Nanoparticle Technologies for Cancer Therapy

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Abstract Nanoparticles as drug delivery systems enable unique approaches for cancer treatment. Over the last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy, including organic and inorganic materials. Many liposomal, polymer–drug conjugates, and micellar formulations are part of the state of the art in the clinics, and an even greater number of nanoparticle platforms are currently in the preclinical stages of development. More recently developed nanoparticles are demonstrating the potential sophistication of

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M. Schäfer-Korting (ed.), *Drug Delivery*,
Handbook of Experimental Pharmacology 197,
DOI 10.1007/978-3-642-00477-3_2,

these delivery systems by incorporating multifunctional capabilities and targeting strategies in an effort to increase the efficacy of these systems against the most difficult cancer challenges, including drug resistance and metastatic disease. In this chapter, we will review the available preclinical and clinical nanoparticle technology platforms and their impact for cancer therapy.

Keywords Nanoparticle · Drug delivery · Targeted · Metastatic cancer · Cancer therapy

Abbreviations

BBB	Blood–brain barrier
DSPC	1,2-Distearoyl-glycero-3-phosphocholine
DSPE	1,2-Distearoyl-*sn*-glycero-3-phosphoethanolamine
EggPG	Egg yolk phosphatidylglycerol
EPR	Enhanced Permeability and Retention effect
FDA	Food and Drug Administration
HPMA	*N*-(2-Hydroxypropyl)methacrylamide
HSPC	Hydrogenated phosphatidylcholine from soybean lecithin
LPS	Lipopolysaccharide
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIR	Near infrared
NSCL cancer	Non-small-cell lung cancer
PAMAM	Polyamidoamine
PDLLA	Poly-DL-lactic acid
PEG	Polyethylenglycol
PLA	Polylactic acid
PLA2	Phospholipase A2
PLGA	Poly(lactic-*co*-glycolic acid)
SEM	Scanning electron microscope

1 Introduction

Nanotechnology is a multidisciplinary field that uses principles from chemistry, biology, physics, and engineering to design and fabricate nanoscale devices (Farokhzad and Langer 2009; Ferrari 2005; Fox 2000; Jiang et al. 2007; Peppas 2004; Sinha et al. 2006; Uchegbu 2006). In its strictest definition, nanotechnology refers to structures with a size range of 1–100 nm in at least one dimension.

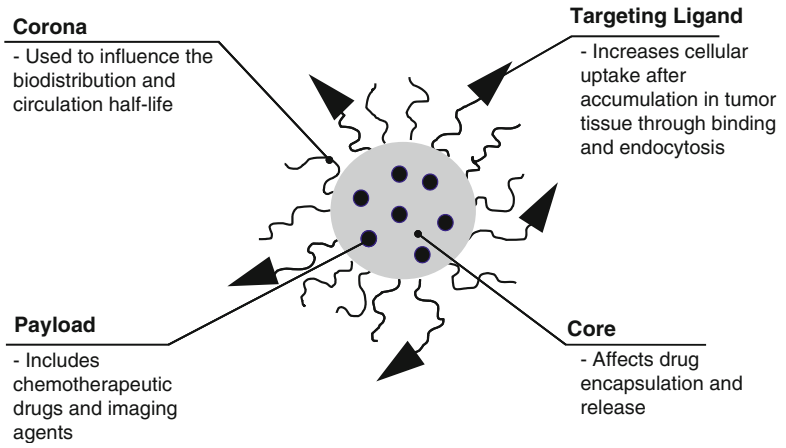

Fig. 1 Schematic of physicochemical structure of nanoparticle platforms for drug delivery, including core, corona, payload, and targeting ligand

However, it more commonly refers to materials up to several hundred nanometers that are developed using top-down or bottom-up engineering. The resulting nanomaterials demonstrate unique capabilities based on intrinsic properties such as shape and size as well as functional properties conferred through surface modifications (Fig. 1).

The field of medicine stands to be a significant benefactor of advances in nanotechnology, with oncology already starting to reap the benefits of novel nanoscale technologies (Alexis et al. 2008b; Alexis et al. 2008c; Davis et al. 2008; Euliss et al. 2006; Farokhzad 2008; Farokhzad et al. 2006b; Farokhzad and Langer 2006; Freitas 2005; Jain 2008; Kawasaki and Player 2005; Lanza et al. 2006; Levy-Nissenbaum et al. 2008; Moghimi et al. 2005; Peer et al. 2007; Pridgen et al. 2007; Riehemann et al. 2009; Rosen and Abribat 2005; Salvador-Morales et al. 2009a; Venugopal et al. 2008; Zhang et al. 2008b). These benefits have included advances in detection, imaging, and therapy of disease. The National Cancer Institute (NCI) has identified nanotechnology as having the potential to make paradigm-changing impacts on the detection, treatment, and prevention of cancer. The level of interest in nanotechnology by both academic and industrial investigators has led to increased development of novel nanotechnology platforms for medical applications, sharp increases in government funding, and venture capital investment. The combination of funding and early clinical success has provided the resources and opportunities for nanotechnology to solve important medical challenges. The early success in oncology has already been a catalyst for the application of nanotechnology to other medical problems, such as cardiovascular disease and vaccines.

One area where nanotechnology has the potential to make a significant impact is drug delivery (Farokhzad and Langer 2009; Pridgen et al. 2007). This impact has

already been felt with the translation of several nanoscale drug delivery systems into the clinic, although the full potential of these systems is only starting to be explored. Nanoscale drug delivery vehicles have shown the ability to encapsulate a variety of therapeutic agents such as small molecules (hydrophilic and/or hydrophobic), peptides, protein-based drugs, and nucleic acids. By encapsulating these molecules inside a nanocarrier, the solubility and stability of the drugs can be improved, providing an opportunity to reevaluate potential drugs previously ignored because of poor pharmacokinetics (Langer 1998). Encapsulated molecules can be released from nanocarriers in a controlled manner over time to maintain a drug concentration within a therapeutic window or the release can be triggered by some stimulus unique to the delivery site (Moghimi 2006). The surface of the nanocarrier can be engineered to increase the blood circulation half-life and influence the biodistribution, while attachment of targeting ligands to the surface can result in enhanced uptake by target tissues (Gref et al. 1994; Moghimi et al. 2001). The small size allows nanocarriers to overcome biological barriers and achieve cellular uptake (Brigger et al. 2002). The net result of these properties is to lower the systemic toxicity of the therapeutic agent while increasing the concentration of the agent in the area of interest, resulting in a higher therapeutic index for the therapeutic agent. In addition to therapeutic drugs, imaging agents can also incorporated into nanocarriers to improve tumor detection and imaging (Kim et al. 2006; Montet et al. 2006). Finally, nanoparticles can be engineered to be multifunctional with the ability to target diseased tissue, carry imaging agents for detection, and deliver multiple therapeutic agents for combination therapy (Nasongkla et al. 2006). The multimodal capabilities of nanoparticle delivery systems offer the opportunity to develop novel approaches to deliver drugs that may result in alternative or complementary therapeutic options for the treatment of disease.

