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Intelligent Nanoparticles for Advanced Drug Delivery in Cancer Treatment

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Abstract

Treatment of cancer using nanoparticle-based approaches relies on the rational design of carriers with respect to size, charge, and surface properties. Polymer-based nanomaterials, inorganic materials such as gold, iron oxide, and silica as well as carbon based materials such as carbon nanotubes and graphene are being explored extensively for cancer therapy. The challenges associated with the delivery of these nanoparticles depend greatly on the type of cancer and stage of development. This review highlights design considerations to develop nanoparticle-based approaches for overcoming physiological hurdles in cancer treatment, as well as emerging research in engineering advanced delivery systems for the treatment of primary, metastatic, and multidrug resistant cancers. A growing understanding of cancer biology will continue to foster development of intelligent nanoparticle-based therapeutics that take into account diverse physiological contexts of changing disease states to improve treatment outcomes.

Keywords

cancer; nanoparticles; drug delivery; hydrogels

1. Introduction

Size, charge and surface properties of nanomaterials will determine their physiological fate. In order to effectively design nanomaterials for cancer therapy, these parameters must be tailored to navigate the restrictions imposed by human and cancer physiology. While chemical synthesis and facile design procedures are widely reviewed, the precise effect of

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modulating these three key parameters to direct their biological fate in the context of cancer treatment is refreshed regularly.

The diverse physiological barriers presented by primary tumors, organs affected by metastasis, and tumor interstitium prevent universal design considerations. As such, nanoparticle-based therapeutics for cancer therapy face unique challenges in that they must integrate features to traverse diverse physiological barriers and cater to changing disease states, expression levels of molecular targets, and vasculature in a scalable and economical manner. Here, we present a review of recent work in the development of intelligent nanoparticles for cancer therapy with a specific focus on delivery to primary, metastatic, and multidrug resistant cancers.

2. Cancer Physiology

Primary tumors vary in size and micro-environmental characteristics depending on progression of growth. As such, nanoscale therapeutic carriers must be designed to circumvent physiological barriers to reach the desired cellular/subcellular targets, including the circulatory system, the tumor interstitium, and the targeted cancer cells [1]. Effective delivery of nanoscale therapeutic carriers is further complicated by metastatic cancer, due to the need for targeted delivery to multiple sites, and the possible presence of metastases in the blood or lymph. Furthermore, multidrug resistance can occur when cancer cells develop mechanisms to resist classes of chemotherapeutic agents [2].

Nanoscale therapeutic carriers are typically administered intravenously, and spend most of their biological presence traversing through the blood circulation. Design considerations to evade circulatory clearance have received tremendous, well-deserved attention. Renal clearance occurs if the size of the nanotherapeutic is smaller than 10 nm [3]. On the other end of the scale, however, if the hydrodynamic diameter is increased beyond 200nm, the nanoscale entity is more likely to adsorb proteins and undergo opsonization in blood flow, subsequently becoming vulnerable to uptake by macrophages and reticuloendothelial clearance [4]. Studies investigating surface charge effects show that the uptake of neutral or positively charged nanoparticles by macrophages/lymphocytes is drastically low as compared to negatively charged nanoparticles. Similarly, the influential role played by poly(ethylene glycol) (PEG) in avoiding non-specific protein adsorption and thus improving circulation time, has driven numerous preclinical studies and engendered the widely accepted DOXIL- a PEGylated liposomal formulation of doxorubicin.

Size of nanoparticles is an important consideration post interstitial/ intravenous administration, as the appropriate size can enable preferential uptake in the lymph and avoid drainage back into the blood. Experimental evidence shows that particles with size less than 10nm are uptaken rapidly by lymph nodes, but are at higher risk of resorption back into the blood flow [5, 6]. On the other hand, particles greater than 100nm may remain accumulated at the injection site instead of being transferred into the lymphatic circulation [7, 8]. In general, smaller nanoparticles have faster clearance kinetics from the blood as well as the lymphatic system.

