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Nanoplatforms for constructing new approaches to cancer treatment, imaging, and drug delivery: What should be the policy?

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Abstract

Nanotechnology is the design and assembly of submicroscopic devices called nanoparticles, which are 1–100 nm in diameter. Nanomedicine is the application of nanotechnology for the diagnosis and treatment of human disease. Disease-specific receptors on the surface of cells provide useful targets for nanoparticles. Because nanoparticles can be engineered from components that (1) recognize disease at the cellular level, (2) are visible on imaging studies, and (3) deliver

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Conflict of interest

The authors declare that there are no conflicts of interest.

therapeutic compounds, nanotechnology is well suited for the diagnosis and treatment of a variety of diseases. Nanotechnology will enable earlier detection and treatment of diseases that are best treated in their initial stages, such as cancer. Advances in nanotechnology will also spur the discovery of new methods for delivery of therapeutic compounds, including genes and proteins, to diseased tissue. A myriad of nanostructured drugs with effective site-targeting can be developed by combining a diverse selection of targeting, diagnostic, and therapeutic components. Incorporating immune target specificity with nanostructures introduces a new type of treatment modality, nano-immunochemotherapy, for patients with cancer. In this review, we will discuss the development and potential applications of nanoscale platforms in medical diagnosis and treatment. To impact the care of patients with neurological diseases, advances in nanotechnology will require accelerated translation to the fields of brain mapping, CNS imaging, and nanoneurosurgery. Advances in nanoplatform, nano-imaging, and nano-drug delivery will drive the future development of nanomedicine, personalized medicine, and targeted therapy. We believe that the formation of a science, technology, medicine law–healthcare policy (STML) hub/center, which encourages collaboration among universities, medical centers, US government, industry, patient advocacy groups, charitable foundations, and philanthropists, could significantly facilitate such advancements and contribute to the translation of nanotechnology across medical disciplines.

Keywords

Nanoplatforms; Nanotechnology; Image-guided therapy; Nanomedicine; Nanoneurosurgery; Nanostructures; Contrast agents; Nanoparticles; Nanotechnology policy; Nano-radiology; Nano-neuroscience; Nano-neurology

Introduction

Modern medicine is not only the product of our greater understanding of biological processes but is also largely dependent on technology to uncover and exploit this deeper understanding. Nanotechnology takes this enterprise to the submicroscopic level, with tools, such as nanoparticles, being developed at the subcellular level (<100 nm; Fig. 1). Nanomedicine refers to the use of nanostructures for the diagnosis and treatment of medical diseases. The specific route of administration (e.g., oral, intravascular, or intratumoral) is chosen according to which method will most safely and effectively deliver nanostructures to the target organ where they can exert their desired effects. Nanostructures have the potential to play a critical role in the future of medicine by serving as carriers for drugs, genes, and imaging agents that will bind to targets on injured or neoplastic tissue.

In 2001, the National Nanotechnology Initiative was established and since then it has received approximately $12 billion in funding. The US government has allocated $1.6 billion for the Nanotechnology Initiative in the 2010 fiscal budget (NNI, 2010 budget: www.nano.gov). Such funding has significantly contributed to the rapid expansion of the field of nanotechnology and to its advances being applied to the area of nanomedicine. Organic and inorganic nanostructures that interface with biological systems have attracted widespread interest in the fields of biology and medicine. For instance, nanoparticles that are novel intravascular or cellular probes are being developed for diagnostic (imaging) and therapeutic (drug/gene delivery) purposes (Fig. 2). These agents could play a critical role in the future of medicine, especially in the areas of target-specific drug/gene delivery, early diagnosis, and disease treatment. Because of their unique characteristics (e.g., amphiphilic, superparamagnetic), nanostructures are well suited for applications in drug delivery, imaging, and early characterization and therapy of brain injuries.

The use of nanotechnology in medicine, more specifically for targeted drug delivery, is set to spread rapidly and to be adopted in neuroscience and neurological surgery. Currently, many substances are under investigation for drug delivery to the brain: nanoparticles for drug delivery may include biological substances such as albumin, gelatin and phospholipids for liposomes, synthetic substances such as polymers, and solid metal particles (Keil et al., 2005).

The safety of nanoparticles requires further investigation. The cellular toxicity of nanoparticles depends on their composition (De Jong and Borm, 2008; Borm and Müller-Schulte, 2006). Many nanostructures incorporate the MRI contrast agent and heavy metal gadolinium, which is thought to cause nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy in patients with poor renal function (Kirsch, 1991; Perazella, 2007; Penfield, 2008; Chrysochou et al., 2009; Neuwelt et al., 2009). Exposure of normal tissue to nanoparticle effects may be reduced by altering the technique of nanoparticle delivery. For example, using real-time imaging during locally administered therapy with nanoparticles will reduce the unpredictability of distribution of nanoparticles that are delivered directly to a tumor. Because nanoparticles provide enhanced signal by nature of their inherent properties or attached moieties, distribution of nanoparticles within an organ can be tracked on real-time imaging studies, providing feedback that directs adjustments in infusion rate and volume, which should improve matching of the distribution to the nanoparticles to the distribution of the tumor (Szerlip et al., 2007).

The ability of some nanoparticles to cross the blood–brain barrier may open new avenues for delivery of drugs to the brain. After crossing the blood–brain barrier (BBB), the nanoscale size of the particles promotes transport into the cell and cellular compartments including the nucleus. Nano-immunology, the use of nanoparticles conjugated to antibodies or bound to immune cells, can direct delivery of nanoparticles to tumor markers on target tissues, thus decreasing systemic exposure to nanoparticles. The capability to design better nanovectors will stimulate development of new agents that provide highly targeted nanotherapy to diseased tissue.

This article provides an overview of current nanovectors and drug delivery systems. It describes the potential benefits and safety concerns of nanoparticles and nanomaterials and describes their present and future use in clinical medicine. The extent of application of nanomedicine to the treatment of diseases of the CNS will depend on further advances being made in nanotechnology and image-guided therapy. The ability to design nanoparticles with a variety of unique targeting, imaging, and therapeutic components is well suited to the coming era of personalized medicine (potentially including the use of gene and siRNA therapy).

Nanoscale platforms

Polymeric nanoparticles

Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective permeation through cell membranes and stability in the blood stream. Polymers are very convenient materials for the manufacture of countless and varied molecular designs that can be integrated into unique nanoparticle constructs with many potential medical applications (Peer et al., 2007) (Fig. 2D).

Polymers are being developed to create delivery systems with excellent drug and protein loading and release properties, a long shelf life, and little toxicity (Portilla-Arias et al., 2008a,b). Amphiphilic block or graft copolymers assemble spontaneously into polymeric nanoconjugates in aqueous solution. Polymers, such as poly-lactic acid (PLA), poly-glycolic

acid (PGA), poly-lactic glycolic acid (PLGA), poly(ε-caprolactone), polyglutamic acid, and polymalic acid, and their copolymers have been the most extensively studied. These polymers have been used in surgery for 30 years and have proven biocompatibility (Gilding and Reed, 1979). Several biodegradable polymers are suitable for preparing nano-sized particles for drug delivery applications. The degradation drug release rate of these polymers can be controlled by adjusting their molecular mass and, in the case of copolymers, their composition and microstructure (Duncan, 2006).

Polymers can also be used to coat other types of nanoparticles. Polyethylene glycol (PEG) is a hydrophilic polymer that has been used to coat the surface of nanoparticles, which allows them to avoid clearance by the reticuloendothelial system (Lockman et al., 2002), reach the central nervous system, and cross the BBB (CNS) (Koo et al., 2006). Although hydrophilic drugs do not penetrate the BBB, the nanoscale size of hydrophilic nanoparticles allows them to pass through the BBB. The mechanism of this phenomenon is thought to arise from receptor-mediated phagocytosis and passive leakage through permeable capillaries in tumors (Koo et al., 2006). In the 9L gliosarcoma model (Moffat et al., 2003), PEG coating of a nanoparticle magnetic resonance imaging (MRI) contrast agent increased the amount of MR signal intensity from the agent. Increased coating with PEG decreased clearance of nanoparticles and increased plasma half-life. Other hydrophilic polymers, including Hydrogel (polyacrylamide), dextran, and polysorbate, have been used to coat the surface of nanoparticles to prolong plasma circulation and improve delivery across the BBB (Koo et al., 2006). Another way of circumventing the BBB and treating brain tumors is by using direct intratumoral injection of PEG hydrogel beads that gradually elute a drug, such as doxorubicin (Saito et al., 2007). The size of these beads can be adjusted of the requirements of the application and can range from nanoscale particles to micrometer-sized particles. These hydrogels have proven to be very biocompatible with the primate brain (Bjugstad et al., 2008). Micrometer-sized particles can also carry out a dual therapeutic strategy in which the core of the particles secretes anti-mitotic or cytotoxic agents to kill tumor cells and the surface of the particles carries neural stem cells to repair tissue damaged by the tumor (Bible et al., 2009a,b; Brekke et al., 2007).

Polymers can also be used in tissue engineering. Functionalized PLGA particles have been prepared that can serve as a scaffold for stem cells that are transplanted into the central nervous system (CNS) (Bible et al., 2009a,b). Stem cells must have a favorable anatomic framework to restore brain and spinal cord regions destroyed by stroke, trauma, or tumor (Bible et al., 2009a,b).

Polymeric nanoconjugates

Polymeric nanoconjugates are highly innovative technologies in nanomedicine (Ljubimova et al., 2008b). These agents bear numerous functional groups that are available for covalent binding to a variety of biochemically active groups, which direct them to malignant tumors where they can deliver functional drugs acting on several tumor targets (e.g., mRNA and/or protein) (Lee et al., 2006a; Ljubimova et al., 2008b; Pinhassi et al., 2010). Nanoconjugates that carry more than one functional group provide the capability to simultaneously inhibit several tumor pathways, deliver optimal drug concentrations to the site of treatment, and reduce adverse effects on healthy tissue (Lee et al., 2006a). Nanoconjugate polymers are generally synthesized around a polymer with pendant functional groups like –OH, –COOH, or –NH2. Synthesis requires a hierarchy of stepwise chemical conjugation reactions and careful avoidance of uncontrollable side chemistry. Long chain all-carbon backbones without heteroatoms (O, N, S) make up non-biodegradable polymer platforms (Lee et al., 2006a). However, nanoconjugate drugs that are biodegradable are preferred to non-biodegradable ones that can accumulate in non-targeted tissues and organs (Chakraborty et al., 2010; Lee et al., 2006a; Ljubimova et al., 2008b). Biodegradability requires metabolic

breakdown of the nanoconjugate and final decomposition to water and carbon dioxide (Chakraborty et al., 2010).

Nanoconjugate delivery systems are chemical entities unlike unconjugated nanodelivery vehicles (micelles, liposomes, etc.), which are physical but not chemical entities of drug, targeting, and/or other functional molecules (Dhanikula and Panchagnula, 2005; Pinhassi et al., 2010). Nanoconjugates are also smaller in size than micelles and liposomes, less immunogenic, and chemically more stable in plasma (Dhanikula and Panchagnula, 2005; Pinhassi et al., 2010). They can be internalized by receptor-mediated endocytosis into a specific type of cell (e.g. cancer cell or cells involved in other pathological conditions, such as macrophages in Gaucher's disease) (Pinhassi et al., 2010). By virtue of their high molecular weight (m.w.), this class of drugs accumulates at the tumor site and has slower clearance than smaller molecules(Chakraborty et al., 2010; Lee et al., 2006a; Ljubimova et al., 2008b). Particularly relevant to anti-cancer therapy is the need to reduce side effects that arise from drug toxicity to normal cells and to minimize cancer drug resistance. Nanoconjugates can overcome drawbacks of conventional chemotherapy such as drug resistance and toxicity by specifically targeting tumor cells, activating cancer cell uptake, and bypassing multidrug resistance transporters (Lee et al., 2006a; Ljubimova et al., 2008b). Although development of multi-functional and biodegradable drugs could advance cancer treatment research, relatively few multi-functional drug-delivery systems have been introduced (Lee et al., 2006a; Ljubimova et al., 2008b; Miller et al., 2009).

