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Nanotech approaches to drug delivery and imaging

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Nanotechnology, a multidisciplinary scientific undertaking, involves creation and utilization of materials, devices or systems on the nanometer scale. The field of nanotechnology is currently undergoing explosive development on many fronts. The technology is expected to create innovations and play a critical role in various biomedical applications, not only in drug delivery, but also in molecular imaging, biomarkers and biosensors. Target-specific drug therapy and methods for early diagnosis of pathologies are the priority research areas where nanotechnology would play a vital role. This review considers different nanotechnology-based drug delivery and imaging approaches, and their economic impact on pharmaceutical and biomedical industries.

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▼ Nanotechnology, the term derived from the Greek word nano, meaning dwarf, applies the principles of engineering, electronics, physical and material science, and manufacturing at a molecular or submicron level. The materials at nanoscale could be a device or a system or these could be supramolecular structures, complexes or composites. An early promoter of nanotechnology, Albert Franks, defined it as 'that area of science and technology where dimensions and tolerances are in the range of 0.1 nm to 100 nm'. In addition to the developments in other scientific disciplines such as in electronics and robotics, nanotechnology is expected to make significant advances in mainstream biomedical applications, including in the areas of gene therapy, drug delivery, imaging, and novel drug discovery techniques [1,2] (Figure 1, Box 1).

Nanotechnology in drug delivery

The development of delivery systems for small molecules, proteins and DNA has been impacted to an enormous degree over the past decade by nanotechnology, and has led to the development of entirely new and somewhat unpredicted fields. For the pharmaceutical industry, novel drug delivery technologies represent a strategic tool for expanding drug markets. The technology can address issues associated with current pharmaceuticals such as extending product life (line extension), or can add to their performance and acceptability, either by increasing efficacy or improving safety and patient compliance [3]. In addition, the newer drugs developed with the help of computational chemistry using the knowledge gained from the human genome project require drug delivery systems for their effective use. This technology permits the delivery of drugs that are highly water-insoluble or unstable in the biological environment.

It is expected that novel drug delivery systems can make a significant contribution to global pharmaceutical sales. This is illustrated by the fact that approximately 13% of the current global pharmaceutical market is accounted for by sales of products incorporating a drug delivery system [4]. In recent years, many new pharmaceutical companies have been established that can provide expertise in innovative delivery technology. Also, many established pharmaceutical industries are gearing-up their efforts towards developing more effective and performance-based new drug delivery systems. The demand for drug delivery systems in the United States alone is expected to grow nearly 9% annually to more than US$82 billion by 2007 [4] (Box 2).

Significance of drug delivery and targeting

Although opportunities to develop nanotechnology-based efficient drug delivery systems extend into all therapeutic classes of pharmaceuticals, the development of effective treatment modalities for the respiratory, central nervous system and cardiovascular disorders remains a financially and therapeutically significant need. Many therapeutic agents have

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not been successful because of their limited ability to reach to the target tissue. In addition, the faster growth opportunities are expected in developing delivery systems for anti-cancer agents, hormones and vaccines because of safety and efficacy shortcomings in their conventional administration modalities. For example, in cancer chemotherapy, cytostatic drugs damage both malignant and normal cells alike. Thus, a drug delivery strategy that selectively targets the malignant tumor is very much needed. Additional problems include drug instability in the biological milieu and premature drug loss through rapid clearance and metabolism. Similarly, high protein binding of certain drugs such as protease inhibitors limits their diffusion to the brain and other organs. However, nanotechnology for drug delivery applications may not be suitable for all drugs, especially those drugs that are less potent because the higher dose of the drug would make the drug delivery system much larger, which would be difficult to administer.