Neutral or negatively charged nanoparticles seeking access to the lymphatics avoid electrostatic interaction with negatively charged glycosaminoglycans, and are able to enter the lymphatic system more readily. Cationic nanoparticles can form high molecular weight aggregates with interacting proteins precluding absorption from the injection site. Lymph node retention of drug delivery devices is commonly increased by using an increased size (physical filtration) or increased hydrophobicity/receptor interactions. By contrast, drainage into the lymphatics from the blood necessitates opposing properties [9].

3.1 Design of Intelligent Nanoparticles for Cancer Therapy

The most commonly researched nanomaterials for cancer therapy are polymers, inorganic nanoparticles such as gold, iron oxide and mesoporous silica, and carbon based materials such as carbon nanotubes or graphene. Polymer nanoparticles have been researched extensively for drug delivery applications and have well characterized synthesis methods including solvent evaporation, nanoprecipitation, emulsion polymerization, and controlled/living radical polymerizations as shown in Fig. 1 [10, 11]. Both degradable and non-degradable nanoparticles have been investigated for cancer therapies, with the most commonly employed polymeric material being poly(lactic acid-co-glycolic acid) (PLGA) due to relatively non-toxic degradation products and FDA approval [12, 13]. Gold and iron oxide nanoparticles have been of great interest because of their ability to be remotely heated by IR light and magnetic fields respectively [14, 15]. In the past decade, mesoporous silica based nanotherapeutics have increased in popularity because of the ability to tailor surface functionality and load drugs into pores [16,17,18]. Carbon based materials such as carbon nanotubes and graphene have also emerged as promising candidates for cancer therapy due to high surface area and ability to be used in photothermal therapies [19, 20].

3.1.1 Size and Shape of Nanoparticles

Based upon current knowledge of cancer physiology, nanomaterials in the range of 100-200nm have the highest chance of reaching cancerous tissues through passive targeting methods. In addition to size, nanoparticle shape plays an important role in the ability of a drug delivery system to reach cancerous tissues. A single step assembly of PLGA-lecithin-PEG nanoparticles loaded with doxorubicin and indocyanine green for a chemotherapy photothermal combination therapy for cancer by a single step sonication method was recently reported by Zheng et al. Loaded particles had a hydrodynamic radius 97.6nm and demonstrated a synergistic effect compared to monotherapies in inducing apoptosis in both doxorubicin sensitive (MCF-7) and doxorubicin resistant (MCF-7/ADR) cell lines in vitro. In vivo studies were conducted in MCF-7 or MCF-7/ADR tumor bearing nude mice, and the authors observed 100% survival in the chemo-photothermal groups at day 30 compared to 50% survival or less for the corresponding control groups at day 30 [21]. Mitragotri and colleagues recently demonstrated that rod shaped nanoparticles conjugated with the targeting antibody trastuzumab demonstrated higher specific uptake and decreased nonspecific uptake in a series of breast cancer cell lines in comparison to spherical nanoparticles [22]. In addition, the antibody conjugated rod-shaped nanoparticles demonstrated an enhanced ability to inhibit growth of BT-474 breast cancer cells in-vitro. This study presents compelling results that the nanoparticle shape and specificity are closely

related, and investigation of non-traditional particle shapes could allow for enhanced delivery capabilities.

3.1.2 Charge of Nanoparticles

The charge on polymeric nanomaterials is a result of functional groups incorporated during polymerization. Cationic polymers result from the incorporation of amine containing monomers, while anionic polymers typically result from acid containing monomers. Advances in controlled/living radical polymerization by Matyjaszewski and colleagues, have allowed for enhanced control over polymer architecture with a reduction in the amount of catalyst required [23, 24, 25]. Forbes et al. recently employed an activators regenerated by electron transfer (ARGET) atom transfer radical polymerization (ATRP) emulsion polymerization technique to synthesize cationic nanogels composed of diethylaminoethyl methacrylate with poly(ethylene glycol) tethers that could be complexed with siRNA and loaded with a small molecule drug. Particle hydrodynamic diameters were 120nm with pH dependent drug release, and have potential for oral delivery to colon cancer or to multi-drug resistant cancer cells by intravenous injection [26]. Hammond and colleagues have utilized layer-by-layer (LbL) nanoparticles for a multitude of applications including drug and siRNA delivery to triple-negative breast cancer. LbL nanoparticles were synthesized by deposition of anionic siRNA and cationic polymer poly-L-arginine on carboxyl-modified polystyrene latex nanoparticle cores. The LbL nanoparticles demonstrated high siRNA loading capabilities and extended serum half-lives of 28 hours in BALB/c mice in vivo. When the LbL method was utilized for siRNA loading onto doxorubicin loaded liposomes, a 4-8 fold reduction in tumor volume was observed in a luciferase expressing MDA-MB-468 xenograft model in NCR nude mice.