A Polycefin system of nanoconjugates (Fig. 3) with a biodegradable, naturally derived universal polymeric platform was recently developed (Fujita et al., 2006; Lee et al., 2006a,b; Ljubimova et al. 2008a). This system offers an easily accessible route for developing highly tumor-specific and efficient multi-targeted drug carriers. Polycefin provides the capability to attach various inhibitors of multiple molecular targets to the same nanoconjugate platform, providing combination therapy with one "superdrug."

Micelles

Micelles are amphiphilic spherical structures composed of a hydrophobic core and a hydrophilic shell (Oh et al., 2004). The hydrophilic shell stabilizes the micelle in an aqueous environment for intravenous delivery and the hydrophobic core stores a payload of drug for therapy (Adams et al., 2003). Due to their nanoscale dimensions (diameter less than 50 nm) (Sahoo and Labhasetwar, 2003) and their hydrophilic shell, polymeric micelles resist elimination by the reticuloendothelial system, which increases their circulation time and ability to deliver drug to the target. A recent article reported production of polymeric micelles with alpha, beta-poly(*N*-2-hydroxyethyl)-D,L-aspartamide (PHEA) backbone molecules and D,L-polylactic acid (PLA) hydrophobic side chains (Craparo et al., 2008). *In vitro* experiments demonstrated that these systems were not cytotoxic to 16 HBE, CaCo2, HuDe, and K562 cell lines and were not hemolytic. Moreover, both PHEA-EDA-PS80-PLA and PHEA-EDA-PLA micelles were able to penetrate into Neuro2a cells and, in the case of PS80 decorated micelles, to escape from phagocytosis by J774 A1 macrophages (Craparo et al., 2008).

Polymeric micelles are highly stable *in vitro* and *in vivo*, are very biocompatible, and can dissolve a broad variety of poorly soluble pharmaceuticals; several types of drug-loaded micelles are currently being tested in preclinical and clinical trials. Among polymeric micelles, a special group is formed by lipid-core micelles, i.e., micelles formed by conjugates of soluble copolymers with lipids (such as polyethylene glycol-phosphatidyl ethanolamine conjugate). Tumor may be targeted with micelles by exploiting the enhanced permeability and retention (EPR) effect, by making micelles of stimuli-responsive

amphiphilic block copolymers, or by attaching specific targeting ligand molecules to the micelle surface (Dabholkar et al., 2006).

Surfactants are being incorporated into anticancer metal-based drugs. The surfactant dodecyl amine reacts with selenious acid to produce a quaternary ammonium salt, which can be complexed to copper (II) or cobalt (II) ions to form copper or cobalt cationic complexes. Initial studies of antitumor effect of these compounds demonstrated effectiveness *in vitro* against five human monolayer tumor cell lines: MCF7 (breast carcinoma), HEPG(2) (liver carcinoma), U-251 (glioma), HCT116 (colon carcinoma), and H-460 (lung carcinoma). These studies support further research into the use of surfactant–metal complexes as novel therapeutic agents for cancer (Badawi et al., 2008).

Peptides and proteins

Peptides and proteins have better defined chemical compositions and molecular weights than most nanomaterials. Large-scale production of peptides and proteins has become routine in industry. Discovery of novel peptides and proteins sets in motion an industrial effort to rapidly produce suitable quantities of pharmaceutical-grade product, which is suitable for rapid biological and pharmaceutical testing and eventual clinical application. Peptides interact non-specifically with cell membrane components and specifically with various cellular receptors. Peptides that specifically interact with certain receptors overexpressed by cancer cells have been successfully developed as targeting molecules for drug delivery and *in vivo* imaging (Laakkonen et al., 2008; Reubi and Maecke, 2008). The interaction of peptides and proteins with the cell membrane results in their penetration into the cell or the formation of pores within the cell membrane. Because of their ability to target and enter cells, peptide and protein carriers hold great potential for the delivery of genes and antisense oligonucleotides to cancer cells (Abes et al., 2009; Duvshani-Eshet et al., 2008). Proteins (antibodies in particular) generally have better receptor-mediated targeting than peptides and more specific interaction with receptors. They are widely used for drug delivery and imaging (Sofou and Sgouros, 2008; Kirpotin et al., 2006). Proteins with novel properties are steadily being discovered by scientists. In the past decade, dozens of fluorescent proteins have been engineered with various excitation–emission wavelengths, brightness, and photostability (Shaner et al., 2005), which allows them to be used to assess protein location and function *in vitro* (Giepmans et al., 2006). Multicolored fluorescent proteins highlight angiogenesis within tumors (Amoh et al., 2008).

Incorporation of nano-sized protein cage architectures into nanomaterials may be another method that leads to new innovations in medical imaging and therapy. An iron oxide (magnetite) nano-particle was synthesized by attaching the cell-specific targeting peptide RGD-4C to the exterior surface of a genetically engineered human H-chain ferritin (HFn) molecule that encaged an iron oxide nanoparticle. The construct bound to C32 melanoma cells *in vitro*, demonstrating that genetically modified protein cage architecture could serve as a multifunctional nanoscale container for iron oxide loading and cell-specific targeting (Uchida et al., 2006).

Metal complexes

Contrast agents that are commonly used in clinical practice for brain and spinal cord MRI are based on gadolinium. However, the use of other metals as contrast agents is currently being investigated. Iron oxide-based nanoparticle MRI contrast agents have in particular shown great promise. Iron oxide-based nanoparticles are super-paramagnetic, having a magnetic moment that can be changed by ambient thermal energy. Superparamagnetic iron oxide contrast agents either form the core of magnetic nanoparticles that have a polymeric

coating or are more homogeneously integrated into polymeric nanoparticles (Koo et al., 2006).

Gold nanoparticles (AuNPs) have also been used for cancer cell imaging and targeting. AuNPs are very attractive nanoscale agents as they are biocompatible, may naturally emit radiation, and have high surface reactivity. One approach is to develop AuNPs that are stabilized by gum arabic (GA), a nontoxic, plant-derived substance, and use them for diagnostic and therapeutic applications. This research group showed that GA-AuNPs have excellent *in vitro* and *in vivo* stability, are nontoxic, distribute minimally to non-target organs in biodistribution studies, and produce contrast on CT imaging (Kattumuri et al., 2007). Another group (Shi et al., 2007) has devised an approach for imaging and targeting cancer cells using dendrimer-entrapped gold nanoparticles (Au DENPs). Au DENPs, when covalently linked to folic acid and fluorescein isothiocyanate molecules, are stable, hydrophilic, biocompatible, and able to specifically bind to cancer cells that overexpress high-affinity folate receptors. The folic acid-conjugated nanoparticles are subsequently endocytosed into lysosomes of cancer cells, providing a means for targeting and imaging these cells (Shi et al., 2007).

Endohedral metallofullerene nanoparticles

Endohedral metallofullerenes have attracted considerable interest over the past decade. These particles are able to transfer electrons from encapsulated metal atoms to the fullerene cage. Metal fullerene cages solubilize metallic agents and prepare them for use in MRI applications (Kato et al., 2003). One group developed a nanoparticle (gadolinium nitride PEGylated-hydroxylated endohedral metallofullerene) consisting of gadolinium-containing metalofullerene (tri-, $Gd_3N@C_{80}$), which was functionalized with polyethylene glycol (PEG) and multihydroxyl groups to significantly increase water solubility and distribution. To investigate if trimetallic nitride endohedral metallofullerene nanoparticles would be useful as an MRI proton relaxation agent, MR imaging was performed after infusing these particles into agarose gel and rat brains. They found that T1–T2 MRI relaxivity characteristics of the nanoparticles were about 40 times higher than that of traditional gadolinium-containing MRI contrast agents, such as gadodiamide. *In vitro* experiments showed that the nanoparticle-based contrast agent produced as much contrast as the control clinical agent but at much lower concentrations, up to an order of magnitude lower. *In vivo* imaging produced similar results, with 0.013 mmol $Gd_3N@C_{80}$ producing as much contrast as 0.50 mmol clinical gadodiamide. The highly stable carbon cage of the nanoparticle prevents the release of toxic metal ions from the metalofullerene core and prevents water molecules from interacting with the metal atoms (Fatouros et al., 2006).

Superparamagnetic iron oxide nanoparticles

Imaging techniques that can selectively image proliferating cells *in vivo* can provide critically important insights into tumor growth rate, degree of tumor angiogenesis, effectiveness of treatment, and vigor of normal cells. Researchers have recently demonstrated the use of superparamagnetic iron oxide (SPIO) nanoparticles to image neovasculature in glioma animal models and to image stem cells *in vivo* and *in vitro* (Sykova and Jendelova, 2005; Anderson et al., 2005, Arbab et al., 2004, 2005a,b; Frank et al., 2003; Cunningham et al., 2005; Daldrup-Link et al., 2003; Bulte et al., 1999, 2002; Magnitsky et al., 2005; Wang et al., 2001). The crystal structure of SPIO nanoparticle has the general formula of $Fe^{3+}O_3M^{2+}O$, where M^{2+} represents a divalent metal ion (i.e., iron, manganese, nickel, cobalt or magnesium). The ferric iron (Fe^{3+}) makes the complex magnetic (Daldrup-Link et al., 2003; Wang et al., 2001) and large, unpaired, thermodynamically independent spines (single domain particles) makes the complex superparamagnetic (Wang et al., 2001). Single domain particles or magnetic domains have a

net magnetic dipole. External magnetic fields can cause the magnetic domain to re-orient (Wang et al., 2001). The signal intensity of these nanoparticles is related to the size of the particle, its position, its concentration within a given voxel, data acquisition parameters, the magnetic field, and dosage of the SPIO (Wang et al., 2001).

SPIO nanoparticles are classified by size as oral or large SPIO agents (ferumoxsil, 300 nm, approved for clinical application), standard or SSIPO agents (Ferumoxide, 80–150 nm, approved for clinical application), ultra-small or USPIO agents (Ferumoxtran, 20–40 nm, approved for clinical application), and mono-crystalline iron oxide nanoparticle or MION agents (5–10 nm, experimental) (Corot et al., 2006; de Vries et al., 2005; Choi et al., 2006). SPIO agents added to water form colloidal suspensions because the energy of Brownian motion exceeds the power of gravity at their size. A 5-μm filter can be used to remove particles that aggregate (Wang et al., 2001). Ferumoxide, a suspension of dextran-coated SPIO, is phagocytosed by cells and accumulates in endosomes of Kupffer cells and other reticulo-endothelial cells (Sykova and Jendelova, 2005; Arbab et al., 2004, 2005a,b; Frank et al., 2003). Biodegradability of this compound in blood is confirmed by serum iron levels increasing within 1 day and serum ferritin levels increasing by 7 days after administration. Iron from nanoparticles is incorporated into red blood cell hemoglobin within 30–40 days (Arbab et al., 2005b). It is important to note that Ferumoxide alone cannot label non-phagocytic or non-rapidly dividing mammalian cells due to its negative *zeta* potential. However, Ferumoxide can be linked through electrostatic interaction to a polycationic transfection agent so it can enter non-phagocytic cells and effectively incorporate its SPIO nanoparticles within the endosome. Polycationic protamine sulfate (-Pro) is an approved drug for reversing heparin anticoagulation. A complex of Ferumoxide and polycationic protamine sulfate (FePro) is currently being evaluated in FDA-regulated clinical trials (Arbab et al., 2005b; Wang et al., 2001). This compound holds promise as an MRI-based *in vivo* cellular imaging agent (Budde and Frank, 2009). Iron-labeled cells can be identified by MR studies, appearing as areas of low signal intensity in T2 and T2* sequences due to iron sensitivity (Sykova and Jendelova, 2005; Arbab et al., 2005b; Frank et al., 2003). Signal changes can be used to observe *in vivo* cellular trafficking on MRI images for days to weeks after implantation, although signal attenuates with each cellular division.

