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Expert Opinion

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Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications

John W Rasmussen, Ezequiel Martinez, Panagiota Louka & Denise G Wingett†

†*Boise State University, Department of Biological Sciences, 1910 University Dr, Boise, ID 83725, USA*

Importance of the field: Metal oxide nanoparticles, including zinc oxide, are versatile platforms for biomedical applications and therapeutic intervention. There is an urgent need to develop new classes of anticancer agents, and recent studies demonstrate that ZnO nanomaterials hold considerable promise.

Areas covered in this review: This review analyzes the biomedical applications of metal oxide and ZnO nanomaterials under development at the experimental, preclinical and clinical levels. A discussion regarding the advantages, approaches and limitations surrounding the use of metal oxide nanoparticles for cancer applications and drug delivery is presented. The scope of this article is focused on ZnO, and other metal oxide nanomaterial systems, and their proposed mechanisms of cytotoxic action, as well as current approaches to improve their targeting and cytotoxicity against cancer cells.

What the reader will gain: This review aims to give an overview of ZnO nanomaterials in biomedical applications.

Take home message: Through a better understanding of the mechanisms of action and cellular consequences resulting from nanoparticles interactions with cells, the inherent toxicity and selectivity of ZnO nanoparticles against cancer may be improved further to make them attractive new anticancer agents.

Keywords: cancer, metal oxide, nanoparticles, ZnO

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1. Introduction

Nanotechnology represents a new and enabling platform that promises to provide a broad range of new uses and improved technologies for biological and biomedical applications. One of the reasons behind the intense interest is that nanotechnology permits the controlled synthesis of materials where at least one dimension of the structure is < 100 nm. This ultra-small size is comparable to naturally occurring proteins and biomolecules in the cell [1], and is notably smaller than the typical diameter (~ 7 μm) of many human cells. The reduction of materials to the nanoscale can frequently alter their electrical, magnetic, structural, morphological and chemical properties, enabling them to interact in unique ways with cell biomolecules and enabling their physical transport into the interior structures of cells. Nanoscale particles typically possess a larger percentage of atoms at the material's surface, which can lead to increased surface reactivity [2], and can maximize their ability to be loaded with therapeutic agents to deliver them to target cells. By appropriate engineering design, these nanomaterials can acquire the ability to target selectively

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Article highlights.

- There is an urgent need to develop new anticancer agents that are better able to target cancer cells while sparing normal cells and tissues. Nanomedicine, including the use of ZnO nanoparticles, offers considerable promise in this regard.
- The development of new physical and chemical properties that can accompany reduction of materials to the nanoscale offers advantages for developing anticancer agents, including the ability to tailor the electrostatic properties and size of nanoparticles to promote cellular uptake and make use of the enhanced permeation and retention effect to promote intra-tumor accumulation.
- Reduction of ZnO to the nanoscale has toxicological ramifications, including the generation of reactive oxidative species, which may be exploited in combination with cancer-specific targeting strategies for developing new therapeutics.
- There is an increasing amount of attention on nanomaterials and their successful use in cancer treatment regimens. The potential of ZnO and other metal oxide nanoparticles is beginning to be realized.
- ZnO nanoparticles have multiple properties that are useful for biomedical applications, including favorable band gap, electrostatic charge, surface chemistry and potentiation of redox-cycling cascades. Notably, ZnO nanoparticles appear to have inherent anticancer cytotoxicity actions.
- A variety of metal oxide nanoparticles have shown success for use as vehicles for drug delivery, targeted gene delivery and tumor imaging. The use of metal oxide ZnO nanoparticles in these applications is beginning to be explored, with some success in areas of drug carrier and targeted gene delivery.
- Careful titration of ZnO nanoparticle-based therapeutic interventions may be successful in increasing antitumor cytokine production and exerting cancer cell destruction, without eliciting harmful systemic pro-inflammatory effects.

This box summarizes key points contained in the article.

particular types of cell or to pass through physiological barriers and penetrate deep into tumor sites.

The application of nanotechnology to medical applications, commonly referred to as 'nanomedicine', seeks to deliver a new set of tools, devices and therapies for treatment of human disease. Nanomaterials that can act as biological mimetics, 'nanomachines', biomaterials for tissue engineering, shape-memory polymers as molecular switches, biosensors, laboratory diagnostics, and nanoscale devices for drug release, are just a few of the applications now being explored [3-5]. Already, nanomedicine represents an emerging industry, with the US National Science Foundation predicting that the market for nanotechnology-containing products will reach US$1 trillion in 10 – 15 years [6]. As such, there is considerable interest in the role of nanomaterials for the rational delivery and targeting of pharmaceutical and diagnostics agents for the treatment of cancer. The potential use of ZnO and other metal oxide nanoparticles in biomedical and cancer applications is gaining interest in the scientific and medical communities, largely owing to the physical and chemical properties of these nanomaterials, and is the focus of this article.

1.1 Cancer treatment today

Cancer is reported as the second leading cause of death in the US and accounts for ~ 25% of all deaths [4]. Even more serious is the recent projection by the World Health Organization, which anticipates total cancer cases will more than double by the year 2030 from the 12.4 million new cases seen in 2008 [7]. Despite the fact that scientific understanding of the functioning of the human body at the molecular level has improved tremendously, advances in therapeutic options for cancer have lagged by comparison. Current anticancer chemotherapies based on alkylating agents, antimetabolites, biological agents and natural products frequently fail to produce a complete anticancer response owing to the development of drug resistance or their failure to differentiate effectively between cancerous and normal cells. This indiscriminate action frequently leads to systemic toxicity and debilitating adverse effects in normal body tissues, including bone marrow function suppression, neurotoxicity and cardiomyopathy, which greatly limits the maximal allowable dose of the chemotherapeutic drug [8,9]. In this regard, recent studies have shown that ZnO nanoparticles show a high degree of cancer cell selectivity with the ability surpass the therapeutic indices of some commonly used chemotherapeutic agents in similar *ex vivo* studies [10,11]. In addition, the rapid elimination or widespread dissemination of the anticancer drug across non-target tissues requires drug administration in large quantities, which can further complicate problems related to nonspecific toxicity. Thus, there is an urgent need to develop new classes of anticancer drugs with new modes of action that better target cancer cells while sparing healthy tissues.