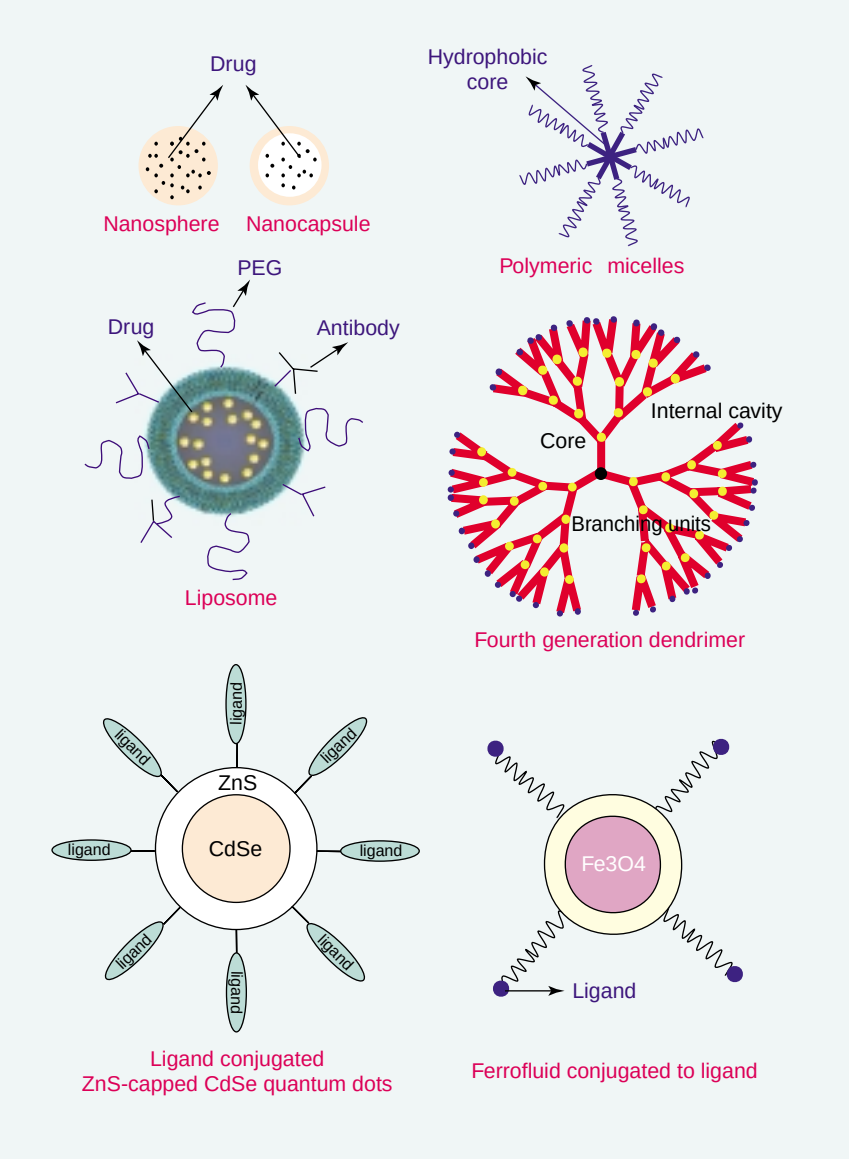

Figure 1. Schematics of different nanotechnology-based drug delivery systems. Nanoparticles are small polymeric colloidal particles with a therapeutic agent either dispersed in polymer matrix or encapsulated in polymer. Polymeric micelles are self-assembled block co-polymers, which in aqueous solution arrange to form an outer hydrophilic layer and an inner hydrophobic core. The miceller core can be loaded with a water insoluble therapeutic agent. Liposomes are lipid structures that can be made 'stealth' by PEGylation and further conjugated to antibodies for targeting. Dendrimers are monodispered symmetric macromolecules built around a small molecule with an internal cavity surrounded by a large number of reactive end groups. Quantum dots are fluorescent nanocrystals that can be conjugated to a ligand and thus can be used for imaging purposes. Ferrofluids are colloidal solutions of iron oxide magnetic nanoparticles surrounded by a polymeric layer, which can be further coated with affinity molecules such as antibodies.

Polymeric biodegradable nanoparticles

Over the past few decades, there has been considerable interest in developing biodegradable nanoparticles as effective drug delivery devices [5–7]. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [5]. The drug of interest is either dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained with different properties and release characteristics for the encapsulated therapeutic agent. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

The advantages of using nanoparticles for drug delivery result from their two main basic properties. First, nanoparticles, because of their small size, can penetrate through

Box 1. Nanotechnologies for drug delivery and imaging applications

Drug Delivery
- Polymeric nanoparticles
- Ceramic nanoparticles
- Polymeric micelles
- Dendrimer
- Liposomes