Carbon nano platforms

Carbon nanotubes—Carbon nanotubes (CNTs) can be fabricated into biodegradable nanostructures (cylindrical buckytubes). These structures are currently being studied for use in nanomedicine, tissue engineering as nanovectors (Bianco et al., 2005a; Kateb et al., 2007; Pancrazio, 2008; MacDonald et al., 2005). They are synthesized by rolling sheets of carbon into hollow tubes that are single-walled (0.4- to 2-nm diameter), double-walled (1- to 3.5-nm diameter), or multi-walled (2- to 100-nm diameter). Some of these nanostructures (Fig. 4) activate the complement cascade. Single-walled CNTs activate the classical pathway, while double-walled CNTs activate both the classical and alternative pathways of the human serum complement system (Salvador-Morales et al., 2006). Although multi-walled CNTs have not resulted in proliferative or cytokine changes *in vitro* (Fig. 5), CNT size and composition must be carefully controlled to promote intracellular delivery of these nanotubes and to prevent immune reaction to them (Kateb et al., 2007). Functionalization and alteration of CNT and other graphite nanoplatfom surface chemistry can reduce or eliminate complement activation while making the CNTs more biocompatiable (Salvador-Morales et al., 2006; Prato et al., 2008; Zhang et al., 2009). One way to significantly enhance biocompatibility of CNT is by heparinizing the nanotubes (Murugesan et al., 2006). Although CNT toxicity is not fully understood and toxicity study results are conflicting, it is important to be aware of potential complications. Systemic application of CNT can result in oxidative stress in end organs (Aillon et al., 2009; Genaidy et al., 2009) and inhalational

exposure of CNT can result in acute lung injury, inflammation, and fibrosis (Sanchez et al., 2009).

Fullerenes—Fullerenes are a family of carbon allotropic compounds that were predicted to exist in 1970 and officially discovered in 1985 (Kroto et al., 1985; Osawa, 1970). The most common form is C_{60}. Their landmark discovery has since led to synthesis of fullerene derivatives, such as C_{61}-butylic acid. It has also led to the discovery or synthesis of other fullerene variations, such as C_{70}, C_{20} (the smallest member), carbon nanotubes (elongated, tube-structured fullerene), carbon nano-onions, and nano buds (Langa and Nierengarten, 2007; Nasibulin et al., 2007; Sano et al., 2001; Prinzbach et al., 2000; Iijima, 1991). Recently, Amsharov et al. reported the synthesis of an “unrolled” C84 fullerene using flash vacuum pyrolysis (Amsharov and Jansen, 2009). Fullerenes have the ability to assume different forms and to encage compounds. The unique physical, chemical, electrical, and optical properties of fullerenes and their derivatives have led to their incorporation into new or improved devices and materials and to advancements in engineering, industry, and science (Koruga et al., 1996; Guldi and Prato, 2000; Bosi et al., 2003; Bakry et al., 2007; Avouris et al., 2007; Zagal et al., 2009). Well-defined fullerene containing polymers and stimuli-sensitive amphiphilic systems can be readily synthesized due to development of the azido coupling and atom transfer radical addition process (Ravi et al., 2007). Hydrated fullerenes are radioprotective. Hydrated C(60) fullerene protects against damage from X-ray irradiation (7 Gy) *in vitro* and *in vivo* in mice by reducing the formation of reactive oxygen species (Andrievsky et al., 2009). Research continues into ways to increase the solubility of fullerenes and to investigate the toxicity of fullerenes and their derived compounds (Johnston et al., 2009).

Nanodiamonds—Nanodiamonds (NDs) are attractive agents for use in biological and medical applications largely due to their greater biocompatibility than other carbon nanomaterials, stable photoluminescence, ease of purification, commercial availability, and minimal cytotoxicity (Krueger, 2008; Xing and Dai, 2009; Holt, 2007; Enoki et al., 2009). Nanodiamonds can be functionalized and conjugated to a variety of molecules for the purpose of cell labeling and drug delivery. Adding certain functional groups to nanodiamonds can improve their solubility, direct them to specific binding sites on target cells and tissues, and reduce their effects on normal tissues. As with most nanomaterials, nanodiamonds can be prepared by covalent and non-covalent modification to absorb or graft a variety of functional groups and complex moieties, including proteins and DNA (Krueger, 2008). The variety of functionalizations that can be attached to nano-diamonds broadens the scope of their potential diagnostic and therapeutic applications.

Nanodiamonds are suitable for controlled drug delivery applications because of their capability to release drug slowly and consistently and their abundant capacity for drug loading due to their large surface area-to-volume ratio (Huang et al., 2007; Lam et al., 2008). A thin film made from nanodiamond clusters and loaded with the chemotherapy drug doxorubicin effectively released the drug and killed target cells (Huang et al., 2007). The film’s shape and size can be modified as required for implantable, localized chemotherapy. Nanodiamonds have also been used to solubilize and efficiently deliver water-insoluble chemotherapeutic agents to breast and liver tumor cells (Lam et al., 2008; Chen et al., 2009).

Nanodiamonds can be used for cell labeling and tracing because they do not interrupt cell division or differentiation, have minimal cytotoxicity, and are easily functionalized with proteins and other markers for targeting purposes. One type of ND, type Ib, naturally fluoresces and is resistant to photo-bleaching and photoblinking. Nanodiamonds have successfully been used as biomarkers or tracers to label or trace HeLa cells, lung cancer cells, and murine fibroblasts (Fu et al., 2007; Chang et al., 2008a,b; Liu et al., 2009;

Vaijayanthimala and Chang, 2009). Deagglomeration to disperse nanodiamond particles may be required for some biological applications because NDs have a tendency to form agglomerates (Krueger, 2008). Research is ongoing to determine the long-term cytotoxicity and stability of functionalized NDs.

Dendrimers—Dendrimers are one of the most versatile and extensively studied nanostructure carrier systems (Tekade et al., 2009). Dendrimers are highly complex molecules with a core, branches, and end groups (Fig. 6). Dendrimers become progressively larger with the addition of each generation (shell) of branches and can be built from the molecular level to nanoscale size (1 nm to over 10 nm). The generation (shell) number and the chemical composition of the core, branches, and surface functional groups determine the size, shape, and reactivity of dendrimers. The ability to precisely control their size, shape, and surface functionality during synthesis makes dendrimers one of the most versatile and customizable nanotechnologies. Dendrimers have myriad applications, including solubility enhancement (Devarakonda et al., 2007; Milhem et al., 2000), gene therapy (Dufes et al., 2005; Hecht and Frechet, 2001; Shah et al., 2000), drug delivery (Tomalia et al., 2007; Lai et al., 2007; Chauhan et al. 2003), nanocomposites (Curry et al., 2007; Esumi et al., 2005; Satoh et al., 2002), photodynamic therapy (Battah et al., 2007; van Nostrum, 2004) and bioimaging and cancer treatment (Barrett et al., 2009; Bharali et al., 2009).

Biocompatible dendrimers have been used as delivery systems for potent drugs, such as cisplatin and doxorubicin, in cancer treatment (Gillies and Frechet, 2005). The surface chemistry of these materials can be modified relatively easily to include ligands (molecules that attach to cell surface receptors) that can be used to target the dendrimer to tumor tissue. Dendrimers have been studied extensively for targeting and delivery of therapeutic agents for cancer and of contrast agents for magnetic resonance imaging (Kobayashi and Brechbiel, 2005; Talanov et al., 2006). Dendrimers can be complexed to metal nanoparticles, but toxicity has been reported with some of these complexes, reducing their attractiveness as imaging agents. Coating the surface of dendrimer–metal nanoparticles with gold has been reported to greatly reduce their toxicity without significantly altering their size and to provide an anchor for attachment of targeting molecules with high affinity to tumor cells, such as folate (Shi et al., 2007, 2008).

Applications

Cancer diagnosis and treatment

The National Cancer Institute (NCI) has recognized the immense potential that nanotechnology holds for cancer diagnosis and treatment (Cuenca et al., 2006). In 2005, NCI's initiative in Centers of Cancer Nanotechnology Excellence led to the creation of eight nanotechnology centers in major academic institutions throughout the US. Research at these centers has focused on improving nanoscale drug delivery systems, such as liposomes, gelatin nanoparticles, polymeric nanoconjugates, and micelles, and on the development of new nanoscale platforms (e.g., quantum dots, nanoshells, gold nanoparticles, paramagnetic nanoparticles, and carbon nanotubes). The overarching goal of this research is to deliver imaging probes and therapeutics in high concentration to the tumor. Novel diagnostic and therapeutic agents for use in oncology will be created using nanotechnology (Cuenca et al., 2006).

Immunoassays that detect the presence of tumor markers are one application of nanotechnology in oncology. A sensitive and specific immunoassay for the detection of human alpha-fetoprotein (AFP), a tumor marker seen with hepatocellular carcinoma, has been developed that uses Ag/SiO_2 core-shell nanoparticles, which are embedded with rhodamine B isothiocyanate dye molecules as Raman tags (Gong et al., 2006). Silica-coated

magnetic nanoparticles with modified amino groups make up the immobilization matrix and separation tool. The novel nanostructure Raman tags have a very high stability compared to traditional tags and the use of the silica-coated magnetic nanoparticles as an immobilization matrix and separation tool is simpler than traditional techniques. This strategy resulted in detection of human AFP at concentrations as low as 11.5 pg/ml (Gong et al., 2006).

Nanoconjugate concept for cancer therapy

Mechanisms of multiple drug resistance may render conventional chemotherapy ineffective. Cancer chemotherapy also is non-specific in that it kills rapidly dividing cells not only within the tumor but also in normal tissue. Nanoconjugates can surmount these drawbacks of classical chemotherapy because they can be designed for (1) sustained release of drug, (2) passive enhanced permeability (EPR) effect-based targeting of macromolecules to tumor tissue, (3) ligand-based targeting of cell surface antigens and modules active in endosomal uptake and membrane disruption, (4) drug release into the cytoplasm, and (5) protection from enzymatic degradation (Maeda et al., 2000; Farokhzad and Langer, 2009). Polymers as platforms for delivering agents into tumor cells have increasingly gained importance because they are unaffected by the multidrug resistance (MDR) effect, have minimal immunogenicity (Kabanov et al., 2002; Luo and Prestwich, 2002), and are able to maintain effectiveness with each cycle of tumor treatment.

The passive enhanced permeability (EPR) effect results from a tendency of high molecular weight macromolecules (m.w.>45 kDa) and lipids selectively to accumulate in tumors (Peterson et al., 2003; Torchilin and Lukyanov, 2003). The EPR effect is thought to occur because solid tumors secrete VEGF that stimulates vascular endothelial cell growth, increases the permeability of tumor-associated neovasculature, and causes leakage of circulating macromolecules and small particles into the tumor. Tumors lack an effective lymphatic drainage system to clear these extravasated substances so macromolecules and nanoparticles that enter the tumor will accumulate in the tumor (Gao et al., 2004). Unlike currently used small molecular weight anticancer drugs, macromolecular (or polymeric) drugs can target tumors with high selectivity through the EPR effect (Maeda et al., 2003; Peterson et al., 2003; Torchilin and Lukyanov, 2003; Nori and Kopecek, 2005). General macromolecular targeting of tumor tissue is referred to as “passive” (EPR effect), whereas site-specific targeting of cell surface molecules and receptors is referred to as “active”. Targeted delivery to tumor vasculature was recently shown using a synthetic non-biodegradable polymer, *N*-(2-hydroxypropyl) methacrylamide (HPMA), conjugated with fumagillol (TNP-470) (Satchi-Fainaro et al., 2004; Nori and Kopecek, 2005; Benny et al., 2008). Targeting of tumor tissue is possible with modern macromolecular nanodelivery systems that deliver high drug concentrations and maximal effects to tumor tissue and minimal drug concentrations and negligible side effects to healthy tissue.