In this chapter, we will focus on nanoparticle technologies (Fig. 2), with a particular emphasis on the development of nanocarrier drug delivery systems for cancer therapy applications. These technologies include polymeric nanoparticles, dendrimers, nanoshells, liposomes, inorganic/metallic nanoparticles, hybrid nanoparticles, micelles, and magnetic and bacterial nanoparticles. Nucleic acid delivery technologies will not be included, but are extensively reported elsewhere (Chen and Huang 2008; Gao and Huang 2008; Gary et al. 2007; Juliano et al. 2008; Li and Huang 2008b; Luten et al. 2008; Tseng et al. 2009; Whitehead et al. 2009). A discussion of how improvements in the understanding of the tumor microenvironment have guided the design of both non-targeted and targeted nanocarriers as therapeutic vehicles for cancer will follow (Bierie and Moses 2006; Bissell and Labarge 2005; Cairns et al. 2006; Fesik 2005; Fidler 1995; Galon et al. 2007; Overall and Kleifeld 2006; Siclari et al. 2006; Zetter 2008). The breakthrough potential of nanoparticle delivery systems is becoming increasingly recognized, with several examples of first generation nanocarriers approved by the FDA for therapy, and targeted nanocarriers in clinical phase development. Many of the nanocarrier systems in clinical phase development will be highlighted in this

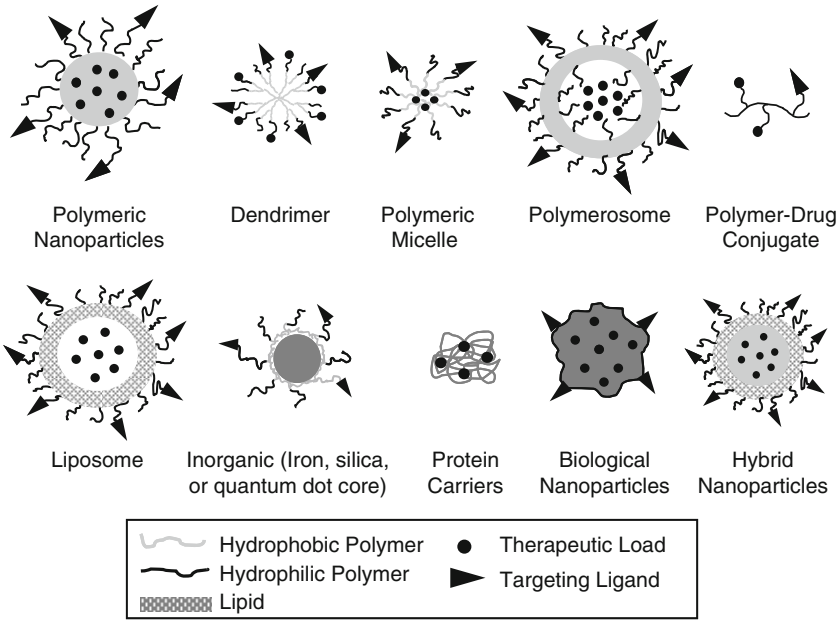

Fig. 2 Nanoparticle platforms for drug delivery. Nanoparticle platforms are characterized by their physicochemical structures, including polymer–drug conjugates, lipid-based nanoparticles, polymeric nanoparticles, protein-based nanoparticles, biological nanoparticles, and hybrid nanoparticles

chapter to demonstrate how these systems are being translated to the clinic and the advantages they provide for cancer therapy.

2 Nanoparticle Technologies

The first nanoscale drug delivery systems were lipid vesicles, which were first described in the 1960s and later became known as liposomes (Bangham et al. 1965). Since then, there have been several key developments that have paved the way for current nanoparticle technologies. In 1976, the first controlled-release polymer systems for the delivery of macromolecules were demonstrated (Langer and Folkman 1976). This was followed in 1980 with the first application of targeted liposomes (Heath et al. 1980; Leserman et al. 1980). The surface modification of liposomes and polymeric nanoparticles with polyethylene glycol (PEG) in 1990 and 1994, respectively, led to increases in circulation time, or "stealth" properties (Gref et al. 1994; Klibanov et al. 1990). These developments culminated in the approval of Doxil (James 1995a, b), a vesicle delivery system encapsulating doxorubicin that has proven to be a potent treatment for multiple types of cancer (Porche 1996;

Tejada-Berges et al. 2002). Since then, research has led to tremendous progress in the development of nanoparticles engineered to have multifunctional capabilities as well as "smart" properties such as the ability to respond to the environment to facilitate more effective drug delivery strategies. Currently, there are 70 reported clinical trials evaluating nanoparticle carriers, 208 evaluating drug conjugates, and 361 evaluating vesicle-based carriers (http://www.clinicaltrials.gov). The clinical trials include combination therapies and treatments through various administration routes, such as pulmonary and oral.

Nanoparticle technologies for cancer therapy include polymeric nanoparticles (Moghimi 2006; Pridgen et al. 2007), vesicle-based carriers such as liposomes (Kaneda 2000; Torchilin 2005), micelles (Fan 2008; Liggins and Burt 2002; Matsumura 2008), dendrimers (Florence and Hussain 2001; Lee et al. 2005; McCarthy et al. 2005; Najlah and D'Emanuele 2007), polymer conjugates (Greco and Vicent 2008; Li and Wallace 2008; Thanou and Duncan 2003), protein carriers (Hawkins et al. 2008; Wang and Uludag 2008), inorganic nanoparticles (Murakami and Tsuchida 2008), and bacterial nanocarriers. The diversity of delivery systems, each of which is discussed below, allows nanoparticles to be developed with a diverse array of shapes, sizes, and components that enables them to be tailored for specific applications. However, the primary consideration when designing any drug delivery system is to achieve more effective therapies by controlling the drug

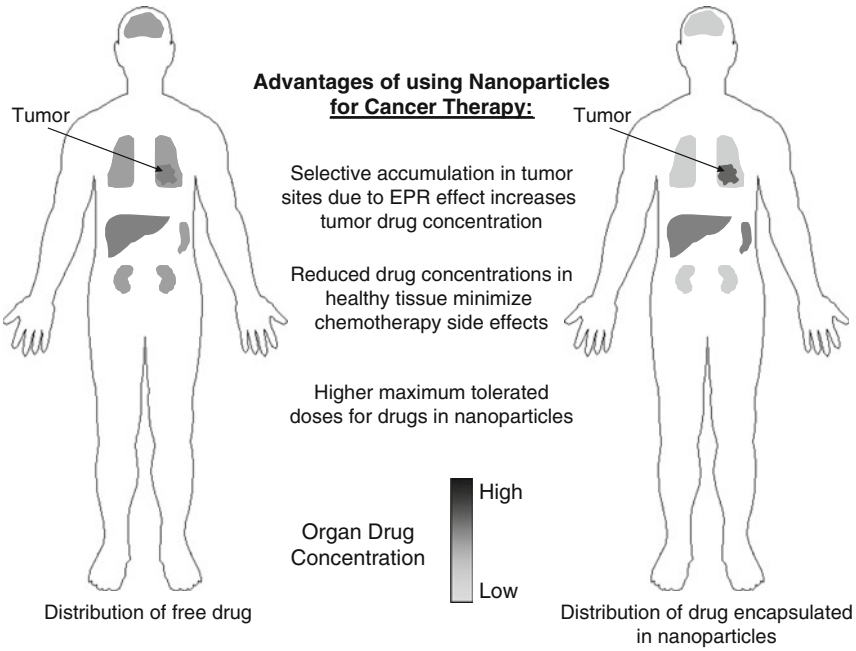

Fig. 3 Advantages of using nanoparticles as drug delivery system for cancer therapy compared to free drug

concentration in the therapeutic window, reducing cytotoxic effects, and improving patient compliance (Fig. 3). This allows effective treatment cycles to be maintained while reducing damage to healthy cells and minimizing the recovery period.