3.1.3 Surface Functionalization of Nanoparticles

Surface functionalization of nanoparticles has traditionally been achieved using PEG for biocompatibility and targeting groups such as peptides or antibodies for specificity. One such carrier is a nanosized chitosan-functionalized graphene oxide, designed as a drug and gene carrier, which served to enhance biocompatibility and solubility. The authors demonstrated the ability to effectively load camptothecin as a result of pi-pi stacking and hydrophobic interactions and transfect HeLa cells using luciferase as a gene reporter in vitro [27]. Liu et al. synthesized polyion complexes with passive and active targeting, cell membrane translocation, pH dependent drug release, and co-delivery capabilities. TAT peptide was conjugated to the distal end of PEG in poly(ethylene imine)-poly(ethylene)glycol copolymers, and doxorubicin was chemically conjugated to amino group of the PEI with a hydrazone linkage. Electrostatic interactions were then used to bind DNA to the PEI backbone, and a NGR functionalized virus mimetic shell to the surface of the polyion complex. This approach was designed to optimally utilize the specificity of the NGR sequence and the enhanced cellular uptake properties observed with TAT by partially shielded the TAT sequence until reaching tumor tissues [28]. In recent years, the field of nanoparticle-based therapeutics for cancer therapy has toward using one or more targeting moieties to enhance therapeutic outcomes and reduce off-target effects.

3.2 Delivery of Nanoparticle-based Therapeutics to Primary Cancers

To demonstrate efficacy, most anti-cancer drugs have to be present in the correct dosage and appropriate activity level, inside the cancer cells, or in the case of monoclonal antibodies, at the cell surface. Loss or inability of active pharmaceutical ingredients to reach their final destination results in ineffective treatment, or sometimes worse- off-target side effects. The ability to encapsulate hydrophobic drug molecules have made liposomes, vesicles, and micelles attractive drug delivery vehicles. Such nanocarriers are constructed with a precise control over molecular architecture, permitting loading of a variety of anticancer agents such as hydrophobic small molecules, proteins, siRNAs, and even plasmids [29]. Block copolymers have commonly been the synthetic building blocks of these composite nanocarriers and have been reviewed elsewhere [30]. Of notable mention, is the recent use of polyion complex vesicles (PICsomes) synthesized from block copolymers. Kishimura and group mixed oppositely charged diblock copolymers to attain self-assembly of PICsomes [31]. Modulating the concentration of uPICsomes allowed for tunability of size and drug release kinetics.

Surface coatings hold immense promise in masking nanotherapeutics from the typical clearance mechanisms in the body include red blood cells/erythrocytes and polysaccharides such as cyclodextrin, heparosan and hyaluronic acid owing to properties such as biocompatibility, biodegradability, and ability to be chemically modified. Self-assembly micelles based on heparosan and deoxycholic acid conjugate have been reported to show superior DOX loading and release, and enhanced cellular uptake in HeLa cells [32]. One reason to seek other surface modification alternatives over PEG is the reported activation of the complement immune pathway by PEGylated liposomes. The use of PEG has been reported to create several problems such as reduced cellular uptake, due to PEG hydrophilicity, and poor endosomal escape subsequent to endocytosis as a result of minimal interaction with endosomal lipids [33].