Nanoparticles containing quantum dots and molecular beacons can aid in the detection of tumor cell markers. Quantum dots are synthetic, inorganic fluorophore semiconductors that are stable, are resistant to photobleaching, and have narrow emission spectra while also possessing wide excitation ranges (Fountaine et al., 2006). They can also be applied in a multiplex manner to detect several signals from a single excitation wavelength. As a result, quantum dot-conjugated probes can be used to measure the expression levels of several specific malignant tumor biomarkers at the same time, providing valuable data for treatment (True and Gao, 2007).

Molecular beacons (MBs) are hairpin-shaped oligonucleotides that act like switches. MBs undergo conformational changes and fluoresce when turned on. When used as probes, MBs have valuable applications in nucleic acid and gene expression monitoring, biosensors, and as aptamers. MBs have the potential to become very useful tools in genomics and

proteomics as they enable real-time detection of protein–RNA–DNA interaction with high sensitivity and specificity (Tan et al., 2005). For example, MB probes have been combined with barcoded metal nanowires to allow for multiplexed detection of nucleic acids (Stoermer et al., 2006).

Blood–brain barrier

Drug delivery to the brain continues to be one of the most significant challenges of modern neuromedicine. For drugs to reverse pathologic changes in the CNS, they must be able to traverse the nearly impervious blood–brain barrier (BBB). Unlike other capillaries in the body, the capillaries of the BBB are extraordinarily selective in permeability; only hydrophobic, nontoxic, and uncharged molecules can pass through the BBB along a diffusion gradient (Juliano, 2007; Silva, 2007). A nanoparticle drug complex could be effective against CNS disease if it could pass through the blood–brain barrier, find the CNS lesion, target tumor cells specifically, and release a payload of therapeutic agent without altering the vital functions of the CNS. To deliver molecules across the BBB, a few invasive and noninvasive methods have been developed and studied, but their clinical effectiveness has not exceeded that of current treatment methods. These methods include lipidization, temporary alteration of the BBB, invasive delivery, convection-enhanced delivery (CED), and active/facilitated cell transport. Nanotechnology may offer solutions to CNS drug delivery problems because (1) the size of the molecular cargo and the carrying complex can easily be controlled and optimized for drug delivery to the CNS; (2) nanoscale technologies offer specificity to site of action, creating drug targeting that is precise enough to avoid damage to the delicate CNS structures; and (3) the requirement of lipid solubility can be circumvented by using microemulsions of nanoparticle complexes in oil that can cross the BBB (Koo et al., 2006).

Nanotechnology is being investigated as a method to increase delivery of antineoplastic drugs to CNS tumors. The attention devoted to this field is not unwarranted; more than 43,800 new CNS tumors afflict Americans every year. With 12,690 deaths per year, brain tumors are the most frequent cause of cancer-related death in children. Current treatment of brain tumors includes surgery, which is invasive, and irradiation, which may damage normal brain structures. Efforts to improve treatment outcomes with non-lipid soluble chemotherapy and photosensitizing drugs for photo dynamic therapy have been frustrated by the quintessential problem of ineffective delivery of agents across the BBB (Koo et al., 2006). The development of nanoscale drug carriers will add a new class of therapy for CNS tumors. Nanoparticle carriers can vastly increase the specificity of antineoplastic drugs, directing their effects to target cells, thus reducing injurious effects on unintended tissues and cells. In a study in a rat model of gliosarcoma, radiolabeled PEG-coated hexadecyl cyanocrylate nanospheres preferentially accumulated around tumor cells (Brigger et al., 2002).

For tumor targeting, a systemically (e.g., intravenously (i.v.)) administered drug has to pass through the blood–tumor barrier (BTB) and/or the BBB, before arriving at the tumor cell surface. One method to facilitate this transport is to use a nanoparticle that is linked to a ligand that will bind to a receptor on the surface of the BTB or BBB. For instance, a nanoparticle linked to transferrin can bind to transferrin receptor (TfR) on the surface of vascular endothelial cells of the BTB/BBB and then traverse these barriers by transcytosis (Duncan, 2006). After it enters the CNS, the nanoparticle can bind to TfR that is overexpressed on the surface of tumor cells. To be effective, the nanodelivery vehicle must be internalized and capable of delivering a lethal payload to the tumor cell (Fujita et al., 2006).

Polymers are able to deliver inhibitory agents to tumor cells but are less immunogenic and less prone to elimination than viral vectors and, therefore, better able than viral vectors to

maintain antitumor activity through repeated cycles of cancer therapy (Duncan, 2003; Satchi-Fainaro et al., 2004; Vinogradov et al., 2004a,b; Kabanov et al., 2005). The last decade has seen successful clinical application of polymer–protein conjugates (e.g., Oncaspar, Neulasta). More than 10 polymer-based anticancer drug conjugates have entered clinical trials. Phase I/II clinical trials involving *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-doxorubicin (PK1; FCE28068) showed a 4-to 5-fold reduction in anthracycline-related toxicity and absence of cardiotoxicity (Nori and Kopecek, 2005).

Another promising drug carrier is poly(β-L-malic acid) (PMLA) (Braud et al., 1985; Korherr et al., 1995; Gasslmaier and Holler, 1997; Cammas et al., 1999; Gasslmaier et al., 2000; Lee et al., 2002; Portilla-Arias et al. 2008a,b). PMLA is a natural product of the slime mold *Physarum polycephalum* (Korherr et al., 1995; Lee et al., 2002). Other biodegradable polymers, such as poly(aspartic acid) and poly (glutamic acid), are more toxic and immunogenic than PMLA (Murphy and Sage, 1970; Wang et al., 1993; Zhou et al., 2004; Zhang and Bhavnani, 2006; Gupta and Yucel, 2007). The favorable properties of PMLA as a carrier matrix for biopharmaceuticals are its lack of toxicity *in vitro* and *in vivo*, non-immunogenicity, biodegradability, stability in the bloodstream, and cellular uptake (Braud et al., 1985; Gasslmaier and Holler, 1997; Gasslmaier et al., 2000; Lee et al., 2002; Domurado et al., 2003). Polycefin is a nanoscale (20- to 30-nm range) drug delivery system containing a PMLA scaffold and a total m. w. up to 680 kDa. It contains special moieties that expedite cellular uptake, including tumor-specific antibodies or other homing devices that promote receptor-mediated endocytosis and a transport vehicle that releases drug intracellularly, and contains antisense oligonucleotides (AON) that target specific tumor mRNA sequences. Polycephin has (1) a disulfide bond cleavable by intracellular glutathione, (2) a pH-sensitive hydrazone bond, (3) a tetrapeptide cleaved by lysosomal cathepsin B, whose activity is elevated in tumors, (4) an intrinsic release function from endosomes (Kabanov et al., 2005; Benny et al., 2008), and (5) PEG for polymer stabilization and protection (Sukhishvili et al. 2000; Bae and Urban, 2006). In addition, it can be readily detected in biological fluids (blood, urine, and spinal fluid) and tissues if a radioactive tracer or fluorescent dye is conjugated to its PMLA scaffold.

Polycefin was initially designed to pass through the BBB/BTB after systemic administration and accumulate in brain tumors, where it would prevent angiogenesis by blocking laminin-411, a protein overexpressed in tumor vasculature. Although laminin-411 normally promotes cell migration during development, wound healing, and angiogenesis, these functions are diverted by the tumor for invasion, growth, and angiogenesis (Miner et al., 1997; Patarroyo et al. 2002; Thyboll et al., 2002; Gonzalez et al., 2002; Ljubimova et al., 2001; Khazenzon et al. 2003). Predominant laminin-411 expression was found in 75% of human glial tumors, 69% of invasive ductal breast carcinomas, and 100% of breast cancer metastases to the brain (Ljubimova et al., 2001, 2004; Fujita et al. 2005). Blocking the synthesis of laminin-411 inhibited tumor cell migration and invasion (Fujita et al., 2006; Ljubimova et al., 2008a). Injection of Polycefin, which contains AON (antisense oligonucleotides) to laminin-411 chains, into GBM-bearing animals results in a significant reduction of brain tumor vessel area, indicating the importance of laminin-411 for tumor angiogenesis. Its suppressive effect on tumor vasculature figured prominently in increasing the duration of survival in brain tumor-bearing animals after Polycefin treatment (Fujita et al., 2006; Ljubimova et al., 2008a). Polycefin is a promising nontoxic, non-immunogenic, biodegradable, and tumor/tissue-specific drug delivery system that is able to simultaneously block several molecular markers at the same time and reduce tumor angiogenesis, invasion, and metastasis.

A group of researchers recently found that embedding paclitaxel into biodegradable poly(lactic-co-glycolic acid), or PLGA, nanoparticles dramatically increases paclitaxel

delivery to primary brain tumors. They found that the addition of PLGA greatly improves solubility and permeation ability of paclitaxel through the BBB, rendering tumor cell destruction more efficient, while reducing healthy cell damage. Nanoparticles loaded with paclitaxel have 13-fold greater potency and significantly fewer side effects than paclitaxel alone (Brigger et al., 2002). A similar project was conducted with the anthracycline aclarubin, usually unable to pass through the BBB. When this agent was loaded into cationic albumin-conjugated pegylated nanoparticles (CBSA-NP-ACL) and administered to rats with C6 glioma, fluorescent probing revealed that the gliomas contained a several fold increase in drug level and drug preservation compared to aclarubin alone. Albumin conjugation further improved accumulation in glioma tissue. Long-term experiments demonstrated increased survival following nanoparticle delivery of aclarubicin, and significantly lower toxicity to kidney and liver tissue, as evaluated by periodic acid Schiff staining and biochemical analysis (Lu et al., 2007).

Another study, which used nanoparticles to deliver the BBB-impermeable drug doxorubicin, showed similar promise (Steiniger et al., 2004). In this study, researchers used polysorbate-coated nanoparticles as the delivery adjuvant, applying the drug complex *in vivo* to glioblastomas implanted in rat brains. Nearly 200 rats, in control and experimental groups, were treated with doxorubicin alone or doxorubicin conjugated to a nanoparticle. The group that received doxorubicin via a nanoparticle vehicle had longer survival than the group that received free drug alone, and almost 20% of the nanoparticle group experienced a long-term remission. The nano-particle group also had less systemic and CNS toxicity than the group treated with doxorubin alone (Steiniger et al., 2004).

In addition to improving drug delivery to CNS cancers, nanoparticles may lead to new treatment methods for other diseases that require improved drug delivery to the CNS. One particular application of nanotechnology in the treatment of pain is to enable systemic delivery of Dalargin to the brain. Previously Dalargin was only effective when administered intra-cerebroventricularly, having little effect following systemic introduction because of its minimal penetration of the BBB. However, systemic delivery of Dalargin to the CNS has been made possible by attaching Dalargin to poly(butylcyanocrylate) nanoparticles; radiola-beling has shown that the particles successfully cross the barrier and enter CNS tissue (Schroeder et al., 1999). Polysorbate 80-coated nanoparticles loaded with Dalargin showed similar results. Another application of nanoparticles is to improve delivery of enzyme to the CNS. To evaluate the feasibility of enzyme delivery to the CNS, one group applied 100-nm pegylated liposomes loaded with horseradish peroxidase (HRP) and tagged with transferrin (Tf) to an *in vitro* model of the BBB (Visser et al., 2005). When brain capillary endothelial cells were incubated at 4 and 37 °C with the liposomes, the cell lysates revealed that not only did the enzymatic activity of HRP in the Tf group exceed that of the control group by four-fold, but also that HRP enzymatic activity specifically targeted the lysosome. These results suggest that liposome-aided delivery of enzymes to the brain is possible and could be used for the treatment of lysosomal storage diseases (Visser et al., 2005). Gene therapy for certain CNS diseases could also be facilitated by nanoparticles improving delivery of genetic vectors to the brain. In the 6-hydroxydopamine rat model of Parkinson’s disease, a tyrosine hydroxylase (TH) expression plasmid conjugated to PEG immunoliposome nanoparticles was able to successfully traverse the BBB and normalize TH expression levels (Silva, 2007).