Imaging
- Magnetic nanoparticles
- Ferrofluids
- Quantum dot technology

smaller capillaries and are taken up by cells, which allows efficient drug accumulation at the target sites [8–11]. Second, the use of biodegradable materials for nanoparticle preparation allows sustained drug release within the target site over a period of days or even weeks. Our laboratory has been investigating biodegradable nanoparticles formulated from poly dl-lactide *co*-glycolide (PLGA) and polylactide (PLA) for intracellular sustained drug delivery, especially for drugs whose target is intracellular [6,12,13]. Recently, we have demonstrated rapid escape of nanoparticles from the endo-lysosomal compartment to the cytoplasmic compartment [12]. Thus, nanoparticles could be an effective drug delivery mechanism for drugs whose targets are cytoplasmic. Greater and sustained antiproliferative activity was observed in vascular smooth muscle cells which were treated with dexamethasone-loaded nanoparticles as compared to that with drug in solution [14]. Nanoparticles were effective in sustaining intracellular dexamethasone levels, thus allowing a more efficient interaction with the glucocorticoid receptors which are cytoplasmic.

Another broader application of nanoparticle uptake is the delivery of antigens for vaccination. Mucosal immunity is extremely important in disease prevention, but continues to be limited by both degradation of the vaccine and its limited uptake by immune cells. Micro- and nanoparticles are capable of enhancing immunization. It has been shown that M cells in the Peyer's patches of the distal small intestine are capable of engulfing large microspheres [15,16]. Lutsiak *et al.* have demonstrated uptake of PLGA nanoparticles by human dendritic cells *in vitro* [17]. This work has implications in selective activation of T cell-mediated immune response.

Box 2. Nanotechnology in drug delivery: cost benefits

- Enhance delivery leads to superior performance characteristics of the product.
- The lifespan of the blockbuster drugs can be resurrected by reformulating the drugs through novel delivery system.
- The effective patent protection can be enhanced.
- Drug delivery formulation involves low-cost research compared to that for the discovery of a new molecule.
- Minimizing use of expensive drugs would reduce the cost of the product.

The development of nanoparticulate delivery systems for targeted drug delivery has been reviewed recently by Moghimi *et al.* [18]. Targeted delivery can be achieved by either active or passive targeting. Active targeting of a therapeutic agent is achieved by conjugating the therapeutic agent or the carrier system to a tissue or cell-specific ligand [7,19]. Passive targeting is achieved by coupling the therapeutic agent to a macromolecule that passively reaches the target organ [20]. Drugs encapsulated in nanoparticles or drugs coupled to macromolecules such as high molecular weight polymers passively target the tumor tissue through the enhanced permeation and retention (EPR) effect [21,22]. The alternative approach involves the infusion of nanoparticle suspension to the accessible target organ or tissue using infusion catheters. Localized delivery of nanoparticles in restenosis may be a useful strategy as it may provide sustained drug effect in the target artery [23,24].

Nanoparticles are also useful for the delivery of pharmaceutical agents after binding to target cellular epitopes by a mechanism called 'contact facilitated drug delivery'. Binding and close apposition to the targeted cell membrane permits enhanced lipid–lipid exchange with the lipid monolayer of the nanoparticle, which accelerates convective flux of lipophilic drugs (e.g. paclitaxel) dissolved in the outer lipid membrane of the nanoparticles into the targeted cells [25]. Such nanosystems can serve as drug depots exhibiting prolonged release kinetics and long persistence at the site.

Another characteristic function of nanoparticles is their ability to deliver drugs across several biological barriers to the target site [26,27]. The brain delivery of a wide variety of drugs, such as antineoplastics and anti-HIV drugs, is markedly hindered because they have great difficulty in crossing the blood–brain barrier (BBB) [28,29]. The application of nanoparticles to brain delivery is a promising way of overcoming this barrier. Recently, it has been demonstrated that poly-(butylcyanoacrylate) nanoparticles coated with polysorbate 80, are effective in transporting the hexapeptide dalargin and other agents into the brain [30].

Ceramic nanoparticles

The newly emerging area of using inorganic (ceramic) particles with entrapped biomolecules has potential applications

in many frontiers of modern material science including drug delivery [31–33]. Ceramic nanoparticles have several advantages such as the preparative processes are relatively similar to the well-known sol-gel process, require ambient temperature condition, and can be easily prepared with the desired size, shape and porosity. Their ultra-low size (less than 50 nm) can help them evade by the reticulo-endothelial system (RES) of the body. In addition, there are no swelling or porosity changes with change in pH. These particles effectively protect doped molecules (enzymes, drugs, etc) against denaturation induced by external pH and temperature [32]. Such particles, including silica, alumina, titania, etc are known for their compatibility with biological systems [32,34]. In addition, their surfaces can be easily modified with different functional groups [34,35]. Therefore, they can be conjugated to a variety of monoclonal antibodies or ligands to target them to desired sites *in vivo*.