1.2 Overview of nanotechnology in cancer applications

Nanobiotechnology has been viewed as having the potential to offer a more targeted approach capable of providing significant treatment improvements for cancer patients. The underlying rationale is that reduction of materials of the nanoscale can sometimes lead to the development of new structural, physicochemical, electronic and magnetic properties that are not present in larger bulk-sized (micrometer or larger) particles consisting of the same material systems. It is these new properties that can potentially lead to unique biological and medical applications. A growing number of research groups have shown that low concentrations of nanomaterials, including metal oxide nanoparticles, can kill human cancer cells, whereas their larger micrometer-sized counterparts are comparatively non-toxic [2,10,12-16]. Even more compelling are recent *in vitro* observations indicating that certain types of metal oxide

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nanoparticle can preferentially kill cancer cells, with strikingly less toxicity against normal cells [10,11]. As a natural outcropping of these studies, there is considerable interest in further improving nanoparticle specificity and anticancer properties by functionalizing them with antibodies or other ligands directed against cancer-associated molecules [17]. Nanomaterials are also being explored for use in intracellular delivery of DNA, RNAi, proteins, peptides and small drugs for inducing cancer cell death, as contrast agents for cancer imaging, and as platforms for targeted gene and chemotherapeutics delivery to tumor sites [4,17].

2. Significance of nanomaterial physical properties and biological applications

The integration of nanotechnology and biology provides the opportunity for the development of new materials in the nanometer size range that can be applied to many potential applications in clinical medicine [1,18]. The most widely studied type of nanomaterial is the nanoparticle, which is largely owing to their ease and efficiency of production from a variety of materials. When reduced to the nanoscale, unique size-dependent properties of nanoparticles are manifested [2]. The principal factors believed to cause properties of nanomaterials to differ from their larger micrometer-sized bulk counterparts include an increase in relative surface area, a greater percentage of atoms at the material's surface, quantum effects that can affect chemical reactivity, and other physical and chemical properties [2,18]. The positioning of the vast majority of nanostructure atoms at the material's surface maximizes their ability to be loaded with therapeutic drugs, and to deliver these agents to target cells and tissues.

The size of nanoparticles, which is comparable to naturally occurring biological molecules, is another feature that makes them well suited for biological applications. Their nanoscale size allows their internalization into cells, and allows them to interact with biomolecules within or on the cell surface, enabling them potentially to affect cellular responses in a dynamic and selective manner. The size of nanoparticles can facilitate their entry into tumor tissues, and their subsequent retention, by a process recognized as the enhanced permeation and retention (EPR) effect. Therapeutic approaches making use of the EPR effect are now recognized as the 'gold-standard' in the design of new anticancer agents. The EPR phenomena can be described as a combination of 'leaky' tumor blood vessels resulting from alterations in angiogenic regulators, enlarged gap junctions between endothelial cells, and compromising lymphatic drainage in the tumor microenvironment. This localized imbalance allows nanoparticles of certain sizes [19] to enter readily, but to be passively retained within the tumor interstitial space, thereby improving therapeutic potential. In a recent report, particles of 100 – 200 nm size showed a fourfold higher rate of tumor uptake compared with particles > 300 nm, or < 50 nm in size [20]. Although smaller nanoparticles do not readily make use of the EPR effect, they typically show more nanotoxicity related to their larger surface area/volume ratio [19,20]. These seemingly conflicting actions with respect to nanoparticle size and antitumor activity can make it difficult to predict reliably nanoparticle characteristics likely to provide the best therapeutic efficacy without direct testing.

The electrostatic nature of nanoparticles is another important consideration as electrostatic interactions between positively charged nanomaterials and target cells are believed to play an important part in cellular adhesion and uptake [21]. Compared with normal eukaryotic cells whose outer leaflet consists of neutral charged zwitterionic phospholipids [22], cancer cells frequently maintain a high concentration of anionic phospholipids on their outer leaflet and large membrane potentials [23-25], and overexpress specific groups of charged proteins and carbohydrates [5]. In addition, studies have shown that intracellular pH increases with cell cycle progression and proliferation [26,27], which could affect electrostatically-driven interactions with charged particles at the cell membrane. Even more compelling are data demonstrating that whereas polycationic polymer particles and cationic fullerenes cause substantial disruption of biomembranes, their neutral or negatively charged counterparts fail to cause measurable effect [28]. Whereas nanoparticles with higher positive charge may be desirable for higher toxicity to cancer cells, very high positive charge may not be suitable for *in vivo* cancer treatment owing to rapid serum clearance [29]. Thus, tailoring the surface charge of nanoparticles is expected to influence their cytotoxicity and will probably be an important parameter for developing cancer therapies.

The overall shape and morphology of the nanomaterial is another important consideration for biomedical applications. In addition to nanoparticles, which are roughly spherical in structure, there are two-dimensional thin films that have been utilized for > 40 years. There is also a class of one-dimensional nanostructures, commonly referred to as nanowires, which have cylindrical cross-sections of < 100 nm but can be hundreds of micrometers long. This later class includes the well-described carbon nanotubes, which have a hollow interior, whereas other types of nanowire made of other materials are frequently solid [30,31]. Other shapes of nanomaterial are emerging concurrent with technological advancements, such as tetrapod-like ZnO nanostructures [32], and are discussed in Section 5.4. As nanoparticles can be readily and efficiently synthesized from a wide variety of materials, including semiconductors, which can participate in cellular redox reactions and have photocatalytic activity, they are increasingly being considered for use in biomedical applications and are the focus of this review.

3. Toxicology concerns of ZnO nanoparticles

Although nanoparticles of many different types of material can be produced, compatibility issues with living cells limits the types of nanomaterial under consideration for use in

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biomedical applications. ZnO is considered to be a 'GRAS' (generally recognized as safe) substance by the FDA. However, the GRAS designation most commonly refers to materials in the micrometer to larger size range, as even these substances when reduced to the nanoscale can develop new actions of toxicity. As a result, a detailed evaluation of nanomaterial toxicity in both *in vitro* and *in vivo* systems is needed, as well as identifying means to reduce unwanted toxicity. One common approach to increase biocompatibility and reduce particle aggregation involves coating nanoparticles with discrete-sized polymers to render them less toxic, more likely to be taken up by cells, and potentially more suitable for drug delivery applications [33].

