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# Nanotechnology, nanotoxicology, and neuroscience

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## Abstract

Nanotechnology, which deals with features as small as a 1 billionth of a meter, began to enter into mainstream physical sciences and engineering some 20 years ago. Recent applications of nanoscience include the use of nanoscale materials in electronics, catalysis, and biomedical research. Among these applications, strong interest has been shown to biological processes such as blood coagulation control and multimodal bioimaging, which has brought about a new and exciting research field called nanobiotechnology. Biotechnology, which itself also dates back ~30 years, involves the manipulation of macroscopic biological systems such as cells and mice in order to understand why and how molecular level mechanisms affect specific biological functions, e.g., the role of APP (amyloid precursor protein) in Alzheimer's disease (AD). This review aims (1) to introduce key concepts and materials from nanotechnology to a non-physical sciences community; (2) to introduce several state-of-the-art examples of current nanotechnology that were either constructed for use in biological systems or that can, in time, be utilized for biomedical research; (3) to provide recent excerpts in nanotoxicology and multifunctional nanoparticle systems (MFNPSs); and (4) to propose areas in neuroscience that may benefit from research at the interface of neurobiologically important systems and nanostructured materials.

### Keywords

Nanotechnology; Nanotoxicology; Neuroscience; Nanoscience; Toxicology; Neurobiology; Nanoparticles; Nanostructured; Nanobiotechnology; Nano—bio interface; Engineered nanomaterials; Nanomaterials; Multifunctional nanoparticle

## 1. Introduction to nanomaterials

The science and technology of nanoscale materials has roots as old as chemistry itself, from the formulation of precious metal colloids for medieval stain glass to the Roman's use of cement (Bergna, 1994; Delatte, 2001; Edwards and Thomas, 2007; Faraday, 1847; Sanchez et al., 2003). As a separate field, nanoscience and nanotechnology began to emerge some 20 years ago (Hodes, 2007), and a database search yields more than 500 review articles in this area. For our discussions here, we will focus on materials with domain dimensions below 100 nm (nm



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= 1 billionth of a meter), e.g. length scales below those observable by simple optical or even confocal microscopy (Fig. 1). For scale, nanosized objects are 100–10,000 times smaller than the size of mammalian cells.

The molecular level contents of neurobiologically important systems are proteins, nucleic acids, lipid bilayers, metal ions, and small molecules, whose sizes are shown schematically in Fig. 1 (lower panel). At this size scale, the most important structural characterization techniques include X-ray crystallography, nuclear magnetic resonance (NMR), scanning, transmission electron microscopy, and optical/fluorescence/confocal microscopy. For instance, the amyloid precursor protein (APP) (Kong et al., 2007;Suh and Checler, 2002) shown as a biomolecule in Fig. 1 (lower panel) is an actual X-ray crystal structure visualized using VMD (visual molecular dynamics) (Humphrey et al., 1996). Compared to this biomolecule, a small molecule such as dehydroevodiamine hydrochloride (DHED) (Ahn et al., 2004;Decker, 2005; Park et al., 1996,2000;Suh et al., 2005), a potent Alzheimer's disease (AD) candidate therapeutic agent, is much smaller in size. Micron sized nanostructured microspheres are readily endocytosed into the cytosol and can carry nanosized cargo into neurobiologically relevant systems (Suh et al., 2006a,b). In this review, we examine several important nanostructured materials that may interface well with neurobiologically important systems and find use in the neuroscience community.

