility. Due to this limitation, many drugs, despite significant biological activity, are disregarded at early stages of drug screening in the laboratory. In addition, distribution of some drugs is too general, with only a small fraction of drugs reaching the cancer site; injected agents are often cleared by the monocytes and macrophages of the reticuloendothelial system (RES) [15]. To be successful, a therapeutically sufficient quantity of the drug, still in a viable state, must survive clearing and be delivered to different regions of tumors via blood vessels, cross the vessel wall and then finally penetrate through the interstitial space to reach the target [16], where unpredictable blood flow and often abnormal vasculature in tumors, particularly in necrotic and semi-necrotic regions, can make accurate delivery even more difficult [17, 18].

Other than conventional chemotherapeutic drugs, biological molecules, such as antibodies and nucleic acids, are being widely explored for the treatment of different diseases, including cancer. Nucleic acid drugs, such as aptamers, anti-sense DNA/RNA, and small-interfering RNA, have shown great promise in the treatment of cancer. However, these drugs are greatly limited by serum nucleases, opsonization and clearance by macrophages and clearance by the renal system. Some of the nucleic acid therapeutics, such as stable nucleic-acid–lipid particle

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(SNALP), have used nanocarriers to effectively overcome the above mentioned barriers and are being used in the treatment of cancer [19].

2.3. Chemoresistance

Chemoresistance, a major cause of cancer treatment failure, is linked to cancer stem cells (CSC). CSCs possess unique properties, such as quiescence, mesenchymal morphology, increased DNA repair ability, overexpression of antiapoptotic proteins, drug efflux transporters and detoxifying enzymes [20]. These properties, together with the favorable tumor microenvironment and hypoxic stability, mean that they often escape elimination by current radio and chemotherapies. Having survived through chemotherapy, they can give rise to metastases and recurrent tumors which then increase in malignancy and resistance [20].

Chemoresistance can be divided into two types: intrinsic and acquired. **Intrinsic chemoresistance** is displayed by tumor cells whose genetic and phenotypic characteristics make them ideally suited to withstand cytotoxic agents. **Acquired chemoresistance** can occur after prolonged exposure to chemotherapeutic agents, which disrupt only one of the many biochemical pathways involved in their pathogenesis. Unfortunately this approach often activates and strengthens the alternative pathways, resulting in chemo resistant mutations in the tumor cells and tumor relapse [18, 21, 22]. **Multidrug resistance, or MDR**, can also occur through a process of cross-resistance in which cancer cells mutate and acquire resistance to multiple structurally-related drugs and also to mechanistically different drugs, either via the overexpression of multidrug transporters or through altered apoptosis [21], resulting in decreased intracellular drug retention and altered tumor response [23].

2.4. The patient — Compliance and individuality

It may seem harsh to list the patient as an obstacle but, through no fault of their own, this is often the case. Genetic variation across individuals affects a drug's pharmacokinetics and pharmacodynamics [24], and a breakthrough with one patient cannot always be replicated in another. Also, each patient has different levels of tolerance to the discomfort and effects of chemotherapy, and in many cases a pre-existing condition or illness may complicate their cancer treatment or lead them to refuse it. Patients with comorbid illnesses and elderly patients are those most likely to forgo or discontinue chemotherapy [14].

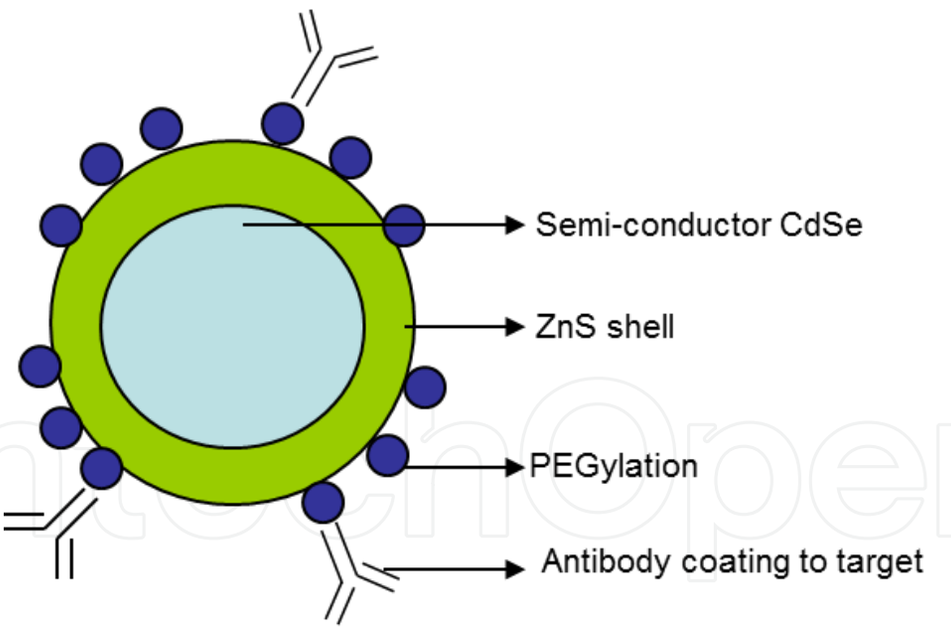
3. Current nanotherapeutics: Overcoming the obstacles