The primary means by which inadvertent nanoparticle exposure in humans can occur is by means of inhalation, ingestion, or dermal contact. After gaining access to the circulatory system, nanoparticles can be distributed throughout the body and to specific organs [34,35], and taken up by cells through phagocytic or endocytic mechanisms [18]. The liver, heart, spleen, pancreas and bone all appear to be targeted sites of ZnO nanoparticles in mice [36], and inhalation of these particles in rats produces potent yet reversible pulmonary inflammation [37]. In humans, a common occupational pulmonary illness known as metal fume fever, an influenza-like illness resulting from inflammation of the respiratory track, occurs when unprotected metal workers inhale metal fumes such as zinc oxide. Another common exposure route of ZnO nanoparticles in humans occurs through topical application of sunscreens and cosmetic products that incorporate these particles owing to their UV absorption and transparent properties. Although there remains some concern whether ZnO nanoparticles in these products can enter the body and cause toxicity, most studies indicate that ZnO nanoparticles do not penetrate the skin and do not cause recognizable illness [38,39].

The mechanisms of cytotoxicity from ZnO nanoparticles are not completely understood, but generation of reactive oxygen species (ROS) is believed to be a major component. When nanoparticles interact with cells, cellular defense mechanisms are activated to minimize damage. However, if ROS production exceeds the antioxidative defensive capacity of the cell, it results in oxidative damage of biomolecules, which can lead to cell death [40,41]. Nel *et al.* have described ROS oxidative stress as a three-tier model [2]. Tier 1 involves increases in antioxidant enzymes to start the initial antioxidant defense, followed by tier 2, which includes an increase in potent pro-inflammatory cytokines leading to inflammation, while tier 3 is characterized by mitochondrial perturbation resulting in cellular death by apoptosis or necrosis. All three of these levels have been observed for ZnO nanoparticles in immortalized phagocytic or bronchial epithelial cells, leading to damage of lipids, proteins and DNA, increased release of lactate dehydrogenase, and death by either necrosis or apoptosis [2,12,37,42,43].

Studies have recorded some degree of toxicity from ZnO nanoparticles in a wide array of organisms, including bacteria, macroalgae, yeast, protozoa, zebrafish and mice [44-47]. Some of this toxicity has been attributed to the potential dissolvability of ZnO nanoparticles into free Zn^{2+} ions [2,48,49], whereas other reports indicate that particle dissolution into Zn^{2+} ions is not a major mechanism of cytotoxicity [42,45,50,51]. These differences in nanoparticle dissolution properties may be related to differences in nanoparticle synthesis conditions and procedures. Typically, physiological levels of zinc are recognized to be important for a variety of normal growth and developmental processes, as well as regulation of the immune system by controlling the activity of many different types of enzyme, including transcription factors, metalloproteinases and polymerases [52,53]. Under normal conditions, the cell has a relatively high concentration of zinc bound to various proteins, whereas the level of free Zn^{2+} ions remains very low and tightly regulated by homeostatic mechanisms [52,54]. Excess zinc can be harmful, however, with intracellular zinc accumulation implicated in neuronal toxicity and brain injury [55]. Excess zinc consumption or inhalation has also been shown to cause ataxia and metal fume fever, respectively [37]. For instances where appreciable nanoparticle dissolution can occur, such as in acidic environments including intracellular lysosomal compartments, hydrated zinc ions in conjunction with intact ZnO nanoparticles are suggested to lead to mitochondrial damage and disruption of cellular zinc homeostasis, leading to cell death. The ultimate cytoprotective or toxic roles of zinc probably reflect the route of administration and dosage, with high concentrations of zinc salt counter-ions capable of causing cell membrane damage on their own owing to osmotic disruption. Nevertheless, reduction of ZnO to the nanoscale has been shown to reveal actions of toxicity that appear to target rapidly dividing cancerous cells preferentially [10,11], which could serve as a foundation for developing new cancer therapeutics.

4. Nanoparticles and cancer treatment

The use of nanomaterials as pharmaceutical carriers to enhance *in vivo* antitumor efficacy has been considered for > 30 years [56]. The first studies on the clinical potential of nano-drug carriers as liposomes occurred in the mid-1970s [57], where treatment of tumor-bearing mice with liposome-entrapped actinomycin D was shown to prolong survival significantly. Today, the use of nanomaterials for delivery of pharmaceutical and diagnostics agents remains at the forefront of nanomedicine, where recent improvements have been described by conjugating cell-specific ligands to the surface of nanoparticles, resulting in greater control of drug targeting at the tissue and cellular levels, and by encapsulating drugs within nanoparticles to improve significantly drug release profiles [58-60].

Numerous preclinical studies using nanoparticle-targeted therapies in oncology are underway, although some ideas have already been brought to the clinic (**Tables 1 – 3**). The FDA-approved Abraxane® (Abraxis BioScience, AstraZeneca,

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Table 1. Cancer nanoparticle-based therapeutics on the market*.

Product	Type of nanomaterial	Indication	Company	Phase
Abraxane [115]	Paclitaxel-albumin nanoparticle	Lung cancer, breast cancer	Abraxis BioScience, AstraZeneca	On market
Myocet [3]	Liposomal doxorubicin	Breast cancer	Cephalon	On market
Depocyt [3]	Liposomal cytarabine	Cancer	SkyePharma	On market
Doxil/Caelyx [3]	Liposomal doxorubicin	Cancer	Ortho Biotech, Schering-Plough	On market
DaunoXome [115]	Liposomal daunorubicin	Cancer	Gilead Sciences	On market
Genexol-PM [115]	Methoxy-PEG-poly(DL-lactide) taxol	Metastatic breast cancer	Samyang	On market
Neulasta [115]	PEG–GCSF	Neutropenia associated with cancer chemotherapy	Amgen	On market
Oncaspar [3]	PEG–L-asparaginase	Acute lymphoblastic leukemia	Enzon	On market
Resovist [3]	Iron nanoparticles	Liver tumor imaging	Schering	On market
Feridex/Endorem [3]	Iron nanoparticles	Liver tumor imaging	Advanced Magnetics, Guerbet	On market

*These nanoparticle-based therapeutics were selected with preference given to late-stage, preclinical, clinical and approved products covering the wide range of modalities (e.g., liposomal platforms, dendrimers, etc.) used in the development of nanomedicines until now, and covering the broad spectrum of cancer types. This is not an exhaustive list.

Table 2. Cancer nanoparticle-based therapeutics in the clinical development pipeline*.