2.1 Liposome Nanoparticles

Lipids form nanoparticle vesicles through the self-assembly of amphiphilic lipids and excipients. The lipids form a bilayer based on hydrophobic interactions in continuous parallel packing, with the hydrophilic head groups positioned towards the aqueous environment. Hydrophilic molecules can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the lipid bilayer. Physicochemical properties of liposomes can be precisely changed to control surface charge, functionality, and size by simply mixing commercially available lipid molecules. This offers a significant advantage over other carriers that require much more controlled synthesis steps and additional chemical modifications. Generally, lipids used to prepare vesicular formulations are found in the human body and approved by the FDA, such as DSPE (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine), HSPC (hydrogenated phosphatidylcholine from soybean lecithin), EggPG (egg yolk phosphatidylglycerol) and DSPC (1,2-distearoyl-glycero-3-phosphocholine). Each of these lipids can be obtained with or without PEG, which can be used to modify the surface of the resulting liposome.

Doxil, a pegylated liposome clinically used to treat multiple types of cancer, is a landmark for liposomal drug delivery systems. Doxil consists of a packed pegylated surface (2 kDa PEG chains) and is loaded with doxorubicin through drug diffusion based on an ammonium salt gradient. This method achieves a stable drug entrapment in a crystal form with reduced leakage over a long period of time. Doxil liposomes have a size of ~100 nm, surface charge of ~−10 mV, and a long-term shelf stability of ~2 years at ~4°C. Recently, Aphios Corp. developed nanosomes (small liposomes, <100 nm) carrying multiple drugs such as docetaxel, camptothecin, bryostatin-1 and vitamin D analog for treatment of multiple cancer types (Castor 2005) using a manufacturing technology based on a super-critical fluid process. In addition, Novosom AG uses amphoteric liposomes to deliver nucleic acids. The liposomal formulation is able to change surface charge properties (zeta potential) with changes in solution pH. The charge switch at acidic pH results in fusion with the cell membrane during endocytosis uptake, allowing escape of the nanocarriers into the cytoplasm to deliver the therapeutic load.

Liposomal formulations have demonstrated multiple benefits as drug delivery vehicles. However, they must be used to carry very potent drugs due to their low encapsulated load. Lipid-based vesicles pose several other challenges such as instability in the bloodstream, poor solubility of many drugs in the lipid/surfactant solution, and a rapid, burst release of drug. Liposomal formulations are also associated with severe side effects due to their accumulation in skin tissue. While

prolonged drug release kinetics are difficult to control using liposomal systems, alternatives such as environmentally triggered release can be easily engineered by inserting destabilizing lipids with amine head groups into the vesicle membrane or including additives such as morpholine in the lipid formulation (Cullis and Chonn 1998; Guo et al. 2003; Kocer 2007; Sudimack et al. 2002; Vial et al. 2005). There are currently no liposomal formulations with triggered drug release approved for clinical use or in early phases of clinical trials. However, LiPlasome Pharma developed non-targeted liposomes consisting of lipids designed to be degraded by phospholipase A2 (PLA2), which is up-regulated in the tumor microenvironment (Andresen et al. 2004; Andresen et al. 2005; Jensen et al. 2004; Jorgensen et al. 2002). The lipid degradation products are converted into anticancer drugs, resulting in local delivery of cytotoxic drugs in the tumor. In-vivo results showed a delay in colon cancer progression using a human tumor xenograft mice model (Tribler et al. 2007). This approach also provides the possibility of multi-drug delivery. Protein stabilization of liposomes is being investigated by Azaya Therapeutics to deliver hydrophobic drugs such as docetaxel for cancer therapy. Docetaxel is encapsulated into the liposome bi-layer and stabilized by albumin to prevent rapid drug leakage (ATI-1123). The results of ATI-1123 efficacy studies in human xenograft mice models for prostate, pancreatic, and non-small-cell lung cancer (NSCL cancer) showed partial tumor regression in 90% of the PC3 tumor xenograft model and improved efficacy in the pancreas model when compared to groups treated with docetaxel at equal doses (25 mg kg^{-1}). This may be explained by the slower plasma elimination and higher bioavailability of ATI-1123 relative to free docetaxel (Zamboni 2008).

2.2 *Polymer–Drug Conjugates Nanoparticles*

Polymer–drug conjugates are one of the most investigated types of nanocarriers and are currently in clinical trials as advanced as phase III. Polymer–drug conjugates are formed through side-chain grafting of drugs to polymer chains, allowing them to deliver high doses of chemotherapeutic drugs. Although the physicochemical properties of a number of formulations are not disclosed, the size of polymer–drug conjugates is generally below 20 nm. HPMA-doxorubicin (*N*-(2-hydroxypropyl) methacrylamide) copolymer (PK1) was the first synthetic polymer–anticancer drug conjugate to enter clinical trials more than a decade ago and the clinical phase II trial for women with advanced breast cancer is still ongoing (Vasey et al. 1999). Similarly, Prolindac (AP5346) is composed of a HPMA backbone copolymer with platinum grafted to the side chains through a pH-sensitive chelator designed for drug release in the tumor environment (Sood et al. 2006). Preclinical data shows superior efficacy of the polymer–drug conjugates using multiple cancer models including a M5076 sarcoma platinum-resistant tumor xenograft mice model, multiple colon xenograft models, L1210 leukemia, and 0157 hybridoma models (Rice et al. 2006). Oxaliplatin drug loading was ~10% (w/w) using a polymer chain of 25 kDa and the drug release was slow. Formulations were injected once a week for

three weeks and the polymer–drug conjugates significantly retarded tumor growth over one month due to higher intracellular concentration of Pt. In the clinical phase I trial conducted in Europe (Campone et al. 2007), systemic injection of 640 mg Pt m^{-2} weekly for 3 weeks resulted in a response by platinum-resistant ovarian cancer. Recently, Access Pharmaceuticals Inc. reported the results of the clinical phase II trial showing that 66% of the patients with ovarian cancer experienced meaningful disease stabilization and limited side effects.

Polyamino acids grafted with drugs on the side chains are another class of polymer–drug conjugates that have demonstrated high drug loading and efficacy (Li 2002; Matsumura 2008). In the case of polyglutamate-glycine-campthotecin (CT-2106), degradable linkers have allowed drug loadings ranging from 5% to 50%. Using a glycine linker, drug loadings were increased threefold over polyglutamate-campthotecin alone due to reduced steric hindrance. However, a formulation with a drug load of ~30% was selected for clinical trials due to superior stability and efficacy in human tumor xenograft mice models (Homsi et al. 2007). Meanwhile, Xyotax, a similar polymer–drug conjugate (polyglutamate-paclitaxel), is in 22 clinical trials at the moment for multiple cancer therapies including prostate cancer, metastatic breast cancer, neck cancer, metastatic colorectal cancer, and recurrent NSCL (Phase III). Paclitaxel is grafted to polyglutamic acid (30–40 kDa) to reach a drug load of 20–40% by weight (Singer 2005; Singer et al. 2003). The clinical data shows an improvement in median survival in Xyotax patients compared with the control group, although there were no differences in the overall survival. One benefit of the treatment was the reduction of multiple side effects including neurotoxicity (Boddy et al. 2005). Overall, polymer–drug conjugates are considered simple nanocarrier systems, but tuning the optimal formulation might require extensive development. For example, small changes in the polymer–drug conjugation efficiency may significantly modify the pharmacokinetic parameters and tissue biodistribution. The resulting formulation could also be considered a new chemical entity, complicating regulatory approval.

2.3 Polymeric Nanoparticles

Polymeric nanoparticles may represent the most effective nanocarriers for prolonged drug delivery. The early in vitro and in vivo development of polymeric nanoparticles loaded with drugs in the 1980s using polyalkylcyanoacrylate-based nanoparticles releasing doxorubicin (Couvreur et al. 1979) led to multiple reports using polymer-based materials for drug delivery. Langer and Folkman (Langer and Folkman 1976) demonstrated the first controlled release of macromolecules using polymers, which allowed the development of anti-angiogenic drug delivery systems for cancer therapy and opened new areas for the delivery of macromolecules. In 1994, Langer et al. described nanoparticles composed of poly(lactic acid)/poly (lactic-*co*-glycolic acid) (PLA/PLGA) and PEG block copolymer as "long-circulating nanoparticles" due to their stealth properties (Gref et al. 1994), leading to an increased

interest in polymeric nanoparticles and their therapeutic applications. Only a few papers per year were published using polymeric nanoparticles as a drug delivery system in the 1990s in contrast to ~200 papers in 2008.