The ability of nanoparticles to permeate the BBB suggests that they could be used for imaging brain disease and monitoring treatment. The most popular nanoparticle agent for MRI, iron oxide, can be mixed with water and administered in colloidal form. While this method is effective for systemic imaging, CNS imaging with this colloid is futile, because the particles cannot penetrate the BBB. However, recent studies have shown that oil

microemulsions of iron oxide nanoparticles can cross the BBB and be detected noninvasively by MRI.

Nanotechnology may also have a role in improving delivery of boron to brain tumors and in enhancing the effectiveness of neutron capture therapy. Boron neutron capture therapy (BNCT) involves the initiation of nuclear reactions in the presence of boron-10 and free low-energy thermal neutrons. Boron-10 captures these neutrons to yield high linear energy transfer (LET) alpha particles and recoiling lithium-7 nuclei, which, in turn, kill tumor cells. Neutron capture therapy currently depends on the use of the low molecular weight agents, sodium borocaptate and boronophenylalanine; however, significant research is being conducted with higher molecular weight compounds, including nanoscale ones. Studies exposing cells to boron-containing nanovehicles have shown promising effects, including more specific targeting of tumor cells, reduced toxicity to healthy cells, and significant permeation through the BBB (Huynh et al., 2005).

The experimental studies mentioned above document that nanoparticles can successfully migrate through the BBB. Both vesicular endocytosis and facilitated transporter binding are potential mechanisms for translocation of nanoparticles through the BBB. Further study is required to discover additional mechanisms for entry of nanoparticles into the CNS and to evaluate if nanoparticles will elicit CNS toxicity (Silva, 2007).

Application of nanotechnology for detection of tumor angiogenesis

Angiogenesis is required for the growth of solid tumors and antagonism of angiogenesis can slow tumor growth. Nanotechnology is being used to identify mechanisms of tumor angiogenesis. To explore the contribution of endothelial precursor cells to the neovascularization of certain tumors, endothelial precursor cells (EPC) of hematopoietic stem cell origin were labeled with FDA-approved dextran-coated superparamagnetic iron oxide (SPIO) nanoparticles (Arbab et al., 2005c). The labeled cells were injected intravenously into mice and then monitored by MRI for migration and incorporation into growing tumor. This method noninvasively detected early migration and incorporation of EPC into tumor vasculature with high spatial resolution. The findings on MRI were verified by findings on histology of EPC within tumor vasculature and of differentiation of EPC into endothelial cells. This study suggests that nanoparticle-loaded EPC might be used clinically to detect sites of tumor angiogenesis.

Nano-imaging

Interest in nano-imaging has grown due to its potential to detect and diagnose cancer and other human diseases at an earlier stage than with current imaging methods. Nanoparticles have been developed with better body compartment distribution and tissue targeting than standard contrast agents (Bulte and Modo, 2007).

Bimodal imaging in cancer detection: MRI and fluorescence imaging

Each imaging modality for tumor imaging has its own strengths and limitations. For example, MRI has excellent spatial resolution but is less sensitive than fluorescent imaging. With the help of technological advancements in polymer engineering and materials science, the development of nanoscale probes with bimodal or multimodal imaging capabilities will likely overcome such limitations of single-modality imaging (McMahon et al., 2008). Talanov et al. (2006) synthesized a dendrimer-based nanoprobe for dual modality magnetic resonance and fluorescence imaging. The platform of the probe was a polyamidoamine (PAMAM) dendrimer, which is a water-soluble, biocompatible macromolecule with amide and amine functional groups (Goldberg et al., 2007). The functional groups conjugated Gd(III) and Cy5.5, a fluorescent marker. Using a mouse model, they demonstrated that the

probe provided MRI enhancement within sentinel lymph nodes and feeding lymphatic channels with high spatial resolution and provided fluorescent labeling of tumor cells not only within the MR-enhancing lymphatic structures but also in parts of the nodes that were not visualized by MRI (Talanov et al., 2006). A nanoprobe has been developed with dye-doped silica as a platform that has both MRI- and fluorescent-imaging capabilities (Lee et al., 2006a,b). The silica nanoprobe has amine groups that can be used to conjugate $(Fe_3O_4)_n$ for MRI. To prepare the nanoparticle for tumor detection, it was conjugated to HmenB1, an antibody against polysialic acid (PSA), which is known to be overexpressed in several cancers including neuroblastoma. *In vitro* testing gave promising results as the probe bound the target antigen and permitted visualization of labeled cells with both MRI and fluorescent imaging (Lee et al., 2006a,b). Another tumor-detecting nanoprobe was constructed using an ultra-sensitive metal-doped magnetism-engineered iron oxide (MEIO) particle conjugated with Herceptin, an antibody against HER2/neu, which is often overexpressed in breast and ovarian cancers. This manganese (Mn)-MEIO-Herceptin nanoprobe detected small tumors (~50 mg) with greater sensitivity than MEIO alone or a cross-linked iron oxide MR contrast agent (Lee et al., 2007). This technology may potentially improve the sensitivity of MRI to identify small primary tumors and metastases. The distribution of nanoparticles in tumors depends on many factors, including *in vivo* colloidal stability, particle size, intracellular uptake of nanoparticle, and tumor angiogenesis (Cho et al., 2007).

Quantum dots, quantum rods, quantum beacons

Quantum dots (QD) are small 2- to 8-nm colloidal semiconductor nanocrystals (Reiss et al., 2009) that can be administered via injection, excited *in vivo* using a long wavelength (Cai and Chen, 2008), and then recognized by their resulting fluorescence using a sensitive charge-captured device (CCD) camera. QDs have unique optical and electronic properties based on their size and composition (Koo et al., 2005; Michalet et al., 2005). The surface of QDs can be engineered or modified to improve QD solubility, sensitivity, specificity, and visualization in target tissue. For instance, QDs used for the study of the lymphatic system need to remain in the lymphatic circulation for an extended period of time. Polyethylene glycol (PEG) can be attached to QDs to protect them from opsonization by the mononuclear phagocytic system and keep the probes from being eliminated, resulting in longer circulation time in the lymphatic system (Koo et al., 2005). In a mouse tumor model, Ballou et al. utilized PEG-QDs to map sentinel lymphatic nodes. In the study, the QDs were injected directly into melanoma and teratocarcinoma. The migrating probes were monitored using a CCD camera. The mapping of the migration of QDs from tumors to nearby lymph nodes could be visualized; histological analysis confirmed the presence of QDs in lymphatic vessels and sinuses (Ballou et al., 2007). While initial studies of the *in vivo* toxicity of QDs suggest that QDs are safe, more research into the potential toxicity of QDs is required before QDs can be used in humans (Hauck et al., 2009).

One group created QD-Gd-wedge nanoparticles functionalized with Annexin A5, a molecule that recognizes phosphatidylserine, which is displayed on the outer membrane of apoptotic cells. These bimodal nanoparticles could then provide contrast on MRI in regions of apoptosis and provide fluorescence in apoptotic cells on histologic sections viewed through the two-photon laser scanning microscope (Prinzen et al., 2007; Hernandez-Sanchez et al., 2006; Reiss et al., 2009). Antibody-conjugated QDs can be suitable for detection and tracking of cells that specifically bind the antibody. In a recent study, antibody conjugation to the tumor antigen alpha fetoprotein (AFP) did not alter the fluorescence of QDs. Moreover, the efficiency of fluorescence under 2-photon excitation was higher for the QD bioconjugates than for the original QDs (Yu et al., 2007). This new class of fluorescent probes could be an excellent alternative to conventional labeling if these findings are replicated using other antibodies.

QDs provide signal to novel probes with unique physical, chemical, and optical properties. As such, they represent promising new tools for *in vivo* molecular and cellular imaging. However, their introduction into central nervous system (CNS) imaging has been delayed because of their poor stability and low blood–brain barrier permeability, which severely limit their delivery to CNS sites following parenteral administration. Recently, a research group developed a QD-based imaging platform for brain imaging by incorporating QDs into the core of poly(ethylene glycol)-poly(lactic acid) nanoparticles, which were then functionalized with wheat germ agglutinin, and delivered into the brain via nasal application. The resulting nano-particles had high payload capacity, were water-soluble and stable, and showed excellent and safe brain targeting and imaging properties. With PEG functional terminal groups available on its surface, this nanoprobe is equipped for conjugation with various biological ligands, which enables it to be a platform for the development of a multitude of CNS disease-specific imaging agents (Xiaoling et al., 2008) (Fig. 2C).

QD-molecular beacons are new variations on QDs. Their ability to detect sequence-specific DNA is currently under study. Molecular beacons are oligonucleotide-based probes that emit light when the oligonucleide hybridizes to a complimentary sequence of DNA and produces a change in probe configuration that separates a quencher from the fluorophore. Scientists who are developing QD-molecular beacons report that selection of appropriate linkage methods and quenchers is critical to improving the sensitivity of target detection (Cady et al., 2007).

Quantum rods (QRs) are semiconductor nanocrystals that are rod-shaped and usually brighter than QDs. Research into using QRs for *in vitro* and *in vivo* imaging began fairly recently and has led to several encouraging reports. The uptake of transferrin (Tf)-conjugated QRs has been tested in HeLa cells overexpressing Tf receptors (Yong et al., 2007). Uptake was verified *in vitro* through confocal microscopy. The uptake of QR-Tf was clearly receptor mediated as QR signal was not observed in cells with saturated Tf receptors or in cells incubated with QR without Tf. *In vivo* testing of QD and QR bioconjugates is required.

Nanobeacons: stem/progenitor cell tracking with multiple unique Perfluorocarbon nanobeacons and 19F MRI

MRI can be a useful tool to investigate migratory behavior of stem cells that are tagged with nanoparticles. In particular, (^{19}F) MRI is useful since its signals are intrinsically quantitative and have excellent contrast-to-noise ratio. One group has successfully tracked mononuclear cells isolated from umbilical cord blood with perfluorocarbon (PFC) nanoparticles conjugated with fluorescent tags. The migration pattern of the progenitor cells could be tracked using MRI and spectroscopy. The system works effectively because (1) cells uptake the PFC nanoparticles readily without requiring transfection, (2) PFC nanoparticles have little effect on cell viability, and (3) spatial localization and quantification of stem cells can be determined by MRI while the signals can be verified using spectroscopy (Partlow et al., 2007).

The ability to track stem cells has the potential to revolutionize nanoneurosurgery. Implementation of this strategy will require (1) design of functional nanoparticles that are personalized to cellular markers and genes, (2) bundling of these functional nanoparticles into a suitable delivery vector, (3) incorporation of nanoparticles *ex vivo* into stem cells, and (4) injection of stem cells into the cell-deficient brain region that requires repair. Once the cells are tagged, their position and their effect on the underlying disease can be evaluated by imaging on an ongoing basis. Because this work could provide a method to monitor and

control stem cell therapy for degenerative diseases of the CNS, there is great need for further investigation in this area that could pave the way for future clinical trials.

Lymph-node MRI

Staging of many types of cancers establishes a prognosis and directs cancer treatment. Accurate staging requires detection of the presence, or confirmation of the absence, of lymph node metastases. MRI provides soft tissue images with excellent resolution but is relatively insensitive to identification of early involvement of lymph nodes by metastatic cells. One study evaluated the use of lymphotropic superparamagnetic nanoparticles in 80 patients to see if these nanoparticles could improve the sensitivity of MRI to detect early involvement of lymph nodes by tumor cells. The study was predicated on the presumed ability of nanoparticles to gain access to lymph nodes via interstitial–lymphatic fluid transport, to preferentially accumulate in lymph nodes, and to be identified by high-resolution MRI. The authors reported that MRI with lymphotropic superparamagnetic nanoparticles correctly identified nodal metastases and had much greater sensitivity than conventional MRI. Nanoparticles accumulated because the metastasis disturbed normal lymph node architecture and lymphatic fluid flow. This technique detected metastases that were smaller than 2 mm in diameter and below the threshold of detection by conventional MRI (Harisinghani et al., 2003). High-resolution MRI with lymphotropic superparamagnetic nanoparticles has the potential to be adopted broadly for clinical use for the identification of occult lymph node metastasis.