Product	Type of nanomaterial	Indication	Company	Phase
Xyotax [115]	Polyglutamate paclitaxel	Non-small-cell lung cancer, ovarian cancer	Cell Therapeutics	Phase III
Onco TCS [115]	Liposomal vincristine	Non-Hodgkin's lymphoma	Inex, Enzon	Phase II/III
NX 211 [116]	Liposomal lurtotecan	Solid tumors	Gilead	Phase II
Panzem NCD [117]	2-methoxyestradiol Nanocrystal	Glioblastoma	EntreMed	Phase II
OSI-211 [115]	Liposomal lurtotecan	Ovarian cancer	OSI Pharmaceuticals	Phase II
SLIT Cisplatin [115]	Liposomal cisplatin	Progressive osteogenic sarcoma metastatic to the lung	Transave	Phase II
ProLindac [115]	HPMA copolymer–DACH platinate	Ovarian cancers	Access Pharmaceuticals	Phase II
SP1049C [115]	Pluronic block-copolymer doxorubicin	Esophageal carcinoma	Supratek Pharma	Phase II
Aroplatin [118]	Liposomal platinum	Solid tumors	Antigenics	Phase I/II
Transdrug [115]	Poly(iso-hexyl cyanoacrylate) doxorubicin	Hepatocellular carcinoma	BioAlliance Pharma	Phase I/II
Hepacid [115]	PEG–arginine deaminase	Hepatocellular carcinoma	Phoenix	Phase I/II
CT-2106 [115]	Polyglutamate camptothecin	Colorectal and ovarian cancers	Cell Therapeutics	Phase I/II
Prothecan [115]	PEG–camptothecin	Various cancers	Enzon	Phase I/II
Sarcodoxome [115]	Liposomal doxorubicin	Soft tissue sarcoma	GP-Pharm	Phase I/II
L-Annamycin [115]	Liposomal annamycin	Acute lymphocytic leukemia, acute myeloid	Callisto	Phase I
Al-850 [3]	Paclitaxel nanoparticles	Solid tumors	Acusphere	Phase I
Aurimune [119]	TNF-α-bound colloidal gold	Solid tumors	Cytimmune	Phase I
IT-101 [115]	Polycyclodextrin camptothecin	Metastatic solid tumors	Insert Therapeutics	Phase I

*These nanoparticle-based therapeutics were selected with preference given to late-stage, preclinical, clinical and approved products covering the wide range of modalities (e.g., liposomal platforms, dendrimers, etc.) used in the development of nanomedicines until now, and covering the broad spectrum of cancer types. This is not an exhaustive list.

London, England), an albumin-paclitaxel (Taxol®) nanoparticle treatment for metastatic breast cancer, has shown a promising overall response rate of 33%, compared with 19% for Taxol alone in a randomized, open-label trial of 454 patients. Overall side effects were fewer with the nano-based drug, even though it delivered a 50% higher dose of the active Taxol than the conventional formulation [8]. Another example is Myocet® (Cephalon, Frazer, PA) a liposomal formulation of doxorubicin that has significantly improved the therapeutic index, the ratio of the amount of an agent that causes the desired therapeutic effect to that which causes unwanted cell death, compared with conventional

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Table 3. Cancer nanoparticle-based therapeutics in the preclinical development pipeline*.

Product/composition	Therapeutic	Indication
Auritol [119]	Taxol and TNF-α-bound colloidal gold	Solid tumors
Platform technology [120]	PRINT™ (Liquidia Technologies, Durham, NC) nanoparticles	Cancer
AuroLase [121]	Gold nanoshell	Head and neck cancer
Antibody–enzyme-conjugated nanoparticles [122]	Antibody-directed enzyme prodrug therapy	Ovarian cancer
Pluronic block copolymers [123]	Doxorubicin	Various cancers
Polymer–lipid hybrid nanoparticles [124]	Doxorubicin	Solid tumors
Poly(lactic-*co*-glycolic acid)-block-poly(ethylene glycol) [125]	Docetaxel	Prostate cancers
Poly(vinyl alcohol) polymeric micelles [126]	PVA polymer antitumor activity	Neuroblastoma, melanoma
Folic acid-PAMAM dendrimers [127]	Methotrexate	Epithelial cancer
Poly(glycerol-succinic acid) dendrimers [128]	Camptothecin	Various cancers
Albumin-bound nanoparticles [129]	Doxorubicin, methotrexate	Various cancers
Aerosol OT (AOT)-alginate nanoparticles [130]	Doxorubicin	Breast cancer
Glycol chitosan nanoparticles [131]	Doxorubicin	Solid tumors
Gold-conjugated cytomegalovirus nanoparticles [132]	Phototherapy, gene therapy	Solid tumors
Aminosilane-coated iron oxide nanoparticles [65]	Thermotherapy	Brain tumors
Anti-HER2 antibody-targeted gold/silicon nanoparticles [133]	Nanoshell-assisted infrared photothermal therapy	Metastatic breast cancer
Silica-based nanoparticles [134]	Photodynamic therapy	Various cancers

*These nanoparticle-based therapeutics were selected with preference given to late-stage, preclinical, clinical and approved products covering the wide range of modalities (e.g., liposomal platforms, dendrimers, etc.) used in the development of nanomedicines until now, and covering the broad spectrum of cancer types. This is not an exhaustive list.

DACH: Diaminocyclohexane; GCSF: Granulocyte colony-stimulating factor; HER2: Human epidermal growth factor receptor 2; HPMA: Hydroxypropylmethacrylamide; PAMAM: Polyamidoamine; PEG: Polyethylene glycol; PVA: Polyvinyl alcohol; TNF-α: Tumor necrosis factor-α.

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doxorubicin. The development of Myocet through nanotechnology has yielded a less cardiotoxic, better tolerated, and equally efficacious doxorubicin capable of extending the therapeutic options for the management of breast cancer [61].

In addition to nano-drug carriers, interest is growing regarding the ability of certain nanomaterials to mediate anticancer effects on their own, including metal oxides. One approach involves the successful use of TiO_2 metal oxide nanoparticles to kill cancer cells when UV irradiated [62-64]. In these studies, HeLa cells were completely killed in the presence of TiO_2 and UV irradiation, and *in vivo* tumor growth arrested up to 30 days, while no cancer cell killing was observed in the absence of TiO_2 nanoparticles and UV light. Although effective for the treatment of skin cancer, a limitation of this photodynamic nanomedicine-based approach is the inability of UV light to penetrate > 1 mm through skin, unless fiber optics or surgery is used in conjunction.