3.1. More accurate detection and diagnosis

Promising results have emerged from combining nanoparticle-based optical contrast agents with existing optical imaging technologies [9]. Their 'programmable' surface properties and potential for passive or active targeting make nanoparticles ideal for diagnostic imaging. The ability of nanoshells, constructed with a silica core and gold shell, to absorb specific wavelengths of light, has great potential for cancer imaging and therapeutic applications [4].

3.2. Quantum dots

Semiconductor quantum dots are luminescent nanocrystals with great potential in both biological and biomedical applications [25]. Their photostability, fluorescence intensity, small size (2–10 nm) and tunable surfaces make them ideal for optical imaging and detecting hundreds of cancer biomarkers in blood assays or tissue biopsies at pg/mL concentrations [25]. The most commonly used agents in the quantum dots are selenides or sulfides of cadmium and zinc [12]. The wavelength of light emitted by the quantum dots depends on their size. The light emitted is much more intense and stable than their other fluorescent counterparts and hence very useful in optical imaging [12]. Cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs) are the most common quantum dot formulations used in biological applications [25]. The inorganic core is covered by an inorganic shell, which imparts greater photostability and increases the fluorescence properties of the core [26]. The surface of the shell is coated with another layer that enhances solubility and stability of quantum dots in the blood [26]. Often times, the surface coating is PEG as it has low toxicity and is biodegradable. A major limitation of quantum dots in imaging is a process called "Blinking". This is due to fluctuation of the quantum dots between the light emitting and non-emitting states. This limits the amount of signal obtained at a specific time [26].



Quantum Dots

3.3. Magnetic resonance imaging

Recently, the development of nanoparticle systems to improve MRI for cancer imaging and diagnosis has made significant progress [8]. Magnetic nanoparticles usually consist of an

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inorganic nanoparticle core and a surface coating that provides stability in aqueous dispersions. This surface coating is manipulated to facilitate targeting, real-time monitoring or both [25]. Their success, particularly as contrast agents for MRI, is largely due to their enhanced proton relaxation and deep-tissue imaging capabilities, non-invasiveness and low toxicity [8, 25].

Supermagnetic iron oxide (SPIO) nanoparticles are now widely used as bowel contrast agents and have been used for some time in spleen/liver imaging. SPIO nanoparticles are readily taken up by macrophages present in the liver parenchyma (Kupffer cells) and, as liver tumors are usually devoid of macrophages, the macrophage-specific uptake of SPIOs increases the contrast between healthy and diseased tissue, allowing liver tumors or micro-metastases as small as 2–3 nm to be detected [25]. SPIO nanoparticles are biodegradable as the iron molecules released into the plasma upon degradation can bind hemoglobin. To avoid clearance of the SPIO nanoparticles, they are often coated with PEG, which enhances the circulation time during the imaging and treatment of prostate cancer. They are conjugated with an aptamer that binds with high specificity and affinity to a cell surface ligand on the prostate tumor cells. The aptamer binding to the cell surface antigen cause a localized increased accumulation of the SPIO that enables imaging. In addition, conjugation of doxorubicin to the SPIO nanoparticles allows the targeted delivery of the chemotherapeutic drug with minimal side effects [27].

3.4. Molecular diagnostics

AuNPs (gold nanoparticles) have brought great benefits in this area, with increased sensitivity and specificity, multiplexing capability and short turnaround times. Aptamer-conjugated NPs can also be used for the collection and detection of multiple cancer cells [8, 28]. Gold nanoparticles scatter light intensely. Based on the size and shape of the gold nanoparticles, the scattering properties of the gold nanoparticles are also changed [29]. The light scattered by the gold nanoparticles have greater photostability than the other imaging agents commonly used [29]. Gold nanorods exhibit a phenomenon called the Surface Enhanced Raman Scattering (SERS), which is also used in cancer diagnosis. In addition, gold nanoshells and gold nanorods have been used to induce photothermal therapy [29]. This is an example for a "theragnostic" agent, as the gold nanorods not only assist in diagnosis of the cancer, but also help in ablation.