Nanocontrast agents for differential tissue imaging

Nanotechnology can also be utilized to create nanocontrast agents that produce imaging contrast and that accentuate differences between normal and diseased tissue. For instance, Su et al. have generated Au_3Cu_1 nanocapsules and used them as an MRI contrast agent. The team found that the nanocontrast agent provides signal contrast in T_1- and T_2-weighted imaging in mice and therefore could potentially be used for MR angiography. One drawback, however, was that the Au_3Cu_1 nanocapsules resulted in dose-dependent cytotoxicity. Nevertheless, due to its ability to attach biological molecules, as well as enhance T1-/T2-weighted imaging, further research may lead to development of Au_3Cu_1 nanocapsules as an alternative to Gd- or non-iron oxide-based bimetallic contrast (Su et al., 2007). A lipidic gadolinium contrast agent for MRI, Gd-DOTA-Chol (MAGfect), is a novel liposome formulation that was found to be an effective vehicle for transporting plasmid DNA (pDNA) to cells and for optimizing cellular uptake (Oliver et al., 2006).

Although most nanocontrast agents have been designed for MRI applications, nanoparticle-based contrast agents for ultrasound and X-ray/CT imaging are now being developed. For ultrasound contrast agents, research has focused on enhancing acoustic reflectivity by modulating microbubbles. Bimodal agents are being created, which contain one component that produces imaging contrast and another component that is detected by another imaging method or that delivers a therapeutic molecule. Recent advancements in engineering have enabled researchers to create microbubbles that produce ultrasound imaging contrast and serve as drug delivery vehicles that carry therapeutic agents to brain tumors and other diseases (Dayton and Ferrara, 2002; Tartis, et al., 2006; Ferrara et al., 2009). There are recent reports of SPIO-emulsion microbubbles that can be used as ultrasound and MRI contrast agents, and multifunctional nanoparticles and hollow spherical nano-aggregates that can simultaneously act as ultrasound contrast agents and drug carrier/delivery vehicles (Yang et al., 2008; Gao et al., 2008; Hadinoto and Cheow, 2009). In addition, Her2-conjugated nanoparticles have been demonstrated to produce ultrasound signal contrast *in vitro* (Liu et al., 2007). These nanoparticles have promise as contrast agents for site-specific

ultrasound imaging and ultrasound-guided cancer therapy. They will require extensive *in vivo* testing to evaluate their safety before they can be used in clinical trials.

Superparamagnetic iron oxide nanoparticles with covalently bound polyethylene glycol (PEG) conjugated to folic acid can detect cancer cells overexpressing folate receptors (Sun et al., 2005). Magnetism-engineered iron oxide (MEIO) nanoprobes conjugated with antibodies can also detect tumor markers with increased magnetic resonance sensitivity as compared to other probes (Lee et al., 2007).

Bimodal contrast agent

Bimodal contrast agents allow the assessment of regions of interest using two independent imaging modalities. In many novel applications, it is highly desirable to verify the reliability of a new modality against a method that is generally accepted to be valid (the gold standard). For instance, the sensitivity and specificity of noninvasive tracking of transplanted stem cells by MRI require MRI detection of transplanted stem cells to be compared against the gold standard of histological demonstration of transplanted cells containing fluorescent markers in the imaged tissue (Modo et al., 2002).

Intraoperative imaging under real-time conditions

Kircher and colleagues have developed and tested in a mouse model a bimodal contrast agent that can be used to localize brain tumors by MRI before surgery and to visualize brain tumors using intraoperative optical imaging during surgery. In this study, cross-linked iron oxide (CLIO) nanoparticles were functionalized with the fluorescent label, Cy5.5. After surgically implanting a gliosarcoma cell line that expressed green fluorescent protein, they infused the bimodal nanoparticle. They then performed MRI imaging and noninvasive optical imaging with a custom-built imaging system that detected Cy5.5 fluorescence within the tumor. The near-infrared fluorescent-imaging system was able to visualize the nanoparticle probe within the glioma through several millimeters of overlying tissue, which suggests that the probe would effectively visualize a subcortical glioma in a patient undergoing brain surgery. These findings suggest that a multimodal nanoparticle could serve as an intraoperative imaging agent and provide a strong localizing signal under real-time conditions (Kircher et al., 2003). Development of this nanotechnology could provide real-time information the neurosurgeon in the operating room about the location of the margins of an intracerebral tumor, which could improve the completeness of surgical removal of the tumor and reduce injury to the surrounding normal brain.

Imaging of cell signaling pathways

Calcium ions play a significant role as secondary messengers in biological systems. There are a variety of imaging methods to investigate cellular processes that involve calcium, but many are only *in vitro* applications or are invasive. A team led by Atanasijevic et al. has developed a calcium-sensitive MRI contrast agent that uses calmodulin, a calcium-binding protein, which is functionalized on SPIO. In the presence of calcium ions, calmodulin–SPIO nanoparticles accumulate and create T2 changes on MRI imaging. This agent may provide a noninvasive method for *in vivo* monitoring of calcium ion dynamics (Atanasijevic et al., 2006; Li et al., 2002).

Glyconanoparticles for in vivo imaging of brain disease

Another potentially important application of nanoparticles is in *in vivo* imaging of brain disorders. Specific visualization of early-activated cerebral endothelium would provide a powerful tool for the pre-symptomatic diagnosis of brain disease and evaluation of new therapies. Recently, carbohydrate-functionalized nanoparticles were described that allow

direct detection of the endothelial markers E-/P-selectin (CD62E/CD62P) in acute inflammation (van Kasteren et al., 2009). These MRI-visible glyconanoparticles contain multiple copies of the selectin ligand. Their sensitivity and binding selectivity promote early diagnosis of inflammatory disease in the central nervous system and may lead to insights and new treatments for an expanding patient population suffering from neurological disorders (van Kasteren et al., 2009).

Drug delivery

For fiscal years 2005 to 2008, the US government allocated $3.7 billion for nanoscale science and engineering (Flynn and Wei 2005), and by 2015, the National Science Foundation (NSF) estimates the market value of all nanotechnologies to be $1 trillion (Roco and Bainbridge, 2003). In medicine, the major thrust for nanotechnology has arisen from a need to improve drug delivery, and this effort has led to rapid growth in this sector of the pharmaceutical industry. Cientifica, a leading nanotechnology information and consulting company, estimates that the total market value of nanotechnology-enabled drug delivery will be $26 billion by 2012, a sharp rise from its current value of $3.39 billion. They project the exponential rise to continue past 2012 and to reach a value of $220 billion by 2015.

The rapid growth of the drug delivery sector is in part driven by the equally rapid growth of annual prescription expenditures. According to the Centers for Medicare and Medicaid Services, Health and Human Services 2001 annual report on prescription expenditures, annual prescription expenditures in the United States were $117 billion, with this figure expected to grow xto $366 billion by 2010 (CMS, 2001; Flynn and Wei 2005). Increasing prescription expenditures will help pharmaceutical companies to increase their investment in nanoscale drug delivery systems that can lead to new and more effective treatments. A variety of different delivery strategies are either being implemented or are being tested for use in treatment of human cancer (Table 2). These strategies are also focused on adjusting the size and delivery system of nanoplatforms, which are important characteristics of a successful biocompatible nano-drug delivery system (Singh and Lillard, 2009 and Table 2). The FDA has approved for clinical use a significant number of drug products in the nanometer size range (Table 3). Please refer to the Supplement for more examples of nanoparticles used in drug delivery.

Conclusion

Scientists throughout the world combined forces to map the human genome. Discovering the sequence of genes for the entire set of human chromosomes was a phenomenal task. Constructing the human genomic map has had a dramatic effect on current medicine and future therapies. For instance, it has accelerated our unraveling of basic disease processes and has provided insights that spurred the development of new drugs and biological agents. Discovering the types and amounts of proteins that are produced by gene expression in every region of the brain will permit construction of a proteomic map of the normal brain. Creation of progressively more complete genomic and proteomic maps of the brain will expand the understanding of the basic underpinnings of normal brain function. These normal maps provide benchmarks that can be compared to the genome and proteome of patients to pinpoint mutated genes or abnormal protein expression that underlie or accompany certain brain diseases. Increased knowledge of the process of gene regulation will also be essential to understanding the workings of a healthy brain. Taken together, increased knowledge of the normal genome and proteome will provide a foundation for the development of novel methods for counteracting disease processes of the CNS.

Scientists are striving to design ways to tailor the characteristics of nanomolecular and cellular agents and to restrict their effects to specific organs and sites. Nano-neuro-

immunotherapy is a developing field based on development of nanoparticles that bind to a target with immune specificity and that deliver their drug payload there. This highly focused drug delivery and therapy technique contrasts sharply with current drug therapies that distribute their effects equally to areas of normal function and disease, the so-called shotgun approach, which results in systemic exposure and toxicity. Another emerging strategy, nanoparticle-augmented cell therapy, provides a method to simultaneously provide treatment and imaging at the site of brain disease. These strategies have the potential to reduce the morbidity and mortality of diseases of the central nervous system and to improve the quality of life of patients.

In the near future, nanomedicine will participate in the development of personalized medicine. Patients will undergo treatment tailored to their unique genetic makeup. Developments in the fields of pharmacogenomics, nutrigenomics, and ecogenomics will assume increasing importance (Odemir et al., 2009). Neurosurgeons will be able to consider the individualized gene and brain maps (anatomic, functional, proteomic) of a patient and choose the treatment that should be safest and most effective. Using techniques of image guided therapy and nanoneurosurgery, neurosurgeons will be able to detect, confirm, and treat brain injury with nanostructures. Surgeons will inoculate cells with various types of nanostructures that carry a regimen of drugs, which can be released and act at different steps of a biochemical pathway. In the case of brain tumors, therapeutic cells will be delivered into tumors, where they will distribute their nanoparticles into tumor cells and release drugs to selectively eliminate tumor cells. The imaging contrast produced by therapeutic nanoparticles will permit imaging to monitor the progress of treatment for each patient.

Nanovectors, nanostructures, nanoplatforms, and nanoscale objects hold the potential to bring about less invasive and more selective treatment of brain tumors and other CNS diseases. Reaching this potential will require more research and the development of nanovectors that are less toxic, more versatile, and more biodegradable that current ones. Poor water solubility of some nanoplatforms must be overcome before they can be utilized in the development of nanodrugs. Many groups have functionalized very stable nanoplatforms such as CNT and gold nanoparticles in order to achieve solubility (Bianco et al., 2005b; Klumpp et al., 2006; Bartczak and Kanaras, 2010). Others have designed soluble nanoplatforms such as poly(malic acid) nanoconjugates, which contain various antibodies and oligonucleotides for multitargeted drug delivery (Lee et al., 2002; Fujita et al., 2006; Lee et al. 2006a,b; Fujita et al. 2007 and Ljubimova et al 2008a). A new generation of nanovectors could incorporate multi-functional compounds and allow multistage, complex delivery of therapeutic compounds and augmented cellular therapies. The fields of nanomedicine, image-guided drug delivery and therapy, and gene therapy will inevitably converge further and to enable personalized medicine and targeted disease therapy. Advances in each field will drive the development of synergistic, more effective, and less toxic therapies for presently incurable neoplastic and non-neoplastic diseases of the CNS.

A coherent and coordinated effort among multiple US governmental agencies, foundations, and industry with a clear focus on translating nanotechnology could contribute significantly to the development of novel targeted and personalized therapeutics. With $40 billion in government-funded nanotechnology research in 2008, there is a strong imperative to increase the breadth and depth of nanotechnology and avoid unnecessary duplication of research efforts (cientifica, 2009). To improve efficiency in moving nano-technology from the laboratory to the clinic, we propose the creation of a central science, technology, medicine and law–healthcare policy (STML) hub/center that fosters and coordinates collaborative efforts across all institutions while creating policies, which could encourage such interaction. The government, regulators, industry, universities, foundations, and scholarly societies would contribute to the hub in order to maximize the impact of funds

allocated by the US government. Such a hub could identify existing gaps between disciplines and direct specific seed funds to those areas. The central hub would encourage cross-disciplinary research that focuses on specific nanotechnology/nanomedicine initiatives. In the US, this would support coordinated efforts across the FDA, NSF, NIH, NCI, NINDS, and NNI. We believe that the creation of the central hub and its efforts will cultivate a spirit of partnership between industry, government, universities, and foundations that will translate innovations in nanotechnology into medicine, where they can be developed and implemented as powerful therapeutics for neurological and other disorders.