## 2. Engineered nanomaterials: overview and recent advances

### 2.1. The first nanoparticles: carbonaceous nanomaterials

Arguably the oldest and easiest nanoparticles to make are of carbon: the use of carbon black from fuel-rich partial combustion for ink, pigment, and tatoos dates back more than 3000 years, but still remains a topic of current research interest (Lee et al., 2006b; Lu and Schuth, 2006; Xia et al., 2006b). The largest modern use of nanophase carbon, by far, is as filler in rubber tires, for which >8 million metric tons are produced each year; roughly another million tons are used as pigments (What is carbon black?). Various synthetic carbon materials exist that have nanometer scale features. Macroporous carbon materials can be created via inverted opal synthesis (colloidal template method) but these materials are usually amorphous (Lee et al., 2006b). Crystalline carbon nanomaterials can be created via high voltage arc electricity, laser ablation, or growth under high temperatures with metal-based precursors or nanoparticles as catalysts (Dai, 2002; Jiao et al., 1996; Satishkumar et al., 1999). In addition, fullerenes (e.g. $C_{60}$, $C_{72}$) and carbon nanotubes, either single-walled or multi-walled, can be synthesized in this way (Burghard, 2003; Dai, 2002; Dosa et al., 1999; El Hamaoui et al., 2005; Hayashi et al., 1996; Hu et al., 1999; Iijima, 1991; Iijima et al., 1999; Iyer et al., 2003; Kroto et al., 1985; Lei et al., 2006; Lu et al., 2006; Odom et al., 1998; Rinzler et al., 1998; Sano et al., 2003; Terrones et al., 1997; Thess et al., 1996). These more sophisticated carbon nanomaterials are finding a variety of applications for electronics (Dai, 2002; Odom et al., 1998), catalysis (Kim et al., 2000), chemical sensing (Barone et al., 2005; Heller et al., 2005, 2006; Jeng et al., 2006; Zheng et al., 2003), and cell biology (Carrero-Sanchez et al., 2006; Dumortier et al., 2006; Kam et al., 2004; Yan et al., 2006). The scope of this review limits us from extensively discussing carbon-based nanomaterials; we will, however, cover some newer versions of carbon nanomaterials in Section 3.2.

Interestingly for neuroscience, Silva (2005) recently reviewed a list of fullerene ($C_{60}$) derivatives studied both *in vitro* and *in vivo* for their neuroprotective ability. The model material responsible for providing neuroprotection is fullerenol which is hydroxyl functionalized fullerene. More recently Yamawaki and Iwai (2006), however, reported the *in vitro* toxicity of fullerenols in human umbilical vein endothelial cells (ECs) that were treated with 1–100 μg/mL concentrations (average diameter 4.7–9.5 nm) for a day which induced cytotoxic morphological changes as well as showing cytotoxicity via LDH and WST assays in a dose-

dependent manner. Eight day chronic treatment (10 μg/mL) also inhibited cell attachment and delayed EC growth. Varying biological effects of a single nanomaterial such as the hydroxy fullerene offers a clear demonstration of extraordinary situations where a single nanomaterial plays both beneficial (neuroprotection) and unfavorable (specific cell toxicity response) roles within a biological system. Choosing, utilizing, and assessing toxicity of any nanostructured material for biomedical applications are not trivial tasks especially for neuroscience applications where biological systems involved in the bioprocesses are more vital functions such as the central nervous systems (CNS) which include the brain and the spinal cord.

Carbon nanotubes, owning to their structural robustness and synthetic versatility, have been utilized in multiple biomedical applications including tissue engineering. Recently, Kotov and co-workers have formulated a nanocomposite matrix comprised mainly of single-walled carbon nanotubes (SWCNT) which was utilized as a growth substrate for murine embryonic neural stem cells (Jan and Kotov, 2007). Differentiation, growth, and biocompatibility reported by the authors supported positive uses of such nanocomposites but a more recent article by Zhu et al. (2007) showed DNA damages (genotoxicity) induced by multi-walled carbon nanotubes (MWCNT) in mouse embryonic stem cells. This additional example clearly demonstrates realistic dilemmas researchers can face while choosing carbon-based as well as other types of nanostructured materials for biomedical uses.

### 2.2. Porous nanomaterials

Long before the recent interest in nanoscience, the IUPAC divided porous materials and pore size into three categories, microporous (<2 nm), mesoporous (2–50 nm), and macroporous (>50 nm) (Rouquerol et al., 1994; Ying et al., 1999; Zdravkov et al., 2007). There is some confusion, however, in the increasingly popular use of “nanoporous” to describe all three of these categories. Synthesis methods for such materials range from crystal engineering to cooperatively assembled template methods and sol—gel chemistry (Boettcher et al., 2007; Eddaoudi et al., 2001). In this section an overview of the synthetic methods to achieve meso- and macroporosity will be briefly covered.

One of the biggest challenges in porous material synthesis is the precise controlling of the pore size while maintaining overall structure integrity as well as overall size (Alfredsson et al., 1994). Mesoporous materials such as MCM-41 (Beck et al., 1992)and SBA-15 (Zhao et al., 1998a,b), and MCF (Han et al., 2007, 1999; Schmidt-Winkel et al., 1999) have been the most successful porous materials to date and their application in catalysis (Boettcher et al., 2007; Corma, 1997; Ying et al., 1999) has been particularly interesting. Synthesis of mesoporous materials involves the use of a surfactant or block copolymer and a polymerizing inorganic precursor, preferably carried out at a pH near the isoelectric point (IEP) of the inorganic species (Huo et al., 1994). It is a cooperative molecular assembly process (Monnier et al., 1993; Huo et al., 1994) that makes use of all components of the synthesis solution.