3.5. Improving targeting, transport and delivery

Nanoparticles are increasingly utilized because of the multiple benefits that they offer [30]. Nanodelivery systems can make the use of chemotherapy drugs more safe and efficient by improving delivery, cell uptake and targeting, and have been shown to improve their pharmacokinetic profiles and enhance their targeting at the required site [21, 31]. This success relies on two main factors: 1] the EPR 2] The potential ability of nanodrug delivery systems to overcome the shortcomings of many anticancer drugs [20].

1. The EPR, or enhanced permeation retention effect, exists because of two properties of tumors. Firstly, tumor tissues have increased vasculature which allows the entry of macromolecules and colloidal particles of diameter up to 600nm. Secondly, the lymphatic

system is not effective in clearing the interstitial fluid from the tumor tissues [6]. Normal tissues other than the spleen, liver and kidney are impermeable to molecules that are larger than 2nm. Hence, nanoparticles can selectively target tumor tissues reducing toxic side effects [6]. Together, the enhanced permeation and retention properties of the tumor over the normal tissues cause the nanoparticle to have prolonged contact with the tumor cells. In addition, nanocarriers also release the drug slowly, ultimately resulting in reduced drug distribution and toxicity to normal tissues [6].

2. Once the nanoparticles reach the target tissue, cell surface receptors interact with ligand-coated nanoparticles leading to their uptake by endocytosis. Cellular uptake of uncoated nanoparticles is governed by their differences in size, shape and charge. It is suggested that positively charged nanoparticles are taken up more readily due to electrostatic attraction [32]. Interaction with specific serum proteins, results in the formation of a corona, promoting cell entry. Recent studies indicate that non-spherical molecules, such as rod-shaped structures, are internalized better than spherical structures [33]. Uptake of larger nanoparticles disrupts the membrane surface, thereby inducing cell death [34]. Non-specific uptake of the nanoparticles by the lung epithelial cells and red blood cells could cause toxic side effects.

3. Nanosized drug delivery systems can potentially overcome the shortcomings of many anticancer drugs, such as low aqueous solubility and stability and high nonspecific toxicity [20]. For example, paclitaxel nanoparticles stabilized with pluronic F68 are stable for years, while the same drug in dissolved form degrades completely in less than 48 hours [30, 35], and magnetic nanoparticles (MNPs) are increasingly used because their targeting ability reduces systemic distribution of cytotoxic compounds *in vivo* and enhances uptake at the target site, resulting in effective treatment at lower doses [8].

3.6. Nanodrug delivery systems

Nanodrug delivery can either use passive targeting mechanisms, such as the EPR effect, or active targeting mechanisms, using ligands directed against differentially overexpressed cell surface markers surface on tumor cells [20]. Drug encapsulation within nanoparticles can also enhance the bioavailability of drugs administered via routes other than intravenous; both insoluble and soluble drugs can be incorporated within nanoparticulate sols, extending their stability as they travel through the blood, which in turn improves their overall pharmacokinetic half-life [30].

By 'pre-programming' the degradation of nanoparticles in the body, prolonged drug release can be achieved, eliminating the need for repetitive dosages and enabling more sustained and consistent drug concentrations in the target area [30]. Brannon-Peppas and Blanchette have compared the uptake of nanoparticles with more hydrophobic surfaces with those of more hydrophilic surfaces. They concluded that a nanoparticle designed to be 100nm or less in diameter with a hydrophilic surface will have a longer circulation time and hence a greater ability to target the required site [17] due to reduced clearance by macrophages.