We also believe that the US government should dedicate funding to establish international consortia that could be administered under the STML hub/Center. These consortia could bring the finest scientists and research programs together across the world, create a united front for translational medicine, and create jobs in participating countries. Some of the funding for the hub and consortia should be allocated for meetings to educate lawmakers about interdisciplinary medicine. These sessions would provide lawmakers with information that would increase their understanding of medical research and science and assist them in meeting the challenge of evaluating legislative proposals that relate to emerging technologies in medicine. These efforts will significantly support efforts toward more personalized medicine, reduce healthcare cost, and eliminate duplicated research. An STML research hub/Center will increase efficiency in healthcare and help cultivate an environment that fosters the growth and development of biotechnologies and the biotechnology industry (e.g., formation of venture capital-backed startups, joint ventures). This approach can contribute to the economic growth and scientific advancement of the country, as new employees are needed to support the development of nanotechnology and nanomedicine in the newly formed companies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.neuroimage.2010.01.105.

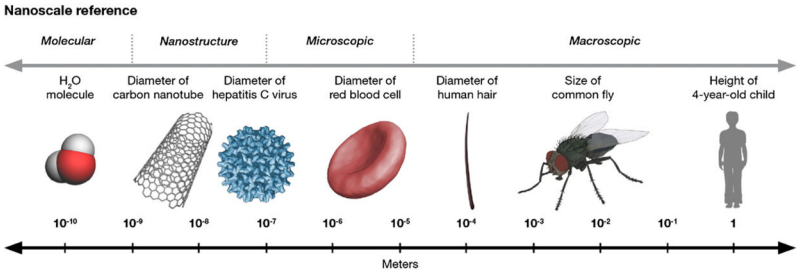

Fig. 1.
Demonstrates the size and scale of nanostructures relative to commonly known objects.

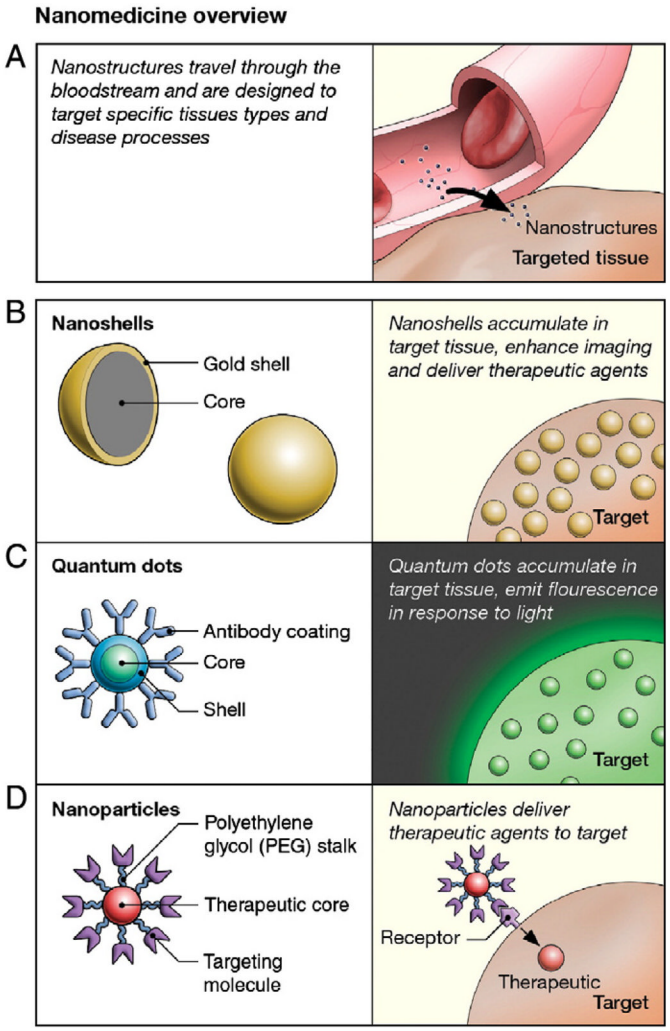

Fig. 2.

(A) One pathway for nanostructures to reach target tissues is via the bloodstream. (B) Nanoshells can be used in imaging, as well as drug delivery. The core can be loaded with therapeutic agents that affect pathophysiological processes in the target tissue. (C) Quantum dots include a semiconductor nanocrystal core, which emits fluorescence in response to light. This schematic shows a quantum dot-based structure with an antibody coating. (D) This shows a nanoparticle functionalized with a targeting molecule interacting with a receptor at the target site. In this way, nanoparticles can deliver therapeutics and have localized versus systemic effects.

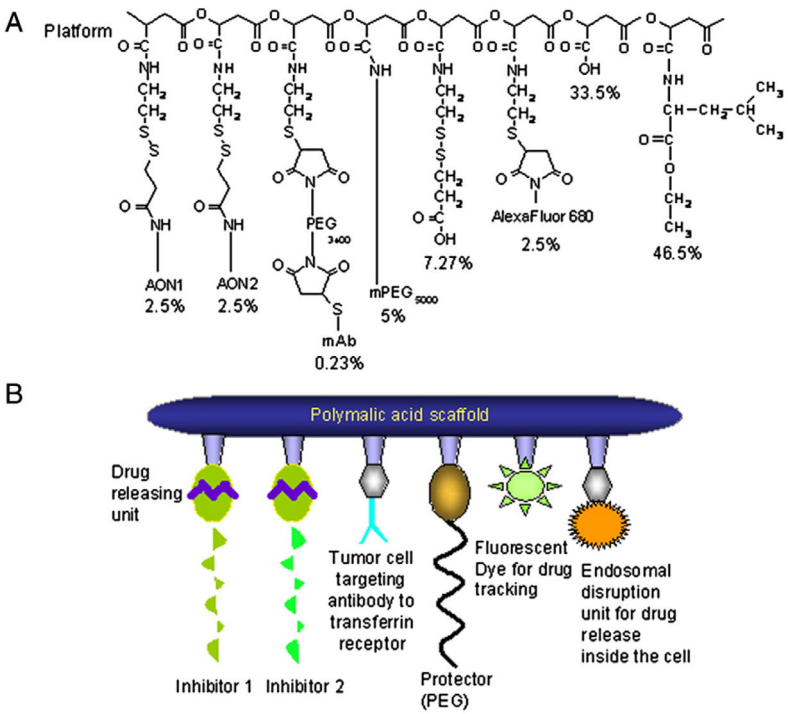

Fig. 3.

Schematic view of Polycefin. (A) Schematic formula showing the composition of the nanoconjugate. The functional units (modules) have been chemically conjugated to the carboxyl groups of the PMLA platform. Percent values refer to total pendant carboxyl residues (100%). AON1 and AON2 are the Morpholino antisense oligonucleotides that target the mRNAs of laminin α4 and β1 chains, respectively. The drug-releasing unit is the disulfide group. Mouse anti-human TfR mAb targets tumor cells at their cell surface. PEG protects against enzymatic degradation. The fluorescent reporter group, AexaFuor 680, serves *in vivo* fluorescence imaging. L-Leucine ethylester moieties function in endosomal escape. The groups of 7.27% are the product of sulfhydryl blocking at the end of Polycefin synthesis and has no function. (B) A cartoon of Polycefin with the functional modules described in panel A.

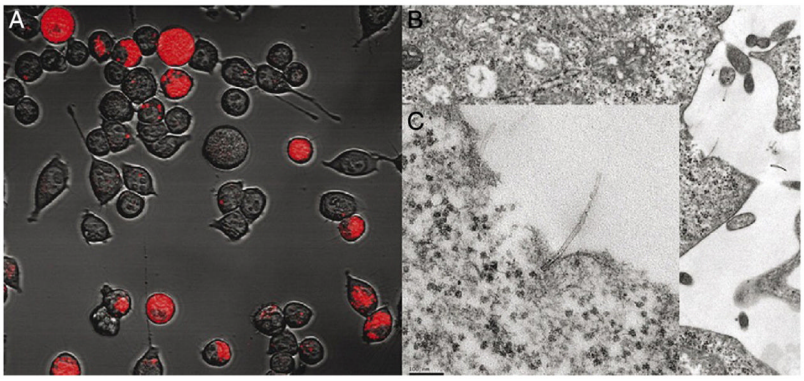

Fig. 4.

MWCNT (multi-walled carbon nanotube) internalization by BV2 microglia: 2.3 μg pMWCNTs-PKH was incubated with 1e6 BV2 cells for 48 h. Images were taken at 15, 24, and 48 h after pMWCNTs-PKH were added. Increasing numbers of pMWCNTs-PKH-positive cells were observed throughout this timecourse. (A) pMWCNTs-PKH-positive BV2 cells were imaged using an LSM 510 Meta confocal microscope at 48 h, mag. 400× (please also see the online video). (B) TEM microscopy was performed on cells incubated with MWCNTs after 2, 6, and 24 h. At 2 h single pMWCNTs were observed penetrating the cells surface, mag. 4400×. (C) A magnified image showing MWCNTs penetrating cell surface, mag. ×26,000.

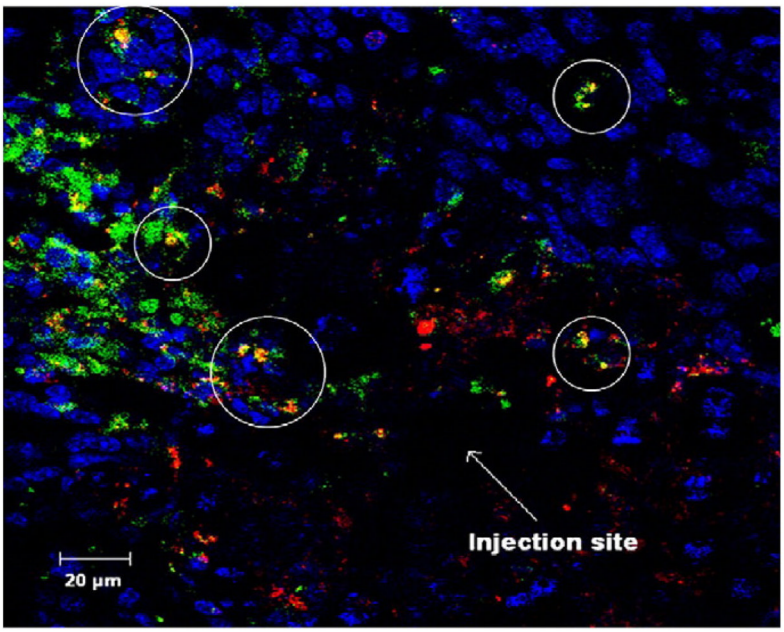

Fig. 5.

In vivo detection of MWCNT-PKH. MWCNT-PKH (5 μg) was injected intratumorally and assessed for internalization by immunohistochemistry 2 days later. MWCNTs are depicted in red (PKH), CD68+ cells (macrophage and microglia) are in green (FITC), and tumor nuclei are in blue (DAPI). MWCNT-PKH-positive CD68+ cells were noted throughout the tumor and tumor periphery (circles).