Localization of nanoparticle-based therapeutics to the tumor interstitial matrix is a major challenge associated with delivery of nanoparticle-based therapeutics due opposing effects of particles size. Research suggests that small particles will prominently extravasate in normal tissues over tumor tissues owing to the higher interstitial fluid pressures in tumors [1]. However, increasing size may exclude extravasation into tumor interstitium due to blood vessel pore diameter. As a result, particle size will have to be optimized to cater to individual tumor microenvironments. Upon penetration into the interstitial space, the heterogeneous nature of the tumor environment makes surface charge and shape of nanoparticles important variables in extravasation and interstitial transport. Jain et al. have revealed that cationic particles permeate better through tumor endothelial cells and blood vessel in relation to neutral or anionic particles. Neutral particles, however, undergo minimal interaction with components of the interstitial matrix and diffuse faster through the interstitium. Polymeric particles comprising of linear chains have been shown to diffuse faster than spherical, rigid particles although there is no consensus on the reason behind this observation.

Strategies relying on the enhanced permeation and retention (EPR) effect typically involve the intravenous administration of nanoparticles with a hydrophobic core and a coating of PEG for biocompatibility for accumulation in tumor tissues, as illustrated in Fig. 2. However, the EPR effect alone may not be sufficient to achieve preferential localization of nanoparticle-based therapeutics within solid tumors. Smith et al. explored using single-walled carbon nanotubes with the overarching aim of improving tumor uptake in intravenously injected nanoparticles by the EPR effect. To gain a deeper understanding of how SWNTs may be internalized by cells, Smith et al. performed in vivo studies in mice and compared internalization of SWNT and PEG by blood cells [34]. They found that SWNTs were rapidly internalized by cells, but were not uptaken by phagocytic cells and did not activate monocytes 6 hours post uptake. The research indicates that SWNTs may further infiltrate the tumor interstitium by entering circulatory cells in addition to the EPR effect.

Active targeting approaches can be used to improve effectiveness and minimize off-target effects. Peptides are a natural choice for use as targeting ligands because of their specificity, but it has been a long standing obstacle to deliver nanocarriers with peptidic ligands due to enzymatic degradation and lower affinity compared to antibodies [35]. Strategies to circumvent such issues include introducing D-amino acids or multivalent sequences into the peptide sequence. The most commonly used peptide sequences include cyclic RGD sequences that recognize $\alpha_v\beta_3$ integrin receptors, CSNIDARAC peptides for lung tumors, EPPT peptides for tumor-specific antigen underglycosylated mucin-1, F3 peptides that target endothelial cells lining the tumor vasculature, and also a wide range of membrane receptors for cholecystokinin, GRP and somatostatin [36].

Aptamers have gained considerable popularity as targeting ligands because of their high specificity, low cost, lower toxicity and immunogenicity, and smaller size. Development of aptamers by the systematic evolution of ligands through exponential enrichment allows for an elegant way to produce a more robust group of targeting biomolecules as opposed to protein-based ones [37]. So far, aptamer ligands have been prepared for IgG receptors, tyrosine kinase receptors, E-selectin, nucleolin, and other tumor molecules and cells [38].

3.3 Delivery of Nanoparticle-based Therapeutics to Metastatic Cancers

Tackling metastatic cancer with the aid of the nanotechnological toolbox has been reviewed in remarkable detail by Schroeder et al. [39]. Researchers designing nanomaterials for treating metastatic cancers must consider delivering to a wide range of physiology based on the organs the cancer has metastasized to, in addition to ensuring delivery to the cancer cell/subcellular organelle. While design considerations remain similar, physiological heterogeneity of the organs may necessitate utilization of nanomaterials to tackle metastases in each organ to achieve maximum efficacy in the diverse landscapes associated with the metastases and the stage of development.

A large unmet need in the treatment of metastatic cancer, is the lack of chemotherapeutic options for bone metastases, which conduce an aggressive form of cancer typically conferred with a selective advantage [38]. One approach that can readily be used for targeted delivery to bone/skeletal tissue, a common site of metastasis, utilizes high affinity apatite

binding molecules like bisphosphonates and oligopeptides. Unfortunately, the negative charge conferred by these targeting moieties can exclude the nanocarriers from the negatively charged cell membranes/cytosol [40]. Solid phase synthesis of peptides allows for rational design of multifunctional peptides that allow for inclusion of diversely charged elements in the same targeting moiety. Applying this method, Wang et al. generated a custom trifunctional peptide that consisted of an anionic targeting element (for apatite targeting), a cathepsin-cleavable linker (to respond to a metastatic microenvironment), and a cationic element (for supporting cellular uptake). The peptide-b-PEG-PTMC (poly(trimethylene carbonate)) polymer self-assembled into micelles that demonstrated up to 90% DOX loading efficiencies into the PTMC hydrophobic core [41]. Further, the 75 nm nanoparticles were able to avoid clearance owing to the presence of PEG, selectively targeted bone metastases and displayed a prolonged survival rate in mice compared to control groups *in vivo*.