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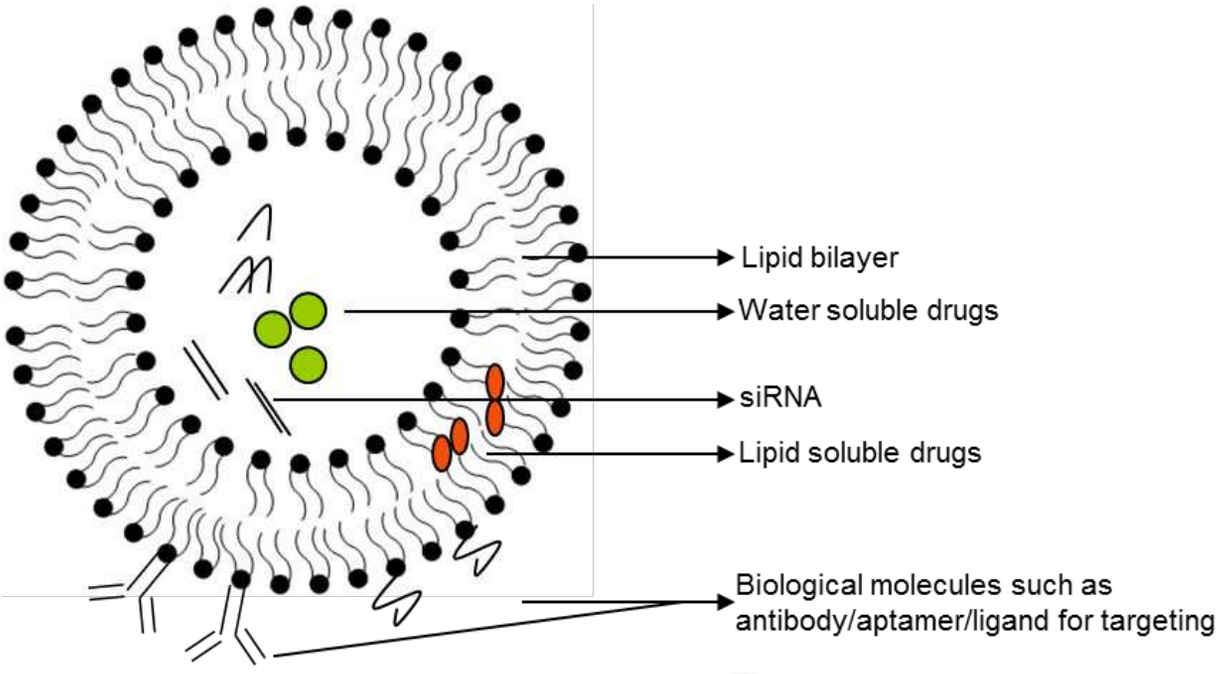
Nanodrug delivery systems can carry one or a combination of therapeutics, including cytotoxic agents, chemo sensitizers, small interference RNA (siRNA) and antiangiogenic agents [22]. The most commonly used platforms are described below.

Liposomes have been in use for the past several decades and are established as drug and imaging agent carriers with proven clinical efficacy [6]. They are artificial phospholipid vesicles 50 nm to ≥1 μm in size, either unilamellar or multilamellar (with one lipid layer or several, arranged in onion-like layers), with one or more aqueous compartments [6, 36]. The 'cargo' can be held in the aqueous compartment(s) or lipid layer [37]. Liposomal nanocarriers provide protection from degradation. Optimization of the pharmacokinetics of the encapsulated drug can improve drug accumulation in the tumor and reduce the adverse effects of bolus administration [37].



Polymeric micelles consist of a hydrophobic core and a hydrophilic shell and are useful drug carriers, due to their tunable size and surface functions, high monodispersity and excellent stability. They have the ability to form hydrogels and are used for drug encapsulation or drug conjugation [38]. Under the right conditions, pluronics, the most well-known thermosensitive polymers, form a hydrogel at body temperature but are water soluble at 2-4°C. This allows them to be injected as a liquid but they form a hydrogel *in situ*, resulting in prolonged drug release of the encapsulated drug [36].

Dendrimers are globular macromolecular compounds consisting of an inner core, which can be manipulated to alter its shape and size, surrounded by a series of branches with surface

functional groups. They can carry a multiple payload of active targeting molecule, diagnostic agent and therapeutic drug, and those with a hydrophobic core and hydrophilic surface groups can form micelles, which can then be designed for site-specific release of their payload, via pH and enzyme dependent mechanisms [39, 40].

Inorganic nanoparticles, such as gold nanoparticles, can be used as a cargo for drug delivery. Gold has a number of appealing surface properties, such as light scattering, which makes them attractive inorganic biomaterials for drug delivery when combined with nanoparticles. Due to their ease of synthesis, biocompatibility, and affluent functionalization, many drugs can be conjugated to the surface of gold through hydrophobic interactions. Gold–thiol conjugates are the most common due to their accurate and predictive functionalization. Various antibiotics, anticancer agents and oligonucleotides are also conjugated with gold nanoparticles to yield more viable drug delivery agents. Other inorganic nanoparticles that are frequently used in drug delivery and diagnostics include silica and iron oxide, which forms the core constituent of many inorganic nanoparticles [41].