Nanomedicine-based hyperthermia is another promising therapy for cancer treatment. Infusing a tumor with magnetic or metal nanoparticles and then exposing the patient to an alternating magnetic field or shortwave radiofrequency energy produces heat that warms areas immediately adjacent to the nanoparticles [65,66]. When sufficient supernormal temperatures are reached, the tumor cells are killed without harming surrounding healthy tissue. Both photodynamic and hyperthermic nanoparticle-based cancer approaches share the challenge of preferentially accumulating at tumor sites, unless targeting strategies are also used. In addition to the above-described applications, emerging approaches using zinc oxide nanoparticles are gaining interest for the development for new anticancer therapeutics and are described below.

5. ZnO nanoparticle properties useful for biomedical and cancer applications

ZnO is a conventional wide band-gap semiconductor that has been greatly explored in multiple areas of science. ZnO nanomaterials have been used as semiconductors in microelectronic devices and for accelerating degradation of water pollutants by means of photocatalytic activity. Owing to their inherent ability to absorb UV irradiation and optical transparency, ZnO nanoparticles are used in the cosmetic industry, typically in sunscreens and facial creams [38,67]. Their recognized antibacterial properties are also encouraging a variety of antimicrobial applications [68,69]. ZnO nanoparticles have gained interest in other biomedical applications based on their high stability, inherent photoluminescence properties, which can be useful in biosensing applications, and wide band-gap semiconductor properties useful in

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photocatalytic systems and promotion of reactive oxygen species generation. ZnO nanoparticles have recently shown promise as cholesterol biosensors, dietary modulators for hydrolase activity relevant to controlling diabetes and hyperlipaemia, as well as cell imaging [11,70]. Also, ZnO nanoparticles show promise in modulating allergic reactions through inhibition of mast cell degranulation [71]. The diversity of these activities has popularized ZnO nanomaterials in interdisciplinary research communities involving physicists, chemists and biologists.

Although ZnO nanoparticles have been used in the cosmetic industry for many years, they have only recently been explored for use in cancer applications, or as active drugs themselves. The question arises as to what makes ZnO nanoparticles an attractive consideration. Clearly, this is not simply a matter of being able to synthesize nanoparticles, as nanoparticles of many different material systems can be produced. The practical limitation for biomedical applications largely comes down to issues of biocompatibility. In this regard, ZnO nanomaterials, at least sizes > 100 nm, are considered to be relatively biocompatible, with bulk ZnO being recognized as a GRAS substance by the FDA, making them reasonable choices for drug delivery. ZnO nanowires have been shown to be biodegradable and eventually to dissolve into ions that can be adsorbed by the body and become part of the nutritional cycle, and thereby proposed for *in vivo* biosensing and biodetection applications [72]. The ability to synthesize ZnO into hollow nanotube-type structures [30,31] also makes them reasonable choices for drug delivery, particularly slow drug-release applications.

One of the primary advantages for considering ZnO nanoparticles for use in cancer is the inherent preferential cytotoxicity against cancer cells *in vitro* [10,11]. It is anticipated that their cancer cell selectivity may be improved even further by engineering design to minimize harmful effects to normal body cells, which has been observed to occur at very high concentrations of ZnO nanoparticles, particularly those in the smaller size range of 4 – 20 nm [73]. In this regard, the surface chemistry of ZnO nanoparticles readily lends them to functionalization with targeting proteins or chemical groups, and may be a key to rendering them benign to normal cells while still retaining their cancer targeting and killing properties.

The electrostatic characteristics of ZnO nanoparticles are another useful feature for biomedical applications. Zinc oxide nanoparticles typically have neutral hydroxyl groups attached to their surface, which plays a key role in their surface charge behavior [74,75]. In aqueous medium and at high pH, the chemisorbed protons (H^+) move out from the particle surface leaving a negatively charged surface with partially bonded oxygen atoms (ZnO^-). At lower pH, protons from the environment are probably transferred to the particle surface, leading to a positive charge from surface $ZnOH_2^+$ groups. The isoelectric point of 9 – 10 [76] indicates that ZnO nanoparticles will have a strong positive surface charge under physiological conditions. Given that cancer cells frequently contain a high concentration of anionic phospholipids on their outer membrane and large membrane potentials [23-25], interactions with positively charged ZnO nanoparticles are expected to be driven by electrostatic interactions, thereby promoting cellular uptake, phagocytosis and ultimate cytotoxicity.

The concentration of various chemical groups ($-ZnOH_2^+$, -ZnOH, $-ZnO^-$) on the surface of ZnO nanoparticles is pH dependent [77]. The availability of chemically reactive groups lends ZnO nanoparticles to antibody/protein functionalization by means of *N*-hydroxysuccinimide/1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (NHS/EDC) coupling chemistry [78], as well as other standard coupling approaches, which can further improve cancer cell targeting. ZnO nanoparticles have also been shown to have strong protein adsorption properties, which can be used to modulate cytotoxicity, metabolism or other cellular responses [79].

Another important feature of ZnO nanoparticles is the relatively straightforward process that allows their size and size distribution to be controlled. Studies demonstrate that the cytotoxic properties of ZnO nanoparticles against cancerous cells are directly related to size, with smaller nanoparticles showing greater toxicity [13,15,73]. By tailoring nanoparticle size, it is possible to take the greatest advantage of the EPR effect for increasing intra-tumor concentrations. Another important consideration is that hydrophilic nanoparticles of 100 nm size or less tend to remain in circulation considerably longer and are more likely to avoid clearance by macrophages and rapid serum clearance by the reticuloendothelial system [17]. By contrast, particles with a preponderance of hydrophobic surfaces tend to be preferentially taken up by the liver, followed by the spleen and lungs [17]. The ability to modify the surface and electrostatic characteristics (zeta-potential) of ZnO nanoparticles is a desirable feature, as well as their spherical morphology, which is well suited for removal from the bloodstream by the kidneys to help avoid build-up of these materials in the liver. The zeta-potential of metal oxide nanoparticles can be varied from -30 mV in uncoated samples to + 50 mV when coated with cationic surfactants such as CTAB (cetyltrimethyl ammonium bromide), by using different anionic, cationic and non-ionic surface groups, including polymethyl methacrylate, sodium dodecyl sulfate, bovine serum albumin, and by varying reaction medium and chemical precursors [80,81]. The detailed evaluation of variations in ZnO nanoparticle electrostatic charge in *in vivo* systems is important for identifying the optimal charge needed to mediate cancer cell adhesion and cytotoxicity, yet avoid rapid circulation clearance and end-organ toxicities.