Recently, Roy *et al*. reported a novel nanoparticle-based drug carrier for photodynamic therapy [36]. They have synthesized ultra-fine organically modified silica-based nanoparticles (diameter ~30 nm), entrapping water-insoluble photosensitizing anticancer drug, 2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide in the nonpolar core of micelles formed by hydrolysis of triethoxyvinylsilane. The resulting drug-doped nanoparticles are spherical, highly monodispersed, and stable in aqueous systems. *In vitro* studies have demonstrated the active uptake of drug-doped nanoparticles into the cytosol of the tumor cells. Irradiation of the photosensitizing drug entrapped in nanoparticles with light of suitable wavelength results in efficient generation of singlet oxygen, which caused significant damage to tumor cells.

Polymeric micelles

Recently, significant attention has been drawn to various amphiphilic block copolymers, which can self-associate to form micelles in aqueous solution, and have been extensively studied as drug carriers [37–39]. Polymeric micelles have several advantages over conventional surfactant micelles in that they have better thermodynamic stability in physiological solution, as indicated by their low critical micellar concentration, which makes polymeric micelles stable and prevents their rapid dissociation *in vivo* [40,41]. Micelles have a fairly narrow size distribution in the nanometer range and are characterized by their unique core-shell architecture, in which hydrophobic segments are segregated from the aqueous exterior. Micellar systems are useful for the systemic delivery of water-insoluble drugs. Drugs can be partitioned in the hydrophobic core of micelles and the outer hydrophilic layer forms a stable dispersion in aqueous media, which can then be administered intravenously.

The distribution of drug-loaded polymeric micelles in the body is determined mainly by size and surface properties. The size of polymeric micelles (less than ~100 nm in diameter) not only makes them ideal drug delivery carriers because they avoid renal exclusion and the RES, but also provides them with enhanced endothelial cell permeability in the vicinity of solid tumors by passive diffusion [37,42]. Following intravenous administration, polymeric micelles have been shown to have a prolonged systemic circulation time because of their smaller size and hydrophilic shell which minimizes their uptake by the RES. Polymeric micelle-incorporated drugs may accumulate to a greater extent than free drug into tumors and demonstrates a reduced distribution in non-targeted areas. Accumulation of polymeric micelles in malignant tissue is because of increased vascular permeability and impaired lymphatic drainage [43,44]. Tumor vessels are leakier and less permselective than normal vessels and hence there is perivascular accumulation of macromolecules and colloidal drug carriers in tumor tissue.

As with other carriers, the drug delivery potential of polymeric micelles may be enhanced by conjugating targeting ligands including antibodies to the micelle surface [45]. Recently, Torchilin *et al.* have formulated anti-tumor antibody-conjugated polymeric micelles (immunomicelles), encapsulating water-insoluble drug taxol inside the hydrophobic core of the micelles [46]. They found that such immunomicelles are effectively recognized and bound to various cancer cells *in vitro*. They demonstrated that, compared to non-targeted micelles, immunomicelles were capable of delivering higher concentrations of drugs to tumors in mice.

Effective targeting of cytotoxic agents to solid tumors by polymeric micelles has been achieved by Kataoka *et al*. with a system based on doxorubicin (DOX) conjugated to poly(ethylene glycol)-poly(α, β-aspartic acid) block copolymer [PEG-PAsp (DOX)] [47]. PEG-PAsp (DOX) micelles, with both chemically bound and physically entrapped DOX in the core, achieved prolonged circulation in the blood compartment because of reduced uptake by the RES and accumulated more in the solid tumor through the EPR effect, leading to complete tumor regression. This system is currently undergoing clinical trial in Japan. Cis–Diamine-dichloroplatinum (II) (cisplatin, CDDP) is a metal complex that exhibits high antitumor activity. However, the clinical use of cisplatin is limited because of its low water-solubility and significant side effects. Kataoka's group formulated polymer–metal complexed micelles with diameters of ~20 nm by simply mixing CDDP with PEG-PAsp [37,48]. In the recent study, the group has reported that micelle-incorporated CDDP has ~5.2 times higher plasma AUC