Porous silica based nanoparticles are highly suitable for carrying hydrophobic drugs. These nanoparticles have a high surface-to-volume ratio and consists of large pores. The drug can be loaded on the nanoparticles by physical adsorption and covalent linkage [42]. Nanostructured mesoporous silicon (PSi), fabricated by electrochemical etching, have nanometer range pores that facilitate high drug loading capabilities, irrespective of different surface chemistries.

3.7. Nanoparticles as therapeutic agents

Nanoparticles can be used as a therapeutic agent themselves. Their ability to alter the substrate molecule, through a process called "intercrossing" upon excitation by light, is used to treat cancer cells in the photodynamic therapy. While in the photothermal therapy, the property of small inorganic molecules to generate heat upon excitation is taken advantage of in the inducing apoptosis or necrosis of cells.

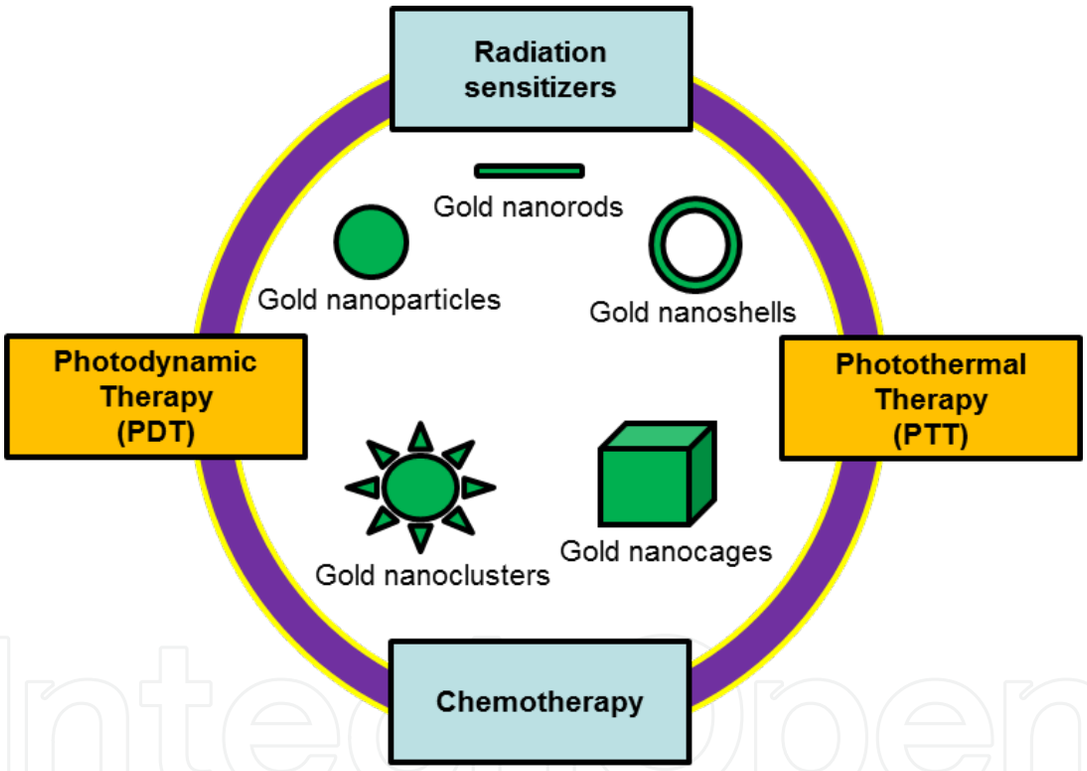
3.7.1. Photothermal therapy

Photothermal therapy (PTT) uses sensitizers that can absorb light in the near-infrared region and convert it to thermal energy, causing heat in the vicinity. The sensitizer used in PTT is usually inorganic molecules, such as gold or carbon nanoparticles. Thermal ablation therapy has been used in the treatment of cancer for many decades, but the damage to nearby tissues has limited the use of this technique in the treatment of cancer [43]. However, with the advent of photodynamic therapy (PDT), targeted destruction of the tumor cell has become possible. PEGylation and active targeting of Au nanotubes have been used in the treatment of many cancers [44].