Another feature of ZnO nanoparticles, as stated earlier, is their ability to induce ROS generation, which can lead to cell death when the antioxidative capacity of the cell is exceeded [12,41,82-84]. The ability of ZnO nanoparticles to generate ROS is related to their semiconductor properties. Unlike metals, which have a continuum of electronic states, the electrons in semiconductors can have energies only

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within certain bands. The void region, which extends from the top of the filled valence band to the bottom of the vacant conduction band, is called the band gap and is ~ 3.3 eV for crystalline ZnO [85]. Consequently, light of certain wavelengths (i.e., UV) contains sufficient energy to promote electrons (e^-) to the conduction band to leave behind electron holes (h^+), or unoccupied states in the valence band. Electrons and holes often recombine quickly, but can also migrate to the nanoparticle surface where they react with adsorbed species enabling (i) electrons to react with oxygen, and (ii) holes to react with hydroxyl ions or water to form superoxide and hydroxyl radicals. Such photo-oxidations by ZnO have traditionally been used for photocatalytic oxidation of organic and inorganic pollutants, and sensitizers for the photodestruction of cancer cells [14,62,63] and bacteria [15] via oxidative damage. However, for nanoscale ZnO, large numbers of valence band holes and/or conduction band electrons are thought to be available to serve in redox reactions even in the absence of UV light [51]. One of the reasons is that as ZnO nanoparticle size decreases, so does the nanocrystal quality, which results in increased interstitial zinc ions and oxygen vacancies, and possibly donor/acceptor impurities [86]. These crystal defects can lead to a large number of electron–hole pairs (e^-–h^+). The holes are powerful oxidants and can split water molecules derived from the ZnO aqueous environment into H^+ and OH^-. The conduction band electrons are good reducers and can move to the particle surface to react with dissolved oxygen molecules to generate superoxide radical anions ($^{\bullet}O_2^-$), which in turn react with H^+ to generate ($HO_2^{\bullet}$) radicals. These $HO_2^{\bullet}$ molecules can then produce hydrogen peroxide anions (HO_2^-) following a subsequent encounter with electrons. Hydrogen peroxide anions can then react with hydrogen ions to produce hydrogen peroxide (H_2O_2) [87,88]. The relative positions of the band edges for the conduction and valence band for ZnO and the redox potential for adsorbed substances provide a sufficiently large overpotential (voltage differences) to drive redox reactions and ROS generation in cellular environments [89-91]. The various ROS molecules produced in this fashion can trigger redox-cycling cascades in the cell, or on adjacent cell membranes, leading to depletion of endogenous cellular reserves of antioxidants such that irreparable oxidative damage to cells occurs.

The doping of ZnO nanoparticles with transition metal ions has been demonstrated [85,92,93], and may be another approach to improve their therapeutic potential as transition metals can potentiate redox-cycling cascades. It is postulated that incorporation of Fe^{3+} into the ZnO crystal lattice enhances the particle's ability to generate ROS by catalyzing the dissociation of H_2O_2 to a hydroxyl radical and hydroxide ion, or to a hydrogen ion and hydroperoxy radical, following the Fenton's reaction [94,95]. In support of this, recent studies have shown that Fe^{3+} supported on bulk ZnO improves catalytic activity for H_2O_2 production [87], and the introduction of free transition metal ions can induce protein oxidation and redox state within cells [96]. Although a conflicting report suggests iron doping of ZnO may not function in this manner [97], recent data from the authors' laboratory are consistent with increased ROS capacity and may reflect differences in nanoparticle synthesis, resulting in variations in surface structure and charge. Thus, the engineering of metal oxide nanoparticles to incorporate metal dopants may be a means to enhance ROS generation, leading to improved cancer cell killing.

5.1 ZnO nanoparticles and cancer cell cytotoxicity

Several studies have suggested an increase in *in vitro* cytotoxicity with nanophase ZnO compared with micrometer-sized ZnO for several types of cancer, including glioma, breast, bone, colon, and leukemias and lymphomas [10,11,13,98]. In most of these studies, however, a systematic review of cancer cell cytotoxicity compared with relevant non-immortalized cell types was not performed. Perhaps the most compelling evidence of ZnO preferential toxicity comes from controlled studies comparing nanoparticle susceptibility of cancerous cells with primary non-immortalized cells of identical lineage. These studies showed that cancerous cells of lymphocytic lineage were ~ 28 – 35 times more susceptible to ZnO nanoparticle-induced cytotoxicity compared with their normal counterparts [10,11,73]. This high degree of selective cancer cell killing exceeds the *ex vivo* therapeutic indices of ≤ 10 reported for commonly used chemotherapeutic drugs such as doxorubicin and carboplatin against a variety of leukemias, lymphomas and solid tumors using similar biological assays. The preferential cytotoxicity was found to be dependent on the proliferation status of cells, with rapidly dividing cells being the most susceptible [10,73]. Based on a growing body of evidence, ROS production is proposed as a key cytotoxic mechanism of ZnO nanoparticles [43,43,50,73], leading to cell death by means of an apoptotic mechanism.

Based on the self-lighting photodynamic therapy concept, photoactivation of ZnO nanoparticles is predicted to lead to greater levels of ROS release, which, if effectively targeted to cancer cells, will lead to their selective destruction. Recent supporting studies have described the ability of ZnO nanoparticles conjugated to porphyrin to synergistically induce cytotoxicity in ovarian cancer on exposure to UV-A light, whereas little cytotoxicity was observed under dark conditions, or with UV exposure in the absence of nanoparticles [16]. Similar studies have demonstrated that co-administration of ZnO nanoparticles and the chemotherapeutic drug daunorubicin resulted in synergistic cytotoxic effects on leukemic cancer cells, which was enhanced further by UV irradiation [13]. Collectively, these reports indicate that photoactivation of ZnO nanoparticles conjugated to tumor ligands may be useful for the targeted destruction of cancer cells. Future efforts in this area of research are expected to investigate direct drug conjugation or encapsulation within the ZnO nanocrystal structure to improve further anticancer efficacy, as discussed below.