Macroporous material syntheses using colloidal template methods have been the focus of recent research. Previously prepared colloidal particles (which can range in size from a few microns down to a few nanometers) are assembled into a “colloidal crystal”, a regular array of close packed spheres, dried, and then a matrix-forming material is interspersed into the interstices between the colloidal particles. This initially liquid solution is then solidified (e.g. polymerized through heat or chemical reduction) and the original colloid particles removed by dissolution or pyrolysis, leaving a porous material whose pore size is controlled by the initial colloid. Materials of these kinds are sometimes referred to as inverse opals. Application of such macroporous materials has been in catalysis (Chai et al., 2004; Yoon et al., 2005), photonics (Norris and Vlasov, 2001; Vlasov et al., 2001), and tissue engineering (Liu et al., 2005b; Zhang et al., 2005), depending on the pore size and type of material. The new trend in porous material synthesis is to combine different levels of porosities (e.g. microporosity with macroporosity)

or inclusion of porosities into materials whose overall dimensions are sub-micron (Yang et al., 1998; Yoon et al., 2002). The bio-applications of such materials include bioseparation, biosensing, drug delivery, and controlling bioprocesses in blood clotting (Blumen et al., 2007; Lee et al., 2006b; Ostomel et al., 2006a,b).

Briefly we will highlight few advances of porous nanomaterials that were designed and successfully used in several key biological applications. First, on the tissue engineering front, Desai and researchers utilized porous aluminum oxide membranes (prepared via electrochemical etching) as cell growth substrates for osteoblast cells which was a comparison study among several different porous and non-porous aluminum oxides. It turns out that the as-prepared nanoporous $Al_2O_3$ substrates showed improved attachment and proliferation of osteoblast cells both short-term and long-term compared to other examples (Swan et al., 2005a,b). More recently, Schmuki and co-workers have demonstrated that vertically aligned titanium oxide nanotubes (also prepared via electrochemical etching) can effectively direct the adhesion and proliferation of mammalian cells on anodized porous substrates (Park et al., 2007). The critical factor in the case of mesenchymal stem cells' adhesion, spreading, growth, and differentiation was the diameter of the as-prepared nanotubes which meant that the porosity of the substrate controlled the bioprocesses involved in stem cell biology to a noticeable degree. Adhesion and spreading of the mesenchymal stem cells (MSCs) were impaired which led to reduction of cellular level activity and eventual cell death when the diameter of the nanotubes increased beyond 50 nm. Such a dramatic influence arising from artificially created sub-100 nm size features is a direct testament that nanotechnology can effectively influence biological processes via careful tuning of variables such as size, volume, and surface electronic characteristics. Secondly, work related to blood coagulations, Grimes and co-workers showed that the electrochemically produced $TiO_2$ nanotubes (100 nm diameter with aspect ratio of approximately 1000) can enhance blood clotting rates (Roy et al., 2007). Metal oxide hemostatic agents such as porous zeolites and bioglass ($SiO_2$—$P_2O_5$—CaO) have been reported much earlier in time by Stucky and co-workers to effectively enhance the rate of clotting times both *in vitro* and *in vivo* (Ostomel et al., 2006a,b,c). These efforts demonstrated by the Stucky group illustrated that porous metal oxides can play key roles in controlling the bioprocesses involved in the blood clotting cascade. Details involved in Stucky group's work in the field of hemostasis will be provided in a later section within this review.

### 2.3. Magnetic nanomaterials

Magnetic properties of materials are controlled by temperature, applied field, alignment and relative orientation of the magnetic domains, and electronic spin states (Hyeon, 2003). Additionally, the size of the particles greatly alters magnetic properties (Campbell et al., 1999). As particle size is decreased to the few tens of nanometers, ferromagnetic materials will have only a single magnetic domain, and all magnetic spins within that domain will be aligned, while thermal motion of such particles relative to one another will control the bulk magnetic properties. These materials are referred to as superparamagnetic and are excellent MRI (magnetic resonance imaging) contrast agents (Gupta and Gupta, 2005; Murray et al., 2001; Wang et al., 2001).