(Area Under Curve) value than that of free CDDP, achieving 14 times higher drug levels in the tumor than that with free CDDP and with reduced nephrotoxicity [49]. Recently, Know's group was able to enhance the antifungal efficiency of amphotericin B and reduced its hemolytic activity by loading the drug into the polymeric micelles [50,51]. It has been suggested that polymeric micelles could stabilize amphotericin B against auto-oxidation and/or enhance membrane perturbation of fungal cells. Thus, polymeric micelles can be a versatile system for the effective delivery of different classes of therapeutic agents.

Liposomes

The first suggested use of liposomes came from the group of Weismann in 1969 [52]. Since then liposomes have been used as a versatile tool in biology, biochemistry and medicine [53]. Liposomes are small artificial vesicles of spherical shape that can be produced from natural non-toxic phospholipids and cholesterol. Because of their size, hydrophobic and hydrophilic character, as well as biocompatibility, liposomes are promising systems for drug delivery. Liposome properties vary substantially with lipid composition, size, surface charge and the method of preparation. They are therefore classified into three classes based on their size and number of bilayers. Small unilamellar vesicles (SUV) are surrounded by a single lipid layer and are 25–50 nm in diameter. Large unilamellar vesicles (LUV) are a heterogeneous group of vesicles similar to SUVs and are surrounded by a single lipid layer. Multilamellar vesicles (MLV), however, consist of several lipid layers separated from one another by a layer of aqueous solution. Moreover, the choice of bilayer components determines the 'rigidity' (or 'fluidity') and the charge of the bilayer. For example, saturated phospholipids with long acyl chains such as dipalmitoylphosphatidylcholine form a rigid, rather impermeable bilayer structure, whereas the unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine) give much more permeable and less stable bilayers. The introduction of positively or negatively charged lipids provides the liposomes a surface charge. Drugs associated with liposomes have markedly altered pharmacokinetic properties compared to drugs in solution. They are also effective in reducing systemic toxicity and preventing early degradation of the encapsulated drug after introduction to the target organism [54,55]. Liposome surfaces can be readily modified by attaching polyethylene glycol (PEG)-units to the bilayer (producing what is known as stealth liposomes) to enhance their circulation time in the bloodstream [56]. Furthermore, liposomes can be conjugated to antibodies or ligands to enhance target-specific drug therapy.

Dendrimers

First discovered in the early 1980s, dendrimers are macromolecular compounds that comprise a series of branches around an inner core [57]. Dendrimers are attractive systems for drug delivery because of their nanometer size range, ease of preparation and functionalization, and their ability to display multiple copies of surface groups for biological reorganization processes [58,59]. Dendrimer molecules are monodisperse symmetric macromolecules built around a small molecule or in a linear polymer core using connectors and branching units. Interaction of dendrimer macromolecules with the molecular environment is predominantly controlled by their terminal groups. By modifying their termini, the interior of a dendrimer may be made hydrophilic while its exterior surface is hydrophobic, or vice versa. Dendrimers can be synthesized starting from the central core and working out toward the periphery (divergent synthesis) or in a top-down approach starting from the outermost residues (convergent synthesis). Because dendrimers are built from ABn-type monomers, each layer or generation of branching units doubles or triples (n=2 or 3) the number of peripheral functional groups.

Dendrimers have some unique properties related to their globular shape and the presence of internal cavities. The most important one is the possibility of encapsulation of therapeutic agents within the macromolecule interior [59,60]. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to surface groups. Water-soluble dendrimers are capable of binding and solubilizing small molecules and can be used as coating agents to protect or deliver drugs to specific sites in the body or as time-release vehicles for biologically active agents. 5-Fluorouracil (5FU) is known to have remarkable anti-tumor activity, but it has high toxic side effects. PAMAM dendrimers after acetylation can form dendrimer-5FU conjugates which upon hydrolysis releases free 5FU, thus minimizing toxicity [61].