Polymeric nanoparticles provide significant flexibility in design because polymers can be biodegradable or nonbiodegradable, and can be made synthetically or derived from natural sources. Some common polymers used for nanoparticle formation include poly(lactic acid) (PLA), dextran, and chitosan. Biodegradable polymers are typically degraded into individual monomers, which are metabolized and removed from the body via normal metabolic pathways. Degradation and drug release kinetics can be precisely controlled by the physicochemical properties of the polymer, such as molecular weight, dispersity index, hydrophobicity, and crystallinity. In general, drugs can be released in a controlled manner with first-order kinetics due to drug diffusion through the polymeric matrix or triggered in response to the local environment. The nanoparticle surface is usually sterically stabilized by grafting, conjugating, or adsorbing hydrophilic polymers such as PEG to its surface, which can also reduce hepatic uptake and improve circulation half-life (Gref et al. 2000; Peracchia et al. 1999).

Several polymeric nanoparticles are now in various stages of preclinical and clinical development. For example, Nanolymf Ltd. developed microparticles carrying encapsulated nanocapsules loaded with drugs. Drug-loaded polymethacrylate nanocapsules (~400 nm) are encapsulated in 2–10 μm cellulose-based microspheres and given orally, resulting in uptake by M-cells and a drug blood bioavailability of ~5%. DeSimone et al. (Euliss et al. 2006; Gratton et al. 2008a; Gratton et al. 2008b; Kelly and DeSimone 2008; Rolland et al. 2005) have shown that physicochemical properties of particles such as shape, size and mechanical flexibility contribute to their interactions with cell membranes and control their internalization pathways. This has led to the preclinical development of polymeric nanoparticles using a "PRINT" technology (Particle Replication In Non-wetting Templates) for cancer therapy and other diseases.

2.4 Micelle Nanoparticles

Micelles are composed of lipids or other amphiphilic molecules, such as polymers or polyamino acids, and self-assemble into small nanoparticles composed of a hydrophobic core. Micelles have been developed as drug delivery carriers for hydrophobic drugs (Aliabadi et al. 2008; Liggins and Burt 2002; Matsumura 2008). There are multiple examples of micellar formulations under investigation or in clinical trials, such as Genexol-PM (Kim et al. 2007a; Kim et al. 2004; Lee et al. 2008), NC-6004 (Uchino et al. 2005), NK105 (Hamaguchi et al. 2007), and NK911 (Matsumura et al. 2004; Tsukioka et al. 2002). Genexol-PM is the first non-targeted polymeric micellar formulation approved for cancer therapy. It was approved in Korea in 2006 as a first-line therapy for metastatic breast and NSCL cancer (currently in Phase III). It is currently being evaluated in a clinical phase II

trial in the USA for metastatic pancreatic cancer therapy. Genexol-PM is composed of a block copolymer PDLLA (1.75 kDa)–mPEG (2 kDa) forming micelles with a size of ~60 nm and paclitaxel loading of ~15% (w/w). The maximum tolerated dose (MTD) of Genexol-PM is threefold higher than Taxol (60 mg kg^{-1} vs. 20 mg kg^{-1}, respectively) and the median lethal tolerated dose (LD_{50}) using Sprague–Dawley rats was reported to be ~20 times higher than Taxol. Interestingly, the area under the plasma concentration (AUC) was similar for both formulations. However, paclitaxel had more significant accumulation in tissues such as the liver and tumor with the Genexol-PM formulation, leading to differential tumor cytotoxicity and reduction of tumor volume (Kim et al. 2001). Results of a clinical phase I trial showed that while the MTD was almost double (390 mg m^{-2}) for Genexol-PM compared to Taxol with similar toxicological profiles, the recommended dose was determined to be 300 mg m^{-2} (Kim et al. 2004). The clinical phase II trial in Korea evaluated Genexol-PM as a co-therapy with cisplatin for advanced NSCL in contrast to a single agent therapy (Kim et al. 2007a). The clinical phase II results showed ~30% of the patients had stable disease status and 60% of the patients had an increased survival of one year using slightly lower doses of cisplatin than with the combined treatment of Taxol with cisplatin (60 mg m^{-2} versus 75 mg m^{-2}, respectively) (Kim et al. 2007a). Other companies such as Labopharm and Intezym are also developing micelle systems for the delivery of a myriad of anticancer agents using formulations with sizes ranging from 10 to 200 nm using polyamino acids and synthetic polymers.

2.5 Dendrimer Nanoparticles

Dendrimers are globular macromolecules (5–10 nm) with well-defined branching architectures and surface functional groups available for further modification. The multifunctional capabilities possible through controlled synthesis methods are leading to new classes of dendrimers that can carry drug molecules, diagnostic agents, and targeting molecules. Dendrimers have remarkable molecular monodispersity and suitable pharmacokinetic properties for systemic drug delivery with cleavable chemistry for drug dissociation (Lee et al. 2005). Amphiphilic dendrimers are able to form micelles by self-assembly with hydrophilic groups on the surface for functionalization. Drug release kinetics are controlled through the properties of the polymer chains, which can be designed to be degraded for release of a payload.

Baker et al. have developed “avidimers” (Majoros et al. 2005, 2006; Myc et al. 2008), which are dendrimers targeted to tumor vasculature using a methotrexate-polyamidoamine (PAMAM) bioconjugate platform functionalized with small targeting ligands (Quintana et al. 2002). Non-targeted and folate-targeted G5-PAMAM dendrimers differentially accumulated into a human KB cell line xenograft tumor model within a day (8%–10% targeted versus 2% non-targeted I.D./g of tissues) (Kukowska-Latallo et al. 2005). Higher accumulation in the tumor resulted

in the inhibition of tumor growth, lower toxicity, and longer survival time compared to free drug at equal dosage. More importantly, recent efficacy studies using targeted transferrin-cyclodextrin-siRNA nanoparticles (CALAA-01, ~70 nm) in animal models of human epithelial cancer showed tumor size reduction and differential distribution in tumors (Bartlett et al. 2007; Davis 2009; Davis and Brewster 2004). The preclinical data motivated further development of CALAA-01. The toxicological results reported in April 2007 for CALAA-01, which was the first targeted, polymeric nanoparticle platform in non-human primates (Heidel et al. 2007), led to the submission of an investigational new drug application and human clinical trials for solid tumor therapy in May 2008.

2.6 Polymersome Nanoparticles

Polymersomes have a structure similar to liposomes, but are composed of synthetic polymer/polypeptide amphiphiles and self-assemble to form polymer shell vesicles (~100 nm) when hydrated and extruded. Discher et al (Discher et al. 1999) described vesicles made of amphiphilic diblock copolymers with low water permeability. The hydrophilicity/hydrophobicity ratio is used to control the morphology of the nanoparticle, which can range from spherical to cylindrical. The membrane core thickness can be controlled by the molecular weight of the diblock copolymer. Polymersomes show higher stability and lateral fluidity than liposomes and the release is triggered by the degradation of the polymer chain and destabilization of the shell layer. Incubation of polymersomes in the blood showed adherence and uptake by white blood cells within 10 h. In vivo results using a breast cancer tumor xenograft model showed therapeutic efficacy after a single i.v. injection using polymersomes loaded with paclitaxel and doxorubicin at the maximum tolerated dose (2.5 mg kg^{-1} for each drug). The tumor size was reduced within five days postinjection in contrast to the free drug formulations (Ahmed et al. 2006).