Another common site for metastases is the lymph nodes. Poorly developed lymphatic vessels surround metastasizing cancers expose gaping holes between adjacent lymphatic cells that eventually facilitate the invasive spread of cancer cells. In fact, the excessively permeable network of lymphatic vessels is touted to be the primary means of cancer metastasis [42]. In particular, PEG drains rapidly from the blood into the lymphatics, but is not retained within the lymphatics owing to its hydrophilicity and minimal phagocytic spread of cancer cells via lymph nodes typically advances through vascular endothelial growth factors- C and -D (VEGF-C and VEGF-D)[43] and integrin $\alpha_v\beta_3$ levels. Consequentially, VEGF inhibitors are good targeting moieties for halting metastatic spread. Chemokine receptor expression-level is another determinant of the site of metastasis, and potential receptor targets include chemokine receptors CXCR4 and CCR7 [44].

Remodeling the tumor microenvironment to discourage cancer cells from proliferating has been the focus of several anti-cancer combination therapies. Extracellular delivery is especially desirable for treatment of metastasizing tumors/ micrometastases since modulating the tumor microenvironment can substantially improve biodistribution and efficacy of accompanying chemotherapy. Interestingly, improved circulation and biodistribution had also been suggested to explain the success of Abraxane (albumin bound paclitaxel) – the first-ever FDA approved intravenous, passive nanomedicinal treatment of metastatic breast cancer.

Nanoparticle-based therapeutics can also play a pivotal role in this by encapsulating multiple drugs with diverse therapeutic roles in appropriate dosage ratios. By inhibiting antiangiogenic activity in a xenograft tumor model, Huang and group revalidate this attractive strategy to halt the metastatic spread of cancer cells. By loading dioleoylphosphatidic acid-cisplatin (DOPA-cisplatin) cores into PLGA nanoparticles, they increased the core hydrophobicity of PLGA, further facilitating improved loading of the hydrophobic anti-angiogenic drug rapamycin, a VEGF and tumor associated fibroblasts inhibitor. Co-encapsulation within the same nanoparticle is crucial as it can help maintain the desired dose ratio, giving better control over the release and synergistic therapeutic effect, while ensuring a lower IC₅₀ value than co-treatment of rapamycin and cisplatin as a result of distinct *in vivo* pharmacokinetics and biodistribution [46,47]. In another study,

albumin-manganese dioxide nanoparticles have been used to regulate the tumor microenvironment with the aim of improving prognosis with radiation therapy [48].

Similarly, Huang and group have also examined the utility of intelligent nanoparticles in cancer immunotherapy to combat metastatic disease [49]. In the study, the antigen-specific response of a therapeutic vaccine against melanoma was boosted by the use of a separately delivered siRNA that reversed the immunosuppressive microenvironment found in an advanced melanoma mouse model.

3.4 Delivery of Nanoparticle-based Therapeutics to Multidrug-Resistant Cancers

Multidrug resistance in cancer cells, a condition which can accompany metastatic cancer, is responsible for numerous cancer-related deaths and can render first line therapies ineffective [50]. Sequence-specific gene silencing has been explored extensively in this regard to favorably sensitize refractory cancer cells to conventional chemotherapy [51][52]. Multidrug resistance is manifested by genetically emutated cancer cells to rapidly expel anti-cancer drugs that are subsequently recycled back into the bloodstream as illustrated in Fig. 3.