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5.2 Metal oxide nanoparticles as vehicles for drug delivery

The development of tumor-specific nanoparticles as vehicles for self-sustained drug delivery is now an area of intense research with the potential to revolutionize cancer treatment. Nanotechnology may make it possible to improve the delivery of poorly water-soluble drugs, target delivery of drugs to specific cell or tissue sites, co-deliver two or more drugs, and aid in the visualization of drug site delivery by combining therapeutic agents with imaging modalities [99]. Using nanoparticles for drug delivery of anticancer agents has significant advantages, including the ability to target specific locations in the body, reduce the overall amount of drug used, and the potential to reduce drug concentrations at non-target sites, resulting in fewer side effects. Recently, the use of ZnO quantum dots loaded with doxorubicin has proved to be an effective drug carrier characterized by an initial rapid drug release followed by a controlled release *in vitro* [100]. In this study, ZnO nanoparticles were encapsulated with chitosan to enhance the nanomaterial stability resulting from its hydrophilicity and cationic charge characteristics. Although ZnO nanomaterials have only recently been investigated for use as a drug delivery system, the feasibility of this approach has been demonstrated in related metal oxide systems. Iron oxide magnetic nanoparticles have been used successfully for loading high doses of water-insoluble anticancer agents to mediate dose-dependent antiproliferative effects in breast and prostate cancer lines [101]. Iron oxide nanoparticles have also been used to deliver therapeutic agents by conjugation to both a chemotherapeutic agent, methotrexate, and a cancer-targeting ligand, chlorotoxin [102]. These multifunctional nanoparticles showed increased cytotoxicity to tumor cells and prolonged tumor retention *in vivo.* Cerium oxide nanoparticles loaded with carboxybenzenesulfonamide have also been used to inhibit human carbonic anhydrase, a metalloenzyme associated with glaucoma, a major cause of blindness [103]. Thus, the relative biocompatibility of metal oxide nanomaterials and the ability to functionalize them with targeting moieties make them important for consideration as drug release platforms.

5.3 Metal oxide nanoparticles and tumor imaging and early cancer detection

Interest is growing regarding the use of ZnO and other metal oxide nanomaterials for use as biomarkers for cancer diagnosis, screening and imaging. Recent studies have shown that ZnO nanoparticle cores capped with polymethyl methacrylate are useful in the detection of low level expression of biomarkers [104]. These nanobeads work by facilitating surface absorption of peptide/proteins from cell extracts, enabling increased sensitivity and accuracy of cancer biomarker detection using mass spectrometry. Using another approach, a ZnO nanorod-based cancer biomarker assay has been developed for high-throughput detection of ultra-low levels of telomerase activity for cancer diagnosis and screening [105].

In another approach, multiple reports have described the successful use of iron oxide nanoparticles as contrast agents for cancer detection. Superparamagnetic oxide nanoparticles coated with a cell-resistant polymer have been shown to accumulate within tumor sites by means of the EPR effect in tumor xenograft mice model using magnetic resonance imaging [106]. In another report, the surfaces of nanoparticles composed of an iron oxide core and oleic acid coating were modified with various pluronic and tetronic block copolymers and shown to provide superior *in vivo* tumor imaging properties compared with Feridex IV, a commonly used contrast agent [107]. These modified nanoparticles showed an extended systemic circulation half-life and reduced clearance properties, allowing them to diffuse throughout the tumor vasculature to act as whole tumor contrast agents. Although the superparamagnetic properties of iron oxide nanoparticles offer an advantage for magnetic resonance imaging compared with ZnO, ZnO composite nanomaterials may ultimately prove useful for tumor imaging in the future.

5.4 Metal oxide nanoparticles and targeted gene delivery

Nanoparticles are also being studied for use as vehicles for targeted gene delivery to tumor sites. One of the advantages of this approach is that the enclosure of the expression plasmid or conjugation/absorption of the nucleic acid to the nanoparticle surface ensures safe and efficient gene delivery to the desired tissue. Another advantage relies on the capability of nanoparticles to be taken up by specific cells and internalized to the nucleus according to their surface chemistry. The feasibility of this approach has been validated by a growing number of studies, including the reported *in vivo* studies demonstrating inhibition of metastasis in melanoma tumor-bearing mice treated with poly-L-lysine-modified iron oxide nanoparticles carrying the *NM23-H1* gene [108]. These findings are consistent with reports that this gene product inhibits metastasis in certain types of cancer. A relatively new non-invasive nanoparticle vehicle called a tetrapod avoids the requirement of cellular internationalization. These nanomaterials can be made of various materials and possess four needle-shaped legs reminiscent of the mechanism by which phages deliver genetic material to bacteria. Recently, ZnO tetrapod-like nanostructures have been synthesized as new carriers for gene delivery. These functionalized tetrapods, consisting of silica-coated amino-modified tetrapod-like ZnO nanostructures, are able to bind plasmid DNA effectively through electrostatic interactions and enhance transfection efficiency of A375 cells [32,109]. Polycation-capped ZnO quantum dots have been developed recently and shown to mediate efficient DNA transfer into COS-7 cells, and at the same time allow for real-time imaging of gene transfer [110]. Thus, with continued research, ZnO and metal oxide nanomaterials may provide an effective means for targeted gene delivery and gene silencing for next-generation cancer applications.

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6. ZnO nanoparticles and pro-inflammatory cytokines

ZnO nanoparticle exposure has been shown to induce the production of a variety of pro-inflammatory cytokines, including TNF-α, IFN-γ and IL-12, in *in vitro* and *in vivo* pulmonary inhalation studies [37,73,111,112]. The ability of ZnO nanoparticles to induce pro-inflammatory cytokines at nanoparticle concentrations below those causing appreciable cell death suggests that, when used at appropriate concentrations, they could enhance tumor cell killing through the production of TNF-α (tumor necrosis factor α), a cytokine named for its potent anti-tumor activities [113]. Nanoparticle-induced cytokines could also facilitate effective anticancer actions by eliciting a cytokine profile crucial for directing the development of Th1-mediated immunity [114]. The Th1 lymphocyte subset plays an essential role in enhancing the natural cytotoxic potential of natural killer cells and T cytotoxic cells against cancer cells. As high-level or chronic exposure to TNF-α has been shown to produce serious detrimental effects on the host [113], the magnitude of TNF-α and other pro-inflammatory cytokines, and their delivery to tumor sites will undoubtedly be important parameters when considering ZnO nanoparticles for biomedical purposes to achieve desired therapeutic response without eliciting potential systemic damaging effects. Thus, a careful titration of ZnO nanoparticle-based therapeutic interventions may be successful in elevating a group of cytokines important for eliciting a Th1-mediated immune response with effective anticancer actions without exacerbating the recognized relationship between chronic inflammation and tumorigenesis.