2.7 Protein Nanoparticles

Protein-based drug delivery systems have recently made a big impact with albumin-bound drug nanoparticles (~130 nm). The recent approval of albumin-bound paclitaxel (Abraxane, ABI-008, January 2005) by the Food and Drug Administration (FDA) for metastatic breast cancer therapy, as well as multiple clinical trials currently in progress for other types of cancer, has now opened the possibility of using protein-based nanoparticles for delivery of therapeutic agents (Gradishar 2006). Given the limiting pharmacokinetic properties and numerous side effects of Taxol (hypersensitivity), the albumin-bound paclitaxel allows the formulation of the hydrophobic drug in a solvent-free solution. Albumin is a natural noncovalent physiological transporter of molecules across endothelial barriers through a

transcytosis-mediated mechanism (caveolae vesicle). Preclinical studies have shown that the concentration of paclitaxel bound to albumin in endothelial cells and in the extravascular space was significantly increased (3–10 fold) (Desai et al. 2006; Nyman et al. 2005). Data suggests that albumin may have intrinsic targeting abilities to tumors, although the enhanced permeability and retention (EPR) effect may play an additional role in tumor accumulation. Overall, the albumin-bound paclitaxel formulation allowed higher dosages than the Taxol formulation (260 mg m^{-2} vs. 175 mg m^{-2}, respectively) and demonstrated improved efficacy and safety (Nyman et al. 2005). Abraxane is currently being tested as a first-line therapy or in combination with other drugs (rapamycin, verinostat, etc.) for metastatic breast cancer and other cancers that have been shown to be sensitive to taxane drugs, such as ovarian and prostate. In addition, albumin is now being tested as a platform for delivery of other molecules that have reduced water solubility, such as rapamycin (~2.5 μg ml^{-1}). Albumin-bound rapamycin (ABI-009) has been in a clinical phase trial for the treatment of non-hematologic malignancies since January 2008.

2.8 *Biological Nanoparticles*

Biological nanoparticles such as bacteria are unicellular microorganisms with different shapes and sizes that encapsulate essential components of the cytoplasm as well as hydrophobic and hydrophilic molecules. One example of biological nanoparticles being evaluated for cancer therapy is a drug delivery system developed by EnGeneIC Pty Ltd called a "nanocell", which consists of anucleate globular bacteria (~400 nm). The absence of DNA prevents endogenous mutations and replication originally reported in 1967 (Adler et al. 1967). It has been demonstrated that a nanocell can be efficiently loaded with molecules of different solubility and charge, such as doxorubicin, paclitaxel, and siRNA, through drug diffusion into the bacteria within a few hours (MacDiarmid et al. 2007). No signs of toxicity have been reported in large animals such as pigs and monkeys with repeated dosages at high titers, although there is the potential for an immunological response to the carrier due to the presence of lipopolysaccharide (LPS).

2.9 *Inorganic Nanoparticles*

Inorganic nanoparticles are primarily metal-based and have the potential to be synthesized with near monodispersity. Inorganic materials have been extensively studied for imaging using magnetic resonance and high-resolution superconducting quantum interference devices while their intrinsic properties have been explored for therapy. Several types of metal nanoparticles (Cheng et al. 2008; Paciotti et al. 2004; Visaria et al. 2007) are able to convert energy into heat at levels up to 70°C

through near-infrared light excitation or oscillating magnetic field stimulation (Johannsen et al. 2005). Iron oxide nanoparticles coated with aminosilane (Nanotherm M01) are in clinical phase II trials in Germany for brain cancer therapy and recurrent prostate cancer therapy using hyperthermia as well as thermoablation methods. The phase I results showed that prostate tumor cells can be locally killed by magnetic iron oxide nanoparticles (Johannsen et al. 2007). Nanoparticles were injected locally using ultrasound to guide tumor injections and patients were treated once a week for 1 h over two months. The small nanoparticles (~20 nm) are able to penetrate tumors, enter cancer cells, and generate heat under magnetic fields (50 and 100 kHz), allowing treatment width between 20 and 30 cm and within a circular area of 20 cm of diameter. The authors report no dose-limiting toxicities and mild discomfort from internal heating. Similarly, silica nanoparticles coated with gold that absorb near-infrared laser energy and covert it into heat to kill solid tumors are currently under investigation in a pilot study for head and neck cancer therapy. In vivo results (Hirsch et al. 2003) of nanoshell-mediated NIR (near infrared) thermal therapy using human breast cancer xenograft models showed that the nanoparticles induced irreversible cancer tissue damage at a temperature ~40°C. However, the temperature variance between different mice treated was quite significant (28–60°C) and was suggested to be due to differential distribution of nanoshells in the treated volume of the tumor. In addition, the maximum recorded temperature was only ~1 mm under the skin. Recently, the same nanoparticles (150 nm) were used for brain cancer treatment in an orthotopic canine model (Schwartz et al. 2009). Tumors were killed using percutaneous infiltrated NIR fibers reaching a temperature of ~70°C in tumor tissues and ~50°C in normal white and grey matter, which is expected to significantly damage non-diseased areas of the brain.

Surface properties and functionalities of gold nanoparticles have also been used for the delivery of surface-bound therapeutics. Aurimune (CYT-6091) is an example of tumor necrosis factor (TNF)-alpha bound to PEG-coated gold nanoparticles (~27 nm) developed by CytImmune Sciences, Inc. for solid tumor therapy (Paciotti et al. 2004). TNF-alpha is a potent cytokine with antitumor cytotoxicity which requires incorporation into a nanocarrier formulation to reduce systemic toxicity. The results show that nanoparticle formulations delayed the tumor growth with local heating (42°C for 1 h) using a SCK mammary tumor xenograft mouse model. However, the combined treatment showed a higher efficacy and suppression of intratumor blood flow (Visaria et al. 2006). Preliminary SEM micrographs of nanoparticles accumulated in breast tumor tissue sections in contrast to healthy tissues showed possible targeting of the nanoparticles by the EPR effect. Many other formulations are still in the discovery stage using combinations of drugs such as TNF with paclitaxel, doxorubicin or interleukin-12. However, the load of therapeutic agent is reported to be several hundreds of molecules due to the surface adsorption density, which may limit the effect of the therapeutic agent. Recently, Adair's group (Kester et al. 2008; Morgan et al. 2008) has reported the encapsulation of organic molecules in calcium phosphate nanocomposite particles (~27 nm) for intracellular imaging and delivery. Calcium

phosphate-based nanoparticles are biocompatible and their pH dissolution properties can be used for controlled release of molecules in the acidic tumor environment. In vitro studies show high uptake of the nanoparticles in bovine aortic endothelial cells and the delivery of hexanoyl-ceramide (Cer-6) to human vascular smooth muscle cells showed 100% inhibition of cell growth at 200 nM of drug (Kester et al. 2008). This technology is now being developed by Keystone Nano for imaging and delivery of therapeutic agents.

Non-specific accumulation into healthy tissues is always a concern for nanoparticle drug delivery systems. Using local sensitization through light or temperature may reduce overall toxicity, but it is expected to damage adjacent healthy tissues as well. Ultimately, inorganic particles may not provide advantages over other types of nanoparticles for systemic targeting of cancer cells because they are not biodegradable, have low payloads, and have no controlled release properties.