From a material design perspective, hyaluronan (HA), a major ligand of CD44 is a suitable active targeting ligand for most types of cancerous cells, as HA receptors are largely upregulated in these cells. Cohen et al. have used HA-coated phospholipid nanoparticles to encapsulate doxorubicin and paclitaxel, both of which are substrates for P-glycoprotein 1 (P-gp) receptors overexpressed in cancer cells [53]. They demonstrated increased cytotoxicity and reduced IC₅₀ values in an NCI/ADR-Res ovarian cancer cell model that was derived by continuous exposure to increasing DOX concentrations in cell culture. Internalization of the ~500 nm drug loaded particles led to evasion of the drug efflux mechanism, and subsequent surge in intracellular DOX concentration in otherwise DOX-resistant cells.

In a recent study, Kim et al. surmounted two key challenges with one nanotherapeutic platform, by gaining access across the blood-brain barrier and sensitizing refractory glioblastoma cells to temozolomide (TMZ), which acts a substrate for the O⁶-methylguanine-DNA methyltransferase (MGMT) enzyme [54]. Incorporation of a wild-type p53 plasmid DNA within a cationic liposome and separate administration of TMZ was shown to have appreciable cytotoxic effect in both in vitro and in vivo models.

Researchers seek to utilize the considerable surface area of carbon nanotubes (up to ~2600 m²/g) and strong optical absorption leading to compatibility with photodynamic therapy, for the development of potent nanoformulations [55][56]. To improve cellular uptake, Bhirde et al. engineered a semiconducting single-walled carbon nanotube (sSWCNT) drug delivery system that showed it is possible to achieve more effectiveness in killing cancer cells by wrapping nanoparticles with hyaluronic acid rather than PEG [57]. The combined π - π stacking resulted in greater DOX encapsulation; while, rapid intracellular trafficking of cholan acid-derivatized hyaluronic acid (CAHA)-sSWCNTs occurs with ease owing to their small size (2-4 nm), especially in drug-resistant OVCAR8/ADR cells that overexpress CD44 receptors and tumor bearing mice xenograft models. Using a similar hyaluronic acid

coating, Choi and others investigated the role of Zn(II)-DPA and a calcium phosphate coating to load RNAi-based therapeutics to accompany small molecule drugs for sensitizing OVCAR8/ADR tumor cells in vitro and in vivo [58].

Although multidrug delivery approaches are typically limited by overlapping toxicity profile, these hurdles can be overcome by a judicious choice of drug solutes and their molar ratios within the same particle. Ensuring rational design of synthesis and encapsulation techniques is another challenge that needs to be addressed. To enable differential release of multiple drugs encapsulated within the same nanoparticles, Liao et al. prepared nanoscopic brush-arm star polymers (BASPs) using a ring-opening metathesis polymerization method (ROMP) [59]. Drug-macromonomer conjugates were developed to allow for improved solubility and responsiveness to environmental stimuli. To enable controlled release for each of the three drugs, drug conjugates were synthesized to respond to three different stimuli. DOX and CPT were conjugated to a PEGylated-norbornene macromonomer using a graft-through ROMP synthesis [60]. DOX conjugate were shown to respond to a photo-trigger such as long-wavelength UV (UVA). Cisplatin was conjugated to Pt(IV) diester derivative that released the cytotoxic ingredient Pt(II) upon reduction in the presence of intracellular glutathione. The triple drug combination therapy demonstrated effectiveness against an otherwise camptothecin-resistant OVCAR3 (human ovarian carcinoma cell line).

Targeting the lysosomal cell death pathway is another premise that holds immense promise for nanomedicine-mediated treatment of multidrug resistant cancers and especially apoptosis-resistant cancers. In refractory cancers that resist apoptosis by conventional chemotherapy, permeabilization of the lysosomal membrane can stimulate release of cathepsins and proteolases, engendering cytosolic protein digestion and induction of apoptosis [61]. In a recent investigation, Sanchez et al. accomplish induction of apoptosis and cell death by activation of the lysosomal death pathway by means of iron oxide nanoparticles grafted with peptidic ligands for targeted delivery to cancer cells [62]. Functionalization of an iron oxide nanocrystal with gastrin, resulted in strong binding and internalization of the composite nanoparticles. Unlike other magnetic stimuli-based approaches, cell death was incurred through lysosomal internalization subsequent to endocytosis instead of hyperthermia.