Superparamagnetic inorganic oxides (SPIO) such as $Fe_3O_4$ are proving especially useful in tumor targeting and MRI imaging in biomedical applications (Huh et al., 2005; Jun et al., 2005; Lee et al., 2003; Song et al., 2005). Water-soluble superparamagnetic iron oxide (WSIO) nanoparticles, for instance, can be additionally passivated with cancer targeting agents (e.g. antibodies) and *in vivo* MRI imaging can be done to monitor the circulation and specific attachment to the cancer induced area (Huh et al., 2005). Iron oxides have also been utilized in bioimaging for neuroscience (Atanasijevic et al., 2006; Bulte et al., 2001; Cengelli et al., 2006; Dunning et al., 2004, [2006]; Faber et al., 2007; Liu et al., 2007b; Moore et al., 2000;

Muldoon et al., 2005; Neuwelt et al., 2007; Petropoulos et al., 1995; Rock et al., 2005; Sykova and Jendelova, 2007; Wadghiri et al., 2003). A recent review by Sykova and Jendelova (2007) highlights the use of labeled SPIO imaging agents for tracking migration and fate of adult stem cells *in vivo* with a focus in the central nervous system. Cell labeling can be done either on the surface of the cell or internalized into the cytoplasm but not the nucleus. The labeling contrast agent is usually comprised of a superparamagnetic core (e.g. $Fe_3O_4$), a water-soluble protective coat with functionalizable chemical groups (e.g. thiol, carboxylic acid), and a targeting agent (e.g. antibody).

Juillerat and co-workers have studied several different SPIO nanoparticles (both synthesized and commercially available) on their biological effects on brain-derived endothelial cells and microglial cells (Cengelli et al., 2006). Among the coated SPIO's, active uptake was observed in the amine functionalized case which should have a positive surface charge. This observation is in agreement with a previous report by Cheon and co-workers where cationic water-soluble iron oxide nanoparticles were efficiently transported into neural stem cells in comparison to the anionic counterparts (Song et al., 2005). The ideas behind such studies where particle uptake was increased via surface charge modification are two-fold: one is to increase the signal level of MRI and the other to achieve drug or small molecule delivery to specific cells and tissues. Recent researches have shown, however, that cationic surface charges (Xia et al., 2006a) and iron oxide (Pisanic et al., 2007) itself may have detrimental effects on cells so extensive toxicology experiments should follow any type of *in vitro* and *in vivo* studies utilizing cationic iron oxide nanoparticles where dosage and procedures are carefully tuned and monitored.

Liu et al. (2007a,b) demonstrated the use of modified SPIO nanoparticles that can target cellular mRNAs and detect active transcriptions of specific mRNAs *in vivo* using antisense imaging agents (e.g. phosphorothioate oligodeoxynucleotide) coupled with MRI imaging. This type of research can lead to the development of real-time MRI detection methods where CNS disease models linked to mRNA alteration can be identified. On a slightly different note, Turnbull and Wisniewski, along with their co-workers, used Aβ1—40 peptide modified iron oxide nanoparticles to detect Aβ in transgenic mice *in vivo* (Wadghiri et al., 2003). In summary, magnetic nanomaterials, especially superparamagnetic iron oxides, can be utilized in three distinctive neurological applications which include tracking transplanted cells (e.g. stem cells), identifying transcription efficiencies, and detecting amyloid beta peptides in diseased brains.

### 2.4. Zeolites and clays

Dramatic responses observed in biomolecules and biomolecular processes involved in interfacial phenomena that involve inorganic surfaces are well demonstrated in biomineralization processes (Zaremba et al., 1996), biomolecular chromatographic separations (Kimura et al., 2004), supported enzyme activities and lifetime (Carrado et al., 2004; Han et al., 2002) and protein folding and denaturation (Charache et al., 1962). Mentioned earlier in Section 2.2, the development of potent wound-dressing materials (blood clotting agents) that are capable of arresting hemorrhage due to traumatic injury is another emerging application using materials chemistry to control bioprocesses (Ellis-Behnke et al., 2006; Fischer et al., 2005; Marris, 2007; Ostomel et al., 2006a) and one of the most effective wound-dressing materials currently available is a nanoporous zeolite called QuikClot® (QC) (Z-Medica). Alam et al. (2005) reported that among several different advanced wound-dressing materials tested using a swine model of fatal femoral injury QC exhibited the highest rates of survival.

The Stucky group has found that the isoelectric points of different inorganic surfaces, as measured in simulated body fluid (SBF), can be used as primary determinants to selectively and in a predictable manner accelerate or inhibit blood coagulation (Baker et al., 2007; Ostomel et al., 2007). One example of the many metal oxides based materials that were investigated was clays. Chemical and physical properties, including variable swelling capacities, particle

morphologies, surface charge, and the ability to control the local electrolyte balance through ion exchange are tunable variables available in clay science. In a recent study, it was found that surface charge in SBF for clays such as kaolin correlated very well with the wide range of blood clotting activities of porcine whole blood or plasma (Baker et al., 2007).