2.10 Hybrid Nanoparticles

Hybrid nanoparticles are recently developed nanocarriers that combine advantages from existing systems with well-characterized properties to form lipid–polymer nanoparticles and solid liposomal nanoparticles. Hybrid nanoparticles are composed of at least two different materials to form the core and the corona structure. In general, metallic and polymeric materials form the core and are coated with a single or multiple lipid layers to form a protecting membrane (corona) similar to a liposome or micelle. We (Chan et al. 2009; Zhang et al. 2008a) and others (Al-Jamal et al. 2008; Kim et al. 2007b; Sengupta et al. 2005; Thevenot et al. 2007; Wong et al. 2007; Wong et al. 2006a; Wong et al. 2006b) have developed hybrid nanoparticles for cancer therapy. Sasisekharan and co-workers (Sengupta et al. 2005) have reported PLGA-core nanoparticles coated with a bi-phospholipid layer to carry multiple drugs for cancer therapy using melanoma and Lewis lung carcinoma models. In their system, doxorubicin is conjugated to PLGA to form the core of the nanoparticle (~1% load by weight of doxorubicin, 70% encapsulation efficiency) while an anti-angiogenesis drug, combrestatin, is mixed with phospholipids and encapsulated in the lipid bi-layer during the self-assembly process to form nanoparticles (~200 nm) described as "nanocells". The drugs were release at different rates over a period of ~3 days, with combrestatin released first to reduce vascular density in the tumor followed by the release of doxorubicin to kill the cancer cells. The results showed a significant delay in tumor growth and increased survival time in both cancer models, suggesting accumulation of the nanocell by the EPR effect and added therapeutic value by delivering multiple drugs. The nanocell technology is now in preclinical development by Cerulean Pharma.

Others have reported solid-lipid nanoparticles using different polymers and formulations in vitro and in vivo for combination therapy. Recently, Thevenot et al. (2007) described a mechanism for the encapsulation of a hydrophobic

polymer core (PLA) in PEG-liposomes. As part of the work, the importance of PEG chain length to sterically stabilize lipoparticles with optimal colloidal stability was demonstrated (PEG (5 kDa) at 10% of lipid content). Our group has reported (Chan et al. 2009; Zhang et al. 2008a) a one-step formulation for self-assembly of a single layer of lipid on the hydrophobic surface of PLA nanoparticles (size < 100 nm). Surface functionalization using different lipid constituents allows the precise control of the charge and targeting ligand density, leading to stable hybrid nanoparticle formulations (Chan et al. 2009). In addition, drug loading was significantly increased up to ~8% by weight and the release kinetics of docetaxel was shown to be controlled by the lipid layer on the surface of the nanoparticles. Multifunctional nanoparticle technologies (Bertin et al. 2006; Schneider et al. 2009; Wang et al. 2008b) are now able to combine multiple therapeutic approaches that are the state of the art for cancer therapy, including the delivery of multiple drugs (Ahmed et al. 2006; Sengupta et al. 2005) or radiation sensitizers (van Vlerken et al. 2008), combined therapeutic approaches such as photothermal and drug delivery (Park et al. 2008; Rapoport et al. 2007), and simultaneous delivery of therapeutic drugs and imaging agents (Gao et al. 2008; McCarthy and Weissleder 2008; Shin et al. 2009).

3 Strategies for Cancer Therapy Using Nanoparticles

3.1 Metastatic Cancer

Metastatic cancer is a clinical description for the spread of cancer cells from the primary tumor site to distant organs, establishing secondary tumor sites. Detachment of cancer cells from the primary tumor site and circulation in the blood allows the cells to arrest in organs such as the lungs, liver, lymph nodes, skin, kidneys, brain, colon, and bones, where they can extravasate and proliferate (Chambers et al. 2002; Fidler 2003). Despite significant increases in the understanding of metastatic cancer pathogenesis, early diagnosis, surgical methods, and irradiation treatment, most cancer deaths are due to metastases that are not curable. Reasons for this include resistance to treatments, difficulty accessing the tumor sites and removing all cancer cells during surgery, or physiological barriers for drug access such as the blood–brain barrier (BBB). Therefore, improving therapy of metastatic cancer is still a challenge even though multiple therapeutic approaches are approved or in clinical development.

An improved understanding of cancer biology, including microenvironment functions, signaling pathways, and metastasis evolution, has resulted in clear advances in cancer therapy. Drugs have now been developed against a range of targets including matrix metalloproteinase inhibitors, epidermal growth-factor receptor inhibitors, transferase inhibitors, migration inhibitors, and angiogenesis inhibitors. However, due the complexity of tumor progression, tumor composition,

blood vessel structures, and drug resistance mechanisms, most of the current therapies have provided limited extension of survival time across multiple cancer types with the exception of imatinib (tyrosine kinase inhibitor) for gastrointestinal stromal tumor (Sawaki and Yamao 2004). Knowledge of drug action pathways and cellular drug resistance mechanisms to specific drugs has allowed the development and evaluation of promising drug combinations (Kim et al. 2008; Szakacs et al. 2006). Trials of combinations of agents are usually designed to enhance the activity of the primary agent or to inhibit different pathways to circumvent drug resistance to the primary agent. The critical advantage of using drug combinations is to prevent drug resistance development during cancer therapy without increasing the known side effects of each drug. Although it is believed that tumor growth and metastases are adaptable mechanisms, higher doses of single drugs are able to prevent resistance mechanisms in vitro in some cases (Kim et al. 2008). However, multi-drug regimens with synergistic combinations have been shown to be more successful in patients, probably due to cell heterogeneity in tumors and between patients. Unfortunately, multi-drug treatment requires complicated dosing regimens. Nanoparticle delivery systems offer solutions to both of these approaches. Delivery of single drugs in nanoparticles results in increased drug concentrations in the tumor, allowing higher doses compared with free drug using both non-targeted and targeted delivery. Nanoparticles can also be engineered to carry multiple drugs that are delivered together in one particle with control over the release rate of each drug, preventing the need for complicated multi-drug dosing regimens and improving patient compliance.

3.2 Non-Targeted Nanoparticles

Non-targeted nanoparticles circulating in the blood have been shown to significantly improve drug bioavailability and accumulation in tumors through the enhanced permeability and retention effect (EPR) (Fig. 4). The EPR effect allows the passive targeting of nanoparticles to tumors due to pathological abnormalities in the tumor vasculature (Maeda 2001; Minko et al. 2000). Interendothelial gap defects increase vascular permeability in tumors, allowing extravasation of nanoparticles up to 400 nm (Hobbs et al. 1998). Accumulation of nanoparticles is further enhanced due to poor lymphatic drainage in tumors. The local release of anti-cancer drugs from nanocarriers in the extravascular space results in an increased intra-tumoral drug concentration. In general, hydrophobic drugs released extracellularly will diffuse and be taken up by cancer cells, leading to enhanced tumor cytotoxicity. Since cancer cell populations, cell density, antigen expression, microenvironment, and vasculature density are significantly different across different cancers and even within primary and secondary metastatic sites, nanoparticle biodistribution and circulation time represent critical parameters for cancer therapy.