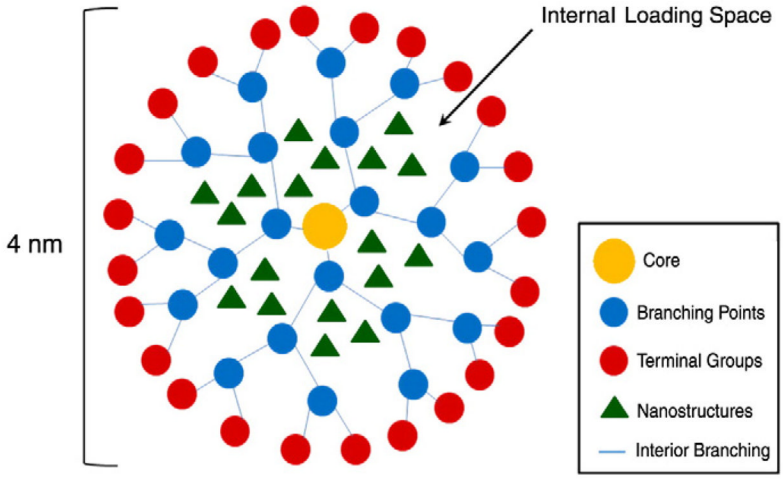

Fig. 6.

This is a schematic of a third-generation (three shells, G3) dendrimer. Dendrimers can range from 1 to 10 nm, depending on the number of generations and properties of the terminal groups. The core can be composed of polymers and other nanoparticles and dendrimers. There is space within the dendrimer to load molecular cargo or other nanostructures. The terminal groups provide the surface functionalities and can include dyes, markers, and target directing groups.

Table 1

Nanoscale platforms presently being developed for use in nanomedicine.

	Complex	Definition/Possible Uses	References
GOLD & SILVER	AuNPs (Gold Nanoparticles) (Figure 2 B)	Present AuNPs are highly stable but also toxic. They have an incredible potential to be developed for imaging and drug delivery applications such as *in vivo* sensors, semiconductive photoactive agents for optical imaging, contrast enhancers for CT imaging, X-ray absorbers at tumor sites, and carriers of free-radical-generating chemicals to tumor sites. As a result, the development of non-toxic AuNP vectors is very important for advances in nanomedicine. A method has been described to synthesize and stabilize AuNPs within a nontoxic phytochemical gum-arabic matrix (GA-AuNPs).	Kattumuri et al., 2007; Sperling et al., 2008
	Silver nanoparticles	Nanosilver structures are used to enhance wound healing and for coating plastic catheters. Coated catheters are non toxic and their sustained release of Silver reduces infection at the site of the implant because silver is anti-bacterial.	Ellis-Behnke et al. 2007 Roe et al. 2008
	Liposome with Sialyl Lewis X (SLX)	Liposome with SLX is not only an efficient imaging reagent, but also an effective drug delivery agent. In the delivery of substances like fluorescent markers, proteins, genes, and chemical substances to regions of inflammation or tumor in a mouse model, the accumulation of liposome with SLX was much higher than control.	Hirai et al., 2006; Hashida et al., 2008
	Lysolipid-based temperature-sensitive liposomes (LTSLs)	In conjunction with local hyperthermia, LTSLs containing chemotherapy drugs have been found to increase tumor drug concentrations and improve antitumor efficacy of the drugs.	Ponce et al., 2007
	Lipid-encapsulated perfluorocarbon nanoparticle molecular imaging contrast agent	Utilizes a paramagnetic chemical exchange saturation transfer (PARACEST) chelate to target and detect antifibrin antibodies. Since PARACEST can be turned on and off by adjusting the pulse sequence settings, this technique avoids the need for pre- and post injection images to define contrast agent binding. Furthermore, PARACEST nanoparticles demonstrate N10% signal enhancement and produce a contrast-to-noise ratio (CNR) of 10 at the clot surface.	Winter et al., 2006
LIPOSOME	MAGfect	A novel liposome formulation containing a lipidic gadolinium contrast agent for MRI, Gd-DOTA-Chol, is designed to enter and label cells. Furthermore, MAGfect is not only an effective vehicle for transporting plasmid DNA (pDNA) into cells but also an optimizing agent for cellular uptake.	Oliver et al., 2006; Terreno et al., 2008
	PEG-coated quantum dots, PEG-PHDCA	When combined with carboxyl, amino, or methoxyl groups, PEG-conjugated quantum dots migrate and confine themselves to sentinel lymph nodes. Localization of the quantum dots within the lymphatic circulation allows for easy tagging of the lymph nodes, aiding the surgeon and the pathologist. Metastasis of tumors to adjacent lymph nodes can also be visualized.	Ballou et al., 2007
		PEG-PHDCA stable imaging marker, which could be used for drug delivery in brain. PEG treated Polyalkylcyanoacrylate nanoparticles cross BBB	Ellis-Behnke et al. 2007
	Complex siRNA-quantum dots	Since variations in delivery of siRNA, cytotoxic effects due to delivery of siRNA, and 'off target' effects at high siRNA concentrations often blur the outcome of many studies, siRNA has been coupled with semiconductor quantum dots (QDs) that act as multi color biological probes. Due to the inherent photostability of QDs and their	Chen et al., 2005

	Complex	Definition/Possible Uses	References
		variable optical properties, the QD-siRNA complex is well-suited for tracking the delivery of nucleic acid, sorting cells by amount of transfection, and purifying silenced subpopulations.	
QUANTUM DOTS	Annexin A5 functionalized quantum dots	These complexes have the potential to be bimodal contrast agents allowing for anatomic and subcellular imaging of structures in the vessel wall.	Prinzen et al., 2007
	Magnetism-engineered iron oxide	Compared with currently available probes, antibody-conjugated MEIO nanoprobes	Lee et al., 2007; Lin et
	(MEIO) nanoprobes	display enhanced MRI sensitivity in detecting tumor markers. Nano-based probes have immense potential to improve visualization of key biological events in diagnostic and therapeutic nanomedicine.	al., 2008; Peng et al., 2008
	Superparamagnetic magnetite nanoparticles coated with lactobionic acid	Superparamagnetic magnetite nanoparticles with surface-attached lactobionic acid allows for better nanoparticle hepatocyte targeting. This could lead to their use as contrast agents in liver diagnosis.	Kamruzzaman et al., 2007
IRON OXIDE	Iron oxide (magnetite) nanoparticle	This nanoparticle complex is synthesized within a genetically engineered human H- chain ferritin (HFn) with a cell-specific targeting peptide (RGD-4C) that binds $\alpha_v\beta_3$ integrins upregulated on tumor vessels. This complex also bound to C32 melanoma cells *in vitro*, illustrating the ability of genetically modified protein cage nanoparticles to act as agents for oxide loading and cell-specific targeting.	Uchida et al., 2006
	Calmodulin	By combining iron oxide nanoparticle-based contrast mechanisms with the calcium-sensing protein calmodulin and its targets, these calcium indicators for MRI can be used for functional molecular imaging of biological signaling networks in live systems.	Atanasijevic et al., 2006
PROTEIN	$\alpha_v\beta_3$-integrin-targeted ^{111}In integrin nanoparticles ($\alpha_v\beta_3$-Targeted ^{111}In)	$\alpha_v\beta_3$-Targeted ^{111}In can be used as another means for sensitively detecting angiogenesis in emerging tumors, especially when combined with high-resolution imaging techniques like MRI. The biochemical and morphological detection and characterization of angiogenesis induced by very small tumors can also be accomplished with the use of $\alpha_v\beta_3$-Targeted ^{111}In. This allows for the localization of emergent cancers and phenotypic characterization of patient populations for therapy.	Hu et al., 2007 Winter et al., 2003
	Multifunctional polymeric nanoparticle	This nanoparticle complex overcomes the drawback of photodynamic therapy (PDT), prolonged cutaneous photosensitization, by encapsulating nanoparticles with photodynamic agent. Consisting of a tumor vasculature targeting F3 peptide and encapsulated PDT and imaging agents, this complex significantly enhances MRI contrast and improves detection of tumors. As a result, this translated into a significant improvement in the survival rate of glioma-bearing rats over the control.	Reddy et al., 2006
MULTIFUNCTIONAL	Fluorescein isothiocyanate conjugated glycol chitosan (FGC) nanoparticles	FGC nanoparticles show highly selective tumor localization as they are able to clearly define tumors from adjacent tissues, allowing for more accurate cancer diagnosis. These complexes also enable better therapy by permitting the delivery of multiple therapeutic agents and imaging probes at high local concentrations.	Cho et al., 2007

Table 2

Drug delivery strategies.

Routes of drug delivery
Intraperitoneal
Intrathecal
Nasal
Oral
Subcutaneous injection or implant
Transdermal drug delivery
Vascular route: intravenous, intra-arterial
Direct introduction of anticancer drugs into tumor
Injection into the arterial blood supply of cancer
Local injection into the tumor for radiopotentiation
Localized delivery of anticancer drugs by electroporation
Local delivery by anticancer drugs implants
Injection directly into the tumor
Tumor necrosis therapy
Systematic delivery targeted to tumor
Pressure-induced filtration of drug across vessels to tumor
Promoting selective permeation of the anticancer agent into the tumor
Two-step targeting using bi-specific antibody
Site-specific delivery and light-activation of anticancer proteins
Heat-activated targeted drug delivery
Tissue-selective drug delivery for cancer using carrier-mediated transport systems
Tumor-activated prodrug therapy for targeted delivery of chemotherapy
Special formulations and carriers of anticancer drugs
Nanoparticles
Microspheres
Monoclonal antibodies
Pegylated liposomes
Albumin based drug carriers
Carbohydrate-enhanced chemotherapy
Delivery of proteins and peptides for cancer therapy
Fatty acids as targeting vectors linked to active drugs
Polymer technology
Biological therapies
Antisense therapy
Gene therapy
Genetically modified bacteria
Oncolytic viruses

RNA interference

Source: Singh and Lillard, 2009.

Table 3

FDA-approved drug products in nanometer size range.

	Drug name	Generic Name	Company	Indication	Route of administration	Approved date
Liposomal platforms	Doxil	Doxorubicin HCl Liposome Injection	Ortho Biotech Products, LP	Antineoplastic	i.v.	17-NOV-95
	Abelcet	Amphotericin B Lipid Complex Injection	Enzon Pharmaceuticals	Antifungal	i.v.	20-NOV-95
	DaunoXome	Daunorubicin citrate liposome injection	Diatos	Antineoplastic	i.v.	8-Apr-96
	Amphotec	Amphotericin B Cholesteryl Sulfate Injection	Three Rivers Pharmaceuticals	Antifungal	i.v.	22-NOV-96
	AmBisome	Amphotericin B Liposome Injection	Astellas Pharma US, Inc.	Antifungal	i.v.	11-Aug-97
	Depocyt	Cytarabine Liposome Injection	Enzon Pharmaceuticals	Lymphomatous meningitis	i.t.	1-Apr-99
	Visudyne	Verteporfin for Injection	Novartis	Photodynamic rherapy for aged-related macular degeneration	i.v.	12-Apr-00
Nanocrystal platforms	Rapamune	Sirolimus	Wyeth	Immunosuppressant	Oral	22-Aug-02
	Emend	Aprepitant	Merck & Co., Inc.	Antiemetic	Oral	26-Mar-03
	TriCor	Fenofibrate	Abbott Laboratories	Hypercholesterolemia and hypertriglyceridemia	Oral	5-NOV-04
	Triglide	Fenofibrate	Sciele Pharma, Inc.	Hypercholesterolemia and hypertriglyceridemia	Oral	7-May-05
	Megace ES	Megestrol acetate	Strativa Pharmaceuticals, subsidiary of Par Pharmaceutical. Inc.	Anorexia, cachexia, or an unexplained significant weight loss in AIDS patients	Oral	5-Jul-05
Other platforms	Oncaspar	pegaspargase: pegylated L-asparaginase	Enzon Pharmaceuticals	acute lymphoblastic leukemia	IM or IV	1-Feb-94
	Estrasorb	estradiol topical emulsion	Graceway Pharmaceuticals, LLC	Vasomotot symptoms associated with the menopause	Transdermal	9-Oct-03
	Abraxane	paclitaxel albumin-bound particles for injectable suspension	Abraxis Oncology	Metastatic breast cancer	i.v.	7-Jan-05
	Feridex	femmoxides injectable solution (superparamagnetic iron oxide)	Bayer Healthcare Pharmaceuticals	MRI Contrast Agent	i.v.	

Source: Zolnik and Sadrieh, 2009.