4. Conclusions

Nanoparticle-based treatments for cancer therapy represent a promising strategy to enhance therapeutic outcomes by reducing off-target side effects compared to intravenously administered chemotherapeutics. Polymer based nanotherapeutics have received the most attention from researchers, but there is a wealth of promising research on inorganic nanomaterials, primarily focused upon photothermal therapy and co-delivery. With respect to the design of these systems, nanomaterials with a size on the order of 100-200nm of various morphologies are popular because of their ability to escape renal, hepatic, and lymphatic clearance. The desired charge of the system depends largely on the application. Recently, increased attention has been focused on the development of cationic nanotherapeutics for the purpose of co-delivery of chemotherapeutics and interfering RNA. Surface functionalizations for nanoparticles have been primarily focused upon using PEG to

enhance circulation time and improve tumor accumulation using the EPR effect. However, recent literature has shown that reliance solely on the EPR effect is insufficient for nanoparticles to penetrate the tumor intersitium, and as a result the use of active targeting agents has become increasingly compulsory. With the prominence of drug-resistant cancers, there is an increasing need to design therapeutic agents with the ability to sensitize or synergistically target cancerous cells over healthy cells to effectively reduce off-target effects. Furthermore, in the case of metastatic cancers, delivery of nanoparticles rationally designed to overcome the characteristic physiological barriers associated with the affected organ will be most effective. Finally, clinical impact of nanotechnology for cancer treatment will strongly benefit from customized nanoparticle-based therapies that are designed to overcome diverse physiological contexts of varying disease states.

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Abbreviations

ADR	Adriamycin
ARGET	Activators ReGenerated by Electron Transfer
ATRP	Atom Transfer Radical Polymerization
BASP	brush-arm star polymers
CAHA	cholanic acid-derivatized hyaluronic acid
CCR7	CC chemokine receptor type 7
CPT	camptothecin
CXCR4	CXC chemokine receptor type 4
DOPA	dioleoylphosphatidic acid
DOX	doxorubicin
DPA	dipicolylamine
EPR	enhanced permeation and retention
HA	hyaluronic acid/hyaluronan
IC₅₀	half maximal inhibitory concentration
LbL	layer-by-layer
MDR	multidrug resistance
MGMT	O ⁶ -methylguanine-DNA-methyltransferase
NGR	Asn-Gly-Arg/Asparagine-glycine-arginine
PEG	poly(ethylene glycol)
PEI	poly(ethylene imine)

PICsome	polyion complex vesicles
PLGA	poly(lactic acid-co-glycolic acid)
PTMC	poly(trimethylene carbonate)
PTX	paclitaxel
RGD	arginine-glycine-aspartic acid
ROMP	ring-opening metathesis polymerization
RNAi	ribonucleic acid interfering
siRNA	small interfering ribonucleic acid
sSWCNT	semiconducting single-walled carbon nanotube
SWNT	single-walled carbon nanotubes
TAT	trans-activating transcriptional activator
TGF-β	transforming growth factor β
TMZ	temozolomide
VEGF	vascular endothelial growth factor

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- Size, charge and surface properties are design considerations for nanoparticles.
- Delivery of nanoparticles to primary, metastatic, and multidrug resistant cancers reviewed.
- Nanoparticle design must be tailored for diverse cancer physiologies.

Figure 1.
Schematic overview of polymer nanoparticles synthesis methods by either polymerization from monomers or preparation from preformed polymers. SCF: supercritical fluid technology, C/LR: controlled/living radical. Image taken from Rao and Geckeler. [10]

Figure 2.
Schematic representation of intravenous injection of nanoparticle therapeutics into the bloodstream, localization into healthy tissues, and localization into tumor tissues.

Figure 3. Schematic of the mechanisms involved in multi-drug resistance and siRNA interference. Nanocarriers bypass efflux pumps by uptake via endosomes and release small molecule drugs and siRNA into the cytosol. siRNA is incorporated into the RNA induced silencing complex (RISC), the sense strand is cleaved, the activated RISC complex degrades complementary mRNA, and the associated proteins are silenced. The silencing effect reduces the activity of drug efflux transporters on small molecule drugs. Image adapted from Creixell and Peppas. [2]