3.7.2. Photodynamic therapy

Photodynamic therapy (PDT) uses photosensitizers in the treatment of cancer or other disorders. Photosensitizers are molecules that can be excited by light, which then alters molecules in the vicinity, causing the release of singlet oxygen species (reactive oxygen

species). ROS are capable of causing oxidative stress to the surrounding cells, causing apoptosis or necrosis [12]. Photosensitizers can be excited using lasers over a wide range of visible wavelengths. Because of the limited penetrability of visible light, photosensitizers can be used to treat only superficial tumors, such as skin, lung, esophagus, prostate, head and neck, colon and rectum to mention a few. Because the half-life of the reactive oxygen species is only a few milliseconds, this therapy can be used to cause targeted cell death in regions where the photosensitizer has accumulated. Photosensitizers can be coated with polyethylene glycol to prevent renal clearance and to enhance the circulation time in the blood. Further antibody conjugation to the surface can target the photosensitizer to the cancer cells that overexpress the antigen on the surface.



Combinational phototherapy

3.8. Overcoming resistance

Nanovehicles carrying therapeutic drug combinations that not only target the tumor cells selectively, but also overcome the mechanisms of drug resistance are the focus of intensive research. This method has been proved especially effective in circumventing multidrug resistance (MDR) in multiple cancer models [21, 36]. MDR was reversed in *in vitro* and *in*

vivo cancer models through the co-delivery of combinations of chemo sensitizing agents and chemotherapeutic agents [22].

3.9. Improving therapy

Nanoshells are nanoparticle beads with a thin gold outer shell and a central silica core. By manipulating the thickness of the shell and core, the beads can be tuned to absorb and scatter specific wavelengths of light across the visible and near-infrared (NIR) spectrum, which is very useful in enhancing imaging properties [4].

Arguably, however, this ability to absorb light is most usefully exploited in thermal ablation therapy. For maximum efficacy, nanoshells with a silica core diameter of ~120 nm and a 10-nm gold shell are used in this therapy as they strongly absorb NIR light (~800 nm) and can then create intense heat that is fatal to cells [4]. As tissue chromophores do not absorb much energy in the NIR range, NIR light can penetrate several centimeters of human tissue without causing harm [4].

3.10. Improving cancer prevention

The complete prevention of cancer occurrence, claims Siddiqui et al, as an unachievable goal; cancer prevention describes 'slowing the process of carcinogenesis' and inhibiting its reoccurrence [45]. Inefficient systemic delivery and bioavailability of chemopreventive agents has so far limited their applicability to human medicine. However, Siddiqui et al have experimented with encapsulating a chemopreventive agent, epigallocatechin-3-gallate (EGCG), in polylactic acid [46] and polyethylene glycol (PEG) nanoparticles [45]. Nano-EGCG had a significantly longer half-life and had more than a 10-fold dose advantage over nonencapsulated EGCG in cell growth inhibition, proapoptotic, and angiogenic inhibitory effects. Curcumin derived from turmeric, when conjugated with polymeric amphiphile, mPEG-PA or PEG, has been shown to have more significant antiproliferative effects than the free curcumin [47, 48]. Another nanoparticle-based formulation, called solid lipid nanoparticles (SLN), is also being used as newer therapeutic modality to address the area of chemoprevention. The advantage is that they act like colloidal carriers which remain as solids at room and body temperature, and so can be efficiently used as alternatives to lipososmes and other polymeric nanoparticles [36]. A multitude of approaches utilizing nanoparticles to combat these existing deficits in the chemopreventive strategies will re-captivate the 'silver bullet' for chemoprevention in the near future.

3.11. Improving compliance

Nanotherapeutics can be less invasive than conventional diagnosis and treatment methods. This leads to shorter recovery times and a decreased risk of infection, and these advantages in turn should lead to a reduction in cost and improved life expectancy and quality [49].

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4. The future: Potential risks, rewards and research

4.1. New risks: The voice of caution

With its obvious potential for breakthroughs in so many fields, it is easy to view nanotechnology as an exclusively positive concept. However, it is not without risk and nanomaterials may present greater risks than their larger counterparts, as their greater relative surface and unique quantum effects mean they have a tendency to be more active and reactive [50]. Their potential to cause harm is harder to predict, as it is determined using factors such as surface area, rather than molecular structure, which is used to risk assess most other chemical hazards, and there are no proven toxicity screening methods to evaluate them. The scarcity of information about how nanomaterials may impact safety, health and the environment, along with the growing number and diversity of nanotechnologies and their associated engineered properties, has raised serious concerns. If nanomaterials escape the laboratory or manufacturing site, their degradation and interaction with substances in the environment would be unpredictable and potentially hazardous [30, 51].