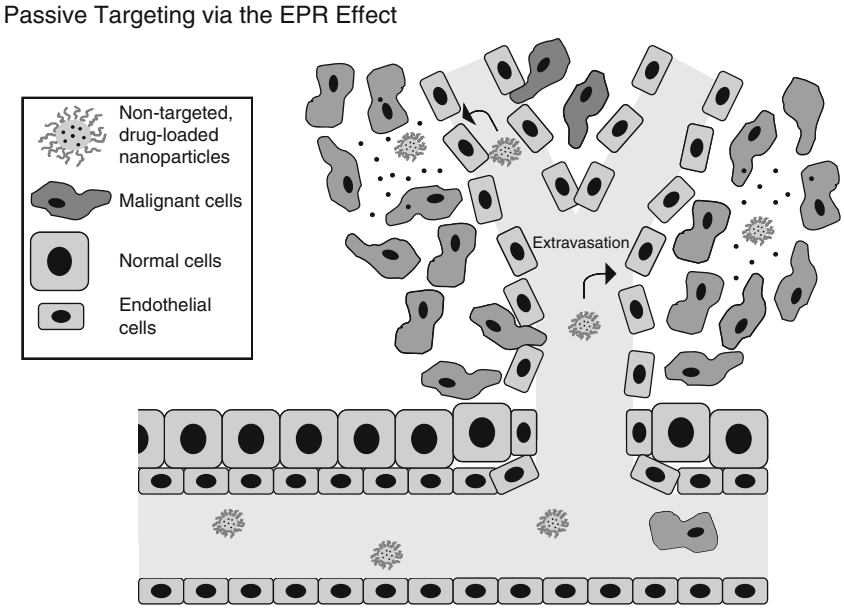

Fig. 4 Schematic of "passive targeting" via enhanced permeability and retention effect (EPR). The small size of nanoparticles allows them to circulate for a long period of time, extravasate, and accumulate into tumor tissues through leaky tumor vasculature

Multiple factors affect the pharmacokinetic behavior of nanoparticles, but the surface charge, size, nanoparticle shape and stealth properties are among the most critical (Alexis et al. 2008b; Li and Huang 2008a). As described in the nanoparticle technologies section above, five common types of nanoparticles are approved or in late stage of clinical trials, including polymer–drug conjugates, micelles, protein-based carrier, liposomes, and polymeric nanoparticles. Overall, non-targeted nanoparticles accumulate in tumor xenograft mice models in the range of 1–4% of I.D./g of tissue, although these numbers are difficult to compare due to different post-injection time assessments (Alexis et al. 2008b; Soepenberg et al. 2005). Polymer–drug conjugates are the smallest (1–20 nm) and have a circulation half-life in human ranging from hours to days depending on the system. To our knowledge, dextran–camptothecin (DE-310) has the longest circulation half-life (~300 h) in humans and has been shown to have no major toxicity compared to the free drug formulation in clinical phase II trials (Soepenberg et al. 2005). However, its therapeutic efficacy might be limited by its dosage regimen compared to PEG–camptothecin and polyglutamate–camptothecin conjugates (7,000 and 25 mg m^{-2}, respectively) (Homsi et al. 2007). These results underline the significant differences of pharmacokinetic parameters using different polymer–drug conjugates due to different loading, release profiles, and molecular weights of the carrier. This is also true for the circulation half-life of other

polymer–drug conjugates such as HPMA–drug conjugates, polyglutamate–drug conjugates, dextran–drug conjugates and pegylated drugs such as PEG–arginine deaminase (Hepacid, 7 days) and PEG–camptothecin (Prothecan, 40 h) (Ascierto et al. 2005; Posey et al. 2005). In general, larger nanoparticles such as micelles and liposomes seem to have a shorter circulation half-life in the blood (2–50 h) but higher maximum tolerated doses. The Genexol-PM formulation of paclitaxel is given at a twofold higher dosage than HPMA–paclitaxel (PNU166945) and polyglutamate–paclitaxel (Xyotax). However, it is not clear whether circulation half-life or maximum tolerated dose is the most critical for optimum accumulation in tumor tissues. For example, polycyclodextrin–camptothecin micelles (IT-101) and PEG–camptothecin conjugates show similar circulation half-life but significantly different accumulation of drug in tumor xenograft models. However, this may be due to the different xenograft models used. Unfortunately, it is difficult to compare the therapeutic efficacy of different systems in humans due to different patient populations and disease stages. Clinical data suggests that the circulation half-life and biodistribution of nanoparticles are related to the physicochemical properties of the vehicle. This is consistent with the in vivo biodistribution and circulation half-life results using animal models (Alexis et al. 2008b). In addition, it is well established that hydrophilic polymers such as PEG can be grafted, conjugated, or absorbed onto the surface of nanoparticles to form a corona, which provides steric stabilization and confers "stealth" properties by reducing protein absorption and rapid clearance.

Recently, we (Salvador-Morales et al. 2009b) and others (Cedervall et al. 2007a; Cedervall et al. 2007b; Lindman et al. 2007) investigated nanoparticle surface properties and adsorption of proteins present in the blood. Lindman et al. (Cedervall et al. 2007b) found that protein adsorption kinetics and composition depends on particle size and surface hydrophobicity. The results show that albumin adsorbed more on the surface of 200 nm nanoparticles than on smaller nanoparticles (70 nm). Nanoparticles with hydrophilic surfaces significantly prevented protein adsorption. It was suggested that smaller nanoparticles (70 nm) have higher curvature which reduce protein adsorption of larger proteins. Interestingly, the results show a binding competition leading to adsorption exchanges between proteins despite different concentrations and affinities. Lundqvist et al. have shown that protein adsorption (Lundqvist et al. 2008) depends significantly on the size and charge of the nanoparticles. Identification of protein compositions bound to the nanoparticles showed a mixture of proteins with different functions such as immunoglobulin, lipoproteins, complement pathways proteins, and coagulation factor proteins. Similarly, our group investigated complement activation, blood clotting, and protein adsorption properties of hybrid nanoparticles with precise control of the charge (Salvador-Morales et al. 2009b).

DeSimone's group has investigated internalization pathways (Gratton et al. 2008b) and in-vivo biodistribution of polymeric nanoparticles with different size and shapes (Gratton et al. 2007). Nanoparticles were more efficiently taken up by Hela cells than microparticles. Rod-like nanoparticles were internalized much more

efficiently than their spherical counterpart in vitro but there was no clear evidence of the effect of shape affecting the biodistribution and circulation half-life of the nanoparticles in vivo. Other groups have also shown differential uptake of nanoparticles with different shapes (Chithrani and Chan 2007; Chithrani et al. 2006; Ferrari 2008). These findings are highlighted by the mechanical modeling reported by Decuzzi (Decuzzi and Ferrari 2006; Decuzzi et al. 2007; Decuzzi et al. 2005; Decuzzi et al. 2009; Gentile et al. 2008a; Gentile et al. 2008b) showing that nanoparticle geometry and physicochemical properties contribute to the cellular internalization rate and adhesion forces on the surface of the cells. Mathematical models suggest that nanoparticle size will control its interaction with cells, especially the endothelial wall of vasculatures through a margination dynamic mechanism (Decuzzi and Ferrari 2008). Finally, the surface structure of the nanoparticle can affect its cellular uptake. Recent studies have shown that nanoparticles coated with sub-nanometer striations demonstrate enhanced uptake compared with random surface structures (Verma et al. 2008).

3.3 Targeted Nanoparticles

The concept of targeted therapy appeared in the late 1970s with the development of antibodies (Schrama et al. 2006), whereas the application of targeted nanoparticles appeared later using immunoliposomes (Heath et al. 1980; Leserman et al. 1980). Advances in cancer proteomics and bioinformatics have allowed the development of targeted therapies, which were referred to as a "magic bullet" by the visionary Paul Ehrlich (Strebhardt and Ullrich 2008). Nanocarriers may be surface functionalized with biomolecules for "active" tumor targeting. Surface ligands include antibodies, aptamers, peptides, or small molecules which recognize tumor-specific or tumor-associated antigens in the tumor microenvironment (Alexis et al. 2008b,c; Bareford and Swaan 2007; Farokhzad et al. 2006a,c; Sudimack and Lee 2000; van Vlerken and Amiji 2006). The active targeting mechanism takes advantage of highly specific interactions between the targeting ligand and certain tissues or cell surface antigens to increase cellular uptake and increase tumor retention. Conjugation approaches have been developed to control the amount of targeting ligands on the surface of the nanoparticles. In the case of weak binding ligands, multivalent functionalization on the surface of the nanoparticles provides sufficient avidity. In general, small molecule ligands such as peptides, sugars, and small molecules are more attractive than antibodies due to higher stability, higher purity, ease of production through synthetic routes, and non-immunogenicity.