7. Conclusion

As nanotechnology increases in scale and novelty, new applications and uses are continually being discovered. Some of the most exciting advances include using nanotechnology to combat cancer. At present, some nano-based cancer treatments are in clinical use or the development pipeline. This review has focused on ZnO nanoparticles, which have only recently begun to be investigated with respect to cancer applications. Specific properties and characteristics of ZnO nanoparticles, such as their inherent toxicity against cancerous cells, at least for cells of lymphocytic origin, their ability to induce intracellular ROS generation leading to death via an apoptotic mechanism, and their physicochemical properties leading to cellular uptake and ease of functionalization make them an appealing candidate for biomedical applications.

8. Expert opinion

Nanotechnology has already provided significant breakthroughs in medicine and cancer applications. The potential benefits of metal oxide nanomaterials for tumor imaging, controlled drug delivery and targeted cancer cell killing can be enormous and may offer clinical therapeutic platforms that simply do not exist today. There are multiple characteristics of ZnO that make these nanomaterials attractive, including their versatility, relative ease of synthesis, ability to tailor their physicochemical characteristics, ability to functionalize them with chemotherapeutic drugs and cancer targeting molecules, and their desirable cancer cell cytotoxicity profile. By building on the inherent cancer cell cytotoxicity of ZnO nanoparticles and fine-tuning their size, shape and surface properties during the synthesis process, it may be possible to identify the physicochemical properties that take the greatest advantage of the EPR effect and bypass multi-drug resistance of the cell membrane. Likewise, the optimum balance of cationic surface charge to encourage cell membrane interactions without promoting rapid clearance from serum by macrophages and the reticuloendothelial system may be identified, as well as the optimum morphology to increase the likelihood of recognizing specific biological targets and controlling blood vessel wall adhesion strength relevant to cellular internalization. It is expected that systematic investigations can identify ZnO nanomaterial characteristics capable of overcoming at least some of the major barriers needed for more effective cancer treatments.

Although metal oxide nanomaterials hold potential for improving human health, there are still multiple challenges to bring these materials to the clinic. One of the obstacles is that there is current misunderstanding regarding the biological effects and cytotoxicity profiles of ZnO nanoparticles. The discrepancies in the literature are probably attributable to the lack of common understanding between life scientists and materials scientists regarding the other's limitations and capabilities. Nanoparticles are not necessarily identical from batch-to-batch and may display alterations in surface chemistry or size distribution. Life scientists might not appreciate the difficulty in controlling the synthesis process, whereas nanotechnologists might not appreciate the sensitivity of mammalian cells to these variations. There is also concern that researchers may treat ZnO nanoparticles made by different synthesis methods as a single entity with insufficient regard to their potential to exert different biological responses. Other confounding factors include differences in handling, pH variations of the dispersion media, long-term stability versus freshly prepared nanoparticles, impurities, humidity variations during the synthesis, and variations in aspect ratio or agglomeration potential. In sum, a lack of careful surface and physicochemical characterizations of ZnO nanoparticles has led to much of the current confusion regarding the biological responses elicited from these materials. What is needed to avoid these types of problem is a better understanding of the intersecting areas of science between nanomaterial scientists and biologists, such that collaborations allow for the effective exchange of information and methodology to advance the field.

At present, the work with metal oxide nanoparticles in medicine is at a preliminary stage. Nevertheless, the use of metal oxide nanomaterials represents an expanding domain for the diagnosis and treatment of cancer. At present,

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insufficient *in vivo* data are available to know the biological effects of these materials with respect to inflammation and functional alterations at the cellular or whole body level. There is a need to deepen this knowledge to determine whether potential advantages for these nanomedicines outweigh potential dangers associated with nanotoxicity. Although ZnO nanoparticles are widely used in the cosmetic industry and evidence against skin penetration is encouraging, there remains some debate regarding epidermal penetration and lingering questions regarding the safety of these materials. Most studies have been performed *in vitro* with limited longitudinal *in vivo* studies to assess long-term effects to kidneys, liver and spleen, and whether the particles are cleared from the body, dissolve, or remain indefinitely. As drug carriers, ZnO nanomaterials have an advantage over dissolvable polymers in that they can exist in the body for considerable periods of time. Nanoparticles can enhance the circulation half-life of drugs to several hours, allowing time to reach the cancer, whereas single drug molecule half-lifes are usually limited to a few minutes and can require repeated injections. Nanoparticle drug carriers also have the advantage of being small enough to pass through the capillaries yet large enough not to slip through endothelial gap junctions. However, ZnO nanoparticles have a potential disadvantage of building up in the body and causing organ toxicities or breakdown in unpredictable ways. The ability of ZnO nanoparticles to induce expression of pro-inflammatory cytokines under certain conditions also indicates that care in dosing regimens will be essential given the recognized relationship of chronic inflammation and tumorigenesis. Although it is tempting to speculate that ZnO nanomaterials may ultimately be developed into a next-generation cancer treatment, clearly more data are needed to determine unequivocally their long-term health risks.

For the *in vivo* potential of nanotechnology in cancer therapy to be fully realized, nanomaterials have to get 'smarter', meaning better able to destroy pathogenic cells while producing negligible off-target effects on normal cells and tissues. For this to occur, it is essential to gain a clear understanding of both physicochemical determinants and physiological processes, which will probably vary with respect to the type and location of the particular cancer, as well as the method of delivery into the body. The future of nanomedicine will depend on the intelligent design of nanomaterials based around a thorough understanding of cancer biology rather than trying to force the application of popular nanomaterials, including ZnO, to cancer treatment. It is important that synergies between clinicians, biologists and materials scientists be strengthened so that future research focuses on developing the tools needed by clinicians rather than what basic scientists perceive as important. A further stumbling block is the uncertainty of whether nanotechnology-specific medical regulations will be implemented that could add further requirements to the approval process and thereby hamper the commercialization potential. Nanomedicine is still technology-driven, with many scientific challenges lying ahead. However, it represents a growing field with promise to address the long-standing need for new and improved anticancer therapies.

Declaration of interest

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Affiliation

John W Rasmussen[1], Ezequiel Martinez[1], Panagiota Louka[1] & Denise G Wingett[†1,2,3]
[†]Author for correspondence
[1]Boise State University,
Department of Biological Sciences,
1910 University Dr,
Boise, ID 83725, USA
Tel: +1 208 426 2921; Fax: +1 208 426 1040;
E-mail: denisewingett@boisestate.edu
[2]University of Washington,
Division of Gerontology and Geriatric Medicine,
Department of Medicine,
Seattle, WA 98195, USA
[3]MSTMRI Research Institute of St Luke's Regional Medical Center,
Boise, ID 83712, USA

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