When assessing the risk to patients, it is important to bear in mind that preclinical trials of nanodrugs may be less indicative of human risks than trials of standard medicines, and that nanomaterials can utilize unique mechanisms and routes of exposure, potentially bypassing the blood-brain barrier [25]. If inhaled, they may aggregate in the alveoli, where their increased surface area places a burden on mucociliary and macrophage clearance [52].

Like any other emerging area of interest in human health, nanotechnology also has its own demerits. A word of caution is that this research is still in its infancy to determine the unforeseen side effects pertaining to nanoparticle related therapies [53]. Although our understanding on the concepts regarding nanotherapeutics has come a long way, the exact nature of nanoparticulate drug interactions has not been tested vigorously. Studies in animals suggest alarming facts affecting the brain function [54-56]. With the limited current literature in humans, it is almost impossible to judge their safety over efficacy. Hence, until a stringent risk assessment strategy is employed, nanotherapeutics should not be viewed exclusively as a positive concept. It is important that, if nanotechnology is to move forward safely and sustainably, a thorough assessment of the biocompatibility and toxicity of nanoparticles is undertaken, with potential toxicities identified and their underlying mechanisms understood [57]. Research into the avoidance of health risks associated with nanotechnology may potentially be used to guide therapy, and vice versa [58].

5. New rewards: A bright future

5.1. Multifunction nanovehicles

Advances in MRI contrasting agents promise a next generation of agents consisting of a core and coating conjugated to tumor-specific moieties for improved efficacy and tumor targeting [25]. Perche and Torchillin have suggested that a possible direction for research may be the

coupling of ligands of different natures (antibodies, proteins, peptides and chemokines, hormone analogs) to target at least two tumor cell populations, providing more sensitive malignant lesion detection and reducing relapses [24, 37]

Shapira looks forward to the development of 'theragnostic' nanovehicles that carry four major components: a selective targeting moiety, a diagnostic imaging aid for localization of the malignant tumor and its metastases, a cytotoxic small molecule drug(s) or innovative therapeutic biological matter, and a chemosensitizing agent to neutralize drug resistance – the advent of "quadrugnostic" nanomedicine [59].

5.2. New detection methods and diagnostic devices

Nanoparticle probes, nanocantilever, nanowire and nanotube arrays are the subject of intensive research and are expected to solve the problem of early detection in the future [9]. Accurate localization of tumors and their metastases, *via* nanoparticles loaded with a diagnostic aid, could in future facilitate the harnessing of other therapies, such as radiotherapy, photodynamic therapy and surgery [59].

Heller group has described the goal of research as 'the development of a cancer therapy monitoring/diagnostic platform device'. This would provide real-time monitoring of patient blood for cancer cells, cell derived nanoparticulates (such as high molecular weight DNA fragments), and carry out cancer-related genotyping, gene expression and immunochemical analysis [60].

5.3. New applications, new targets

Superparamagnetic iron oxide nanoparticles (crystalline magnetite structures coated with dextran and dextran derivatives) are promising candidates for a number of applications, including magnetic resonance imaging and drug delivery [6]. Bharali and Mousa believe that a major potential application of these nanoparticles is the diagnosis and treatment of central nervous system (CNS) tumors, particularly if USPIOs (ultrasmall supermagnetic iron oxide particles) are used, as they can be utilized as intravascular contrast agents, as well as for cellular imaging [25] One USPIO already showing great promise is Combidex, which has been undergoing clinical trials for the detection of lymph node metastases [25].

Talekar et al predict that multifunctional superparamagnetic nanocarriers, with FR (folate receptor) targeting and pH mediated drug release, can be developed to achieve a decrease in tumor volume, as well as improved MRI sensitivity and decreased adverse effects [6]. Metal coordination complexes also offer a diversity of formulations and the prospect of mechanisms that differ from those of organic drugs, including ligand substitution and metal-and ligand-centered redox properties [31].

Therapeutic and imaging nanoparticles have normally used passive targeting to date, but active targeting needs to be used and further developed if drugs are to be delivered to specific classes of cells and specific intracellular sites in cancer cells [31].