There are two common approaches for receptor-mediated targeting. This first approach is to target the tumor microenvironment, including the extracellular matrix or surface receptors on tumor blood vessel endothelial cells (Fig. 5), which is usually most efficient for the delivery of immune induction or anti-angiogenesis molecules. The second approach is to target tumor cell surface

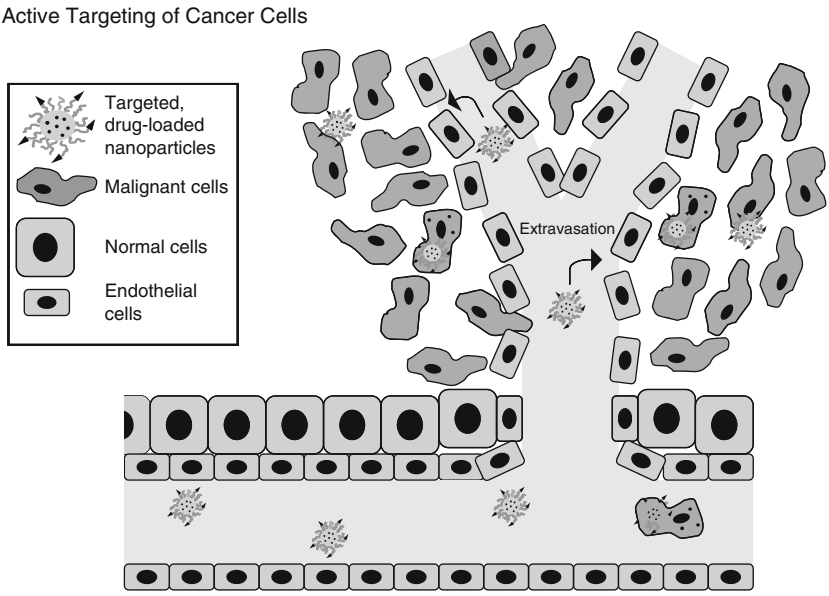

Fig. 5 Schematic of "active targeting" of functionalized nanoparticles to cancer cells. Targeting ligands on the surface of nanoparticles are able to bind to receptors on malignant cells, causing local drug delivery or uptake through receptor-mediated endocytosis

receptors for intracellular delivery (Fig. 6) of cytotoxic agents or signal-pathway inhibitors. Nanocarriers targeted to the extracellular portion of transmembrane tumor antigens are generally specifically taken up by cancer cells through receptor-mediated endocytosis for efficient delivery of therapeutic loads intracellularly. Although it is not clear which approach will provide the highest therapeutic efficacy for treatment of cancer metastases, a recent report using integrin receptor targeted nanoparticles delivering a cytotoxic drug (doxorubicin) showed promising data in primary and metastatic sites of human renal and pancreatic carcinoma mouse xenograft models (Murphy et al. 2008). Targeted nanoparticles showed tumor accumulation and decreased the tumor weight in the primary tumor and hepatic lymph node metastasis. We (Alexis et al. 2008a; Bagalkot et al. 2006, 2007; Dhar et al. 2008; Farokhzad et al. 2004; Gu et al. 2008; Wang et al. 2008a; Zhang et al. 2007) and others (Brannon-Peppas and Blanchette 2004; Peppas 2004) have developed targeted nanoparticles for multiple cancer types. Our group has developed nucleic acid aptamer functionalized nanoparticles for controlled drug delivery. Aptamers are able to bind to specific targets with high affinity and specificity, resulting in clinical development for multiple applications. We are developing multiple technologies using targeted nanoparticle–aptamer bioconjugates for drug delivery to prostate cancer. In a proof-of-concept study, polymeric nanoparticles utilizing aptamers as the targeting ligand showed

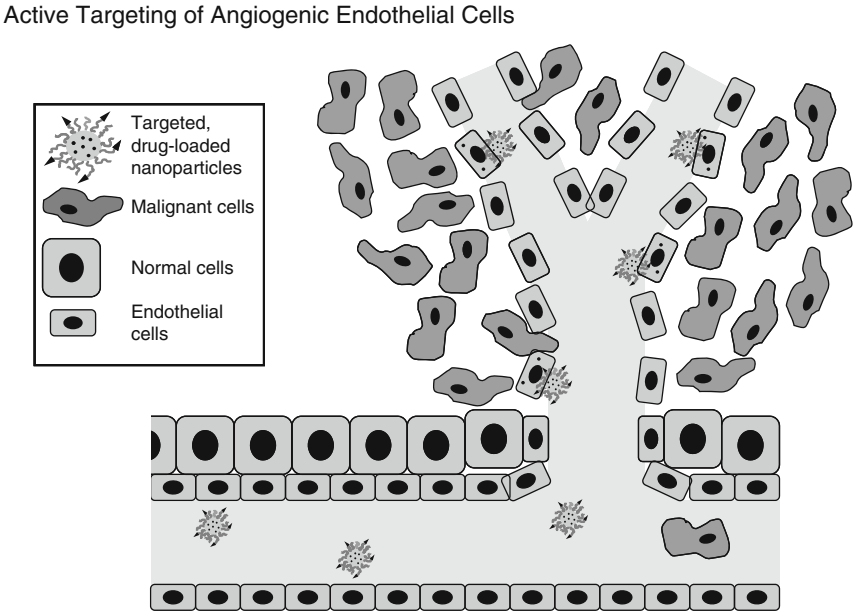

Fig. 6 Schematic of "active targeting" of functionalized nanoparticles to endothelial wall. Targeting ligands on the surface of nanoparticles are able to bind to receptors on endothelial cells or basement membrane matrix, causing local drug delivery on the endothelial wall for anti-angiogenesis therapy

almost complete reduction in tumor growth in a human prostate cancer tumor xenograft mice model (Farokhzad et al. 2004, 2006a). All the treated mice survived more than three months in contrast to other controls. Subsequently, we reported a novel strategy for formulating targeted nanoparticles that was tested in vivo (Gu et al. 2008). We also engineered hydrophilic cisplatin drugs for efficient encapsulation into PLGA–PEG nanoparticles (Dhar et al. 2008).

4 Summary

Metastasis is still an extremely complex disease with multiple questions still remaining. While 90% of human cancer deaths are due to cancer metastases, the hope for fighting cancer is sustained by the fact that there were more than 50 new agents approved in the past 10 years for cancer treatment and hundreds of new agents in clinical development. The development of nanoparticle drug delivery systems is expected to have a big impact on the clinical approaches for cancer therapy. The ability to specifically target nanoparticles along with the controlled delivery of a therapeutic payload provides powerful new ways to treat cancer which are only starting to be realized. By rationally designing nanoparticles based on

improved knowledge of cancer biology and the tumor microenvironment, improved efficacy can be achieved. In addition, multifunctional nanoparticles able to carry imaging agents and deliver multiple drugs are now being developed for enhanced detection and treatment of cancer. The application of nanotechnology to cancer has already produced some exciting results and holds even greater promise for cancer patients in the future.

Acknowledgements This work was supported by National Institute of Health Grants CA119349 and EB003647 and a Koch-Prostate Cancer Foundation Award in Nanotherapeutics. EMP is supported by a National Defense Science and Engineering Graduate Fellowship (NDSEG).

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