Nanocrystals for drug delivery and imaging

Nanotechnology can be exploited to improve the utility of fluorescent markers used for diagnostic purposes. Although fluorescent markers are routinely used in basic research and clinical diagnostic applications, there are several inherent disadvantages with current techniques, including the requirement of color-matched lasers, the fluorescence bleaching, and the lack of discriminatory capacity of multiple dyes. Fluorescent nanocrystals potentially overcome these issues. Nanocrystals [also called quantum dots (QDs; Qdots) or nanodots] are crystalline clumps of a few hundred atoms, coated with an insulating outer shell of a different material [62]. Qdots are generally composed of atoms

from group II–VI or III–V of the periodic table and are defined as particles with physical dimensions smaller than the excitation Bohr radius [63,64]. When a photon of visible light hits such a minute particle, a quantum-physics reflect confines all the photon's energy to the crystal core before being emitted as an extraordinary bright fluorescence. The QDs absorb light at a wide range of wavelengths, but emit almost monochromatic light of a wavelength that depends on the size of the crystals [65].

Quantum Dot Corp. (http://www.qdots.com) is commercially developing Qdot technology. Qdots can be attached to biological materials, such as cells, proteins and nucleic acids. Qdots can be designed to emit light at any wavelength from infrared to ultraviolet. Larger Qdots emit red light, whereas smaller crystals emit light at the blue end of the spectrum. Qdots' fluorescence is so bright that it is possible to detect a cell carrying a single crystal [66]. Qdots are inorganic and so these are very stable, and their inert surface coating makes them less toxic than organic dyes.

A related technology called Probes Encapsulated by Biologically Localized Embedding (PEBBLES) allows dye-tagged nanoparticles to be inserted into living cells to monitor metabolism or disease conditions [67,68]. As one example, this system was recently used to quantify zinc levels within living cells. The sensing compounds were entrapped within a polymer matrix using a microemulsion polymerization process that produced spherical sensors with a size of 20–200 nm. The system was highly sensitive, had a rapid response time and used a reversible and photostable nanosensor that was insensitive to interference from intracellular or extracellular proteins.

Magnetic nanoparticles

Magnetic nanoparticles are a powerful and versatile diagnostic tool in biology and medicine [69,70]. Bound to a suitable antibody, they are used to label specific molecules, cell populations, structures or microorganisms. Magnetic immunoassay techniques have been developed in which the magnetic field generated by the magnetically labeled targets is detected directly with a sensitive magnetometer. Binding of antibody to target molecules or disease-causing organism is the basis of several tests.

Superparamagnetic nanoparticles are used as contrast agents in magnetic resonance imaging. They consist of an inorganic core of iron oxide (magnetite Fe_2O_3, maghemite or other insoluble ferrites) coated with polymer such as dextran. Lumiren (silicon-coated iron oxide particles with diameter 300 nm) and Endorem (magnetite nanoparticles of 150 nm in diameter coated with dextran) are commercial names of Superparamagnetic nanoparticles. These nanoparticulate contrast agents are being used for imaging of tissue for diagnostic applications.

Superconducting quantum interference device (SQUID) is a technique for specific, sensitive, quantitative and rapid detection of biological targets by using supermagnetic nanoparticles and a microscope based on a high transition temperature [71]. In this technique, a mylar film to which the targets are bound is placed on the microscope alongside SQUID. A suspension of magnetic nanoparticles carrying antibodies directed against the target is added to the mixture in the well and 1-s pulse of magnetic field is applied parallel to the SQUID. In the presence of this aligning field, nanoparticles develop a net magnetization, which relaxes when the field is turned off. Unbound nanoparticles relax rapidly by Brownian rotation and contribute no measurable signal. Nanoparticles that are bound to the target on the film are immobilized and undergo a slowly decaying magnetic flux, which is detected by the SQUID.

Ferrofluids

Ferrofluids are colloidal solutions of iron oxide magnetic nanoparticles surrounded by a polymeric layer coated with affinity molecules, such as antibodies, for capturing cells and other biological targets from blood or other fluid and tissue samples [72,73]. Ferrofluid particles are so small (25–100 nm in radius) that they behave in liquids as a solution rather than suspension. When the coated ferrofluid particles are mixed with a sample containing cells or other analytes, they interact intimately and completely. These properties enable the development of specialized reagents and systems with extremely high sensitivity and efficiency and capture [74,75].