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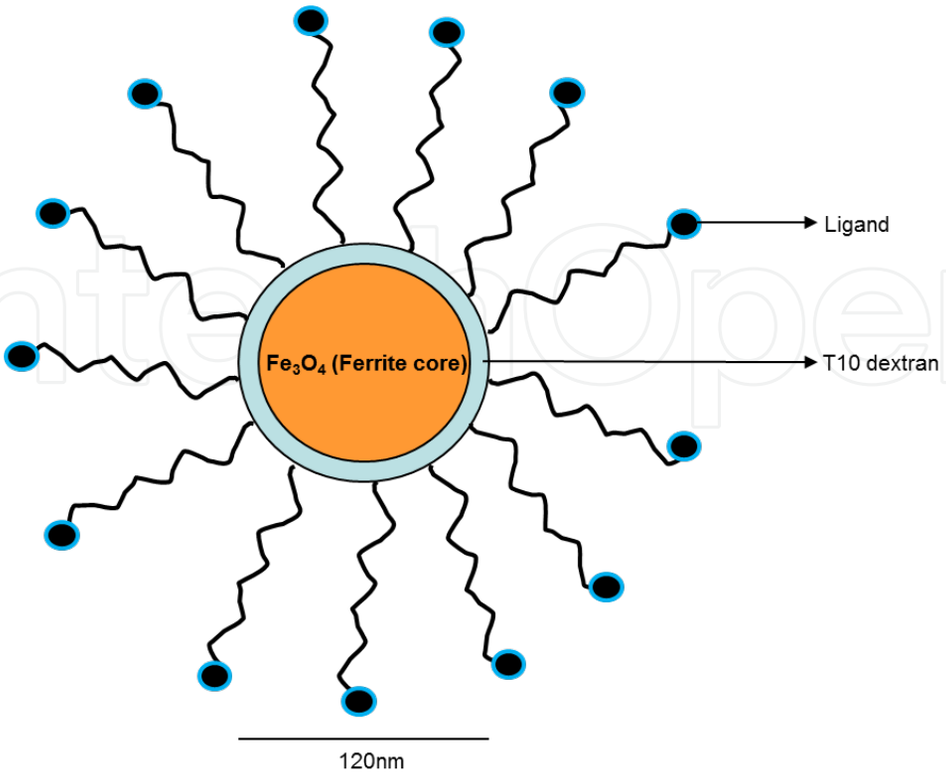

5.4. Reducing the side effects

Nanoparticle encapsulation has already been shown to reduce unwanted accumulation of platinum in the kidneys from the platinum [59] prodrug mitaplatin, and reports show that metallodrugs loaded in nanoparticles cause less damage than the drugs on their own. So these formulations are predicted to be in line for further research and exploitation in the near future [31].

6. Bench to bedside: Translational perspectives

Nanotechnology has raised as many questions as it has answered, and spawned new and unpredicted fields [61]. With its vast array of potential applications in so many fields of science and industry, it is a prime candidate for multidisciplinary collaboration, and the urgent need to see laboratory breakthroughs translated to clinical successes is increasingly recognized. Biochemists are increasingly working with scientists from fields not usually associated with medicine, and the NIH's Nanomedicine Development Centers are staffed by multidisciplinary research teams, including biologists, physicians, mathematicians, engineers, and computer scientists, whose first task has been to research the chemical and physical properties of

nanoscale biological structures [58]. Baseline work of this sort is vital if clinicians are to have the knowledge to develop new therapies.

Murday et al claim that translational research has been 'a powerful process that drives the clinical research engine', but feel that a stronger research infrastructure is needed in future to 'strengthen and accelerate this critical part of the clinical research enterprise [58]. Kawasaki and Player agree that scientists from all fields must make a strenuous effort to integrate and coordinate the research in an approach that might now be described as 'systems biology'. They hold up the 2004 article 'Electronic structure and bonding of Au on a SiO2 cluster: a nanobullet for tumors' [46], produced by physicists, as a prime example of how research in other fields can advance nanomedicine [46, 62].

7. Conclusions

Nanotherapeutics have already yielded significant breakthroughs in the detection, diagnosis and treatment of cancer, and appear to have the potential to yield many more, with extensive and focused routes of research planned for the future and the possibility of nanotechnology-based cancer prevention. But it is clear that nanotechnology must be thoroughly understood and its risks assessed if it is to be developed safely, and that the expertise of researchers in many fields needs to be brought together to move new discoveries out of the laboratory and into the clinical environment where patients can reap the benefits.

Author details

Samaya R Krishnan[1] and Suraj K George[2*]

*Address all correspondence to: skonnath@mdanderson.org, surajrcc@gmail.com

1 Dept. of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

2 Dept. of Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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