Surface engineering and targeting

The ability to target pharmacologically active molecules to specific sites in the body has been actively pursued ever since Ehrlich first envisaged the use of 'magic bullets' for the eradication of diseases [76]. Interest in this concept has increased significantly in recent years with the advent of new technology and better understanding of the processes involved in drug delivery both at cellular and sub-cellular levels [77,78]. Drug delivery systems may function through their ability to recognize certain types of target cells. However, the challenge with these drug delivery systems is that they are treated as foreign by the host when injected and end up mainly in the cells of the RES, namely macrophages of the liver, spleen, lungs, bone marrow and lymph nodes [79]. In situations in which the RES is the target site, such as in case of infection by certain viruses, bacteria or protozoa, such drug delivery systems are ideal for the

delivery of appropriate therapeutics. However, when tissue or organs other than the RES are the target, it is often necessary to redirect drug delivery systems away from the RES to these targets [79]. The other process that also affects the fate of the intravenously administered colloidal carrier systems is their opsonisation, which is the adsorption of plasma proteins onto their surface [80]. Many targeting systems with promising outlook based on *in vitro* results have faced the above problems when tested *in vivo*. Surface properties of colloidal carrier systems play a pivotal role in influencing these processes [81]. As a result, there has been a growing interest in engineering surface characteristics of colloidal carrier systems that upon intravenous injection avoid rapid recognition by RES and have reduced deposition of plasma proteins to diminish their recognition by phagocytes [18]. These systems are called 'Stealth' particles, which are 'invisible' to macrophages and have been demonstrated to have prolonged half-life in the blood compartment [82]. These are usually achieved by surface modification of carrier systems such as by PEGylation [83,84].

Surface engineering of colloidal carrier systems allows them to selectively extravasate in pathological sites, such as tumors or inflamed regions with a leaky vasculature [5]. Recently, long-circulating micelles have been demonstrated to deliver the drug more selectively to the injured artery following their intravenous administration in a restenosis model. Because the endothelial is disrupted, the injured artery becomes more permeable to micellar system than uninjured artery, resulting in greater accumulation of the drug in the target artery. This strategy was effective in inhibiting hyperplasia in a rat carotid model of restenosis [85]. In their several studies, Luisa Corvo *et al.* have demonstrated significantly better anti-inflammatory activity of the long-circulating liposomes containing superoxide dismutase (SOD) as compared to free SOD in rheumatoid arthritis model [86]. It is proposed that SOD encapsulated in liposomes is taken-up by the inflamed joint tissue, primarily because of leaky vascular endothelium at the site of inflammation. Jain *et al.* have suggested in their study the potential of negatively charged and RGD-coated magnetic liposomes for monocytes or neutrophils-mediated active delivery of drugs to relatively inaccessible inflammatory sites, i.e. brain [87]. The study opens a new perspective of active delivery of drugs for a possible treatment of cerebrovascular diseases.

In addition to therapeutic applications of targeted carrier systems based on the above principles, the discipline of medical imaging is expanding for the functional assessment of the presence and extent of disease with specially designed contrast agents to localize the targeted molecular signature or physiologic system [88]. Recently, a novel method has been presented to detect Abeta plaques in the brains of transgenic mice by magnetic resonance microimaging (muMRI). The presence of amyloid-β (Abeta) plaques in the brain is a hallmark pathological feature of Alzheimer's disease (AD). In this method, Abeta1–40 peptide, known for its high binding affinity to Abeta, was magnetically labeled with either gadolinium (Gd) or monocrystalline iron oxide nanoparticles. Intraarterial injection of magnetically labeled Abeta1–40, with mannitol to transiently open the BBB, enabled the detection of many Abeta plaques. The results suggest that the above diagnostic MRI method can be used to detect Abeta in AD patients [89].

Concluding remarks

The multidisciplinary field of nanotechnology holds the promise of delivering the technological breakthrough and is moving very fast from concept to reality. The flexibility to modify or adapt nanotechnology to meet the needs of pathologic conditions either for therapeutic applications or as a diagnostic tool is the important characteristic of the technology. The United States, Japan and the European Union have already established nanotech research initiatives to explore the potential applications of nanotechnology. Pharmaceutical industries and academic institutes are also set to launch major initiatives in this direction. The emergence of Nanotechnology Research Centers, established in recent years and some of which are funded through the National Institutes of Health and the National Science Foundation, demonstrate the enthusiasm of investigators and granting agencies in the technology.

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