Surface charge modulation is not the only way to direct the bioprocesses associated with the blood coagulation cascade as seen in the case of QC where local heating, dehydration, and electrolyte release also contribute to the overall biological process (Baker et al., 2007). Recent studies of the hemostasis properties of high-surface-area porous silica, the Stucky group has shown that the selective variation of window/pore sizes at the sub-50 nm range strongly dictated the rate at which blood clots are formed in human plasma (Baker et al., 2008). This indicates that pore sizes in this size range directly impact the accessibility and diffusion of clotting-promoting proteins to and from the interior surfaces of the porous silica particles. These studies point toward a critical pore size, ≥20 nm, at which clotting speed is maximized. Interestingly, this size regime very closely resembles the pore size at which electrochemically prepared porous $TiO_2$ nanotubes affected mesenchymal stem cell fate as highlighted earlier in this review (Park et al., 2007). Another important capability of such porous metal oxides is that the clotting times of plasma can be even further dramatically reduced by immobilizing selected enzymes within the large pores. This validates the utility of enzyme-immobilized mesoporous silicas in biomedical applications and further expands their possible use in the field of drug delivery systems (Han et al., 1999, 2002; Kim et al., 2006a, 2007b; Luckarift et al., 2004; Tischer and Wedekind, 1999). Porous metal oxides because of their surface chemistry and high internal surface area will allow facile incorporation of proteins in high loading. Fine tuning of nanostructured surfaces including pores and expanded structures to facilitate neurochemicals and important proteins involved in various biological pathways responsible for key neurological functions will prove to be key factors in the development of nanobiotechnology in the field of neuroscience along with the ability to incorporate and release such entities in a controlled fashion.

## 3. Nano—bio interface and nanotoxicology

### 3.1. Nano—bio interface

Proteins and nucleic acids have been the focus of many types of research involving nanotechnology (Kim et al., 2006a; Samori and Zuccheri, 2005; Sarikaya et al., 2003; Seeman, 2003; Zhao and Zhang, 2006). A single cell, usually tens of microns in size, is huge compared to a 10 nm nanoparticle (Figs. 1 and 2). In this sense, researchers around the world have been utilizing various inorganic, organic, and composite nanoparticles to study biological processes involved in drug delivery and cellular level bioimaging (Akerman et al., 2002; Allen and Cullis, 2004; Arap et al., 1998; Gref et al., 1994; Martin and Kohli, 2003). Recently, growing number of papers examine the interaction between a protein and a nanoparticle (Klein, 2007; Sui et al., 2005; Taylor et al., 2000). Compared to a 10 nm nanoparticle (Fig. 2), the APP and a small drug molecule (e.g. DHED) is extremely small which makes probing biologically relevant molecules on nanoparticles extremely difficult. In reality, an injected nanoparticle into a living system will have an uncountable number of interactions with the surrounding system regardless of size. Efforts studying the interface between nanostructured materials and biological systems starting with proteins and then the cell will be a key development that will aid in the study of bio-systems relevant to neuroscience, pharmacology, and medicine.

Studying the bio—nano interface is a very different task since there are no simple ways of probing the interaction in real time or *in situ*. On the other hand, nanotoxicology (the examination of bioeffects of nanomaterials) is a rapidly developing field of some direct relevance. Over the past few years, substantial efforts have begun in the study of the toxic effects of nanomaterials on the environment and living systems. For instance, University of

California has a focused nanotoxicology program sphere headed by UCLA and UCSB under its UC Toxic Substances Research and Teaching Program (http://www.bren.ucsb.edu/news/press/nanotoxicology.htm; http://www.cnsi.ucla.edu/staticpages/education/nanotox-program). As a city, Berkeley (CA), for the first time in US history, has decided to regulate nanotechnology by law with UC Berkeley and LBNL (Lawrence Berkeley National Laboratory) being involved in many nanotech projects but without any implemented safety related protocols (Berkeley, 2006; Monica et al., 2007). Rice University has a center called CBEN (Center for Biological and Environmental Nanotechnology) and an organization called ICON (International Council on Nanotechnology) dedicated to establishing a database for nanotechnology based materials (http://cben.rice.edu/; http://icon.rice.edu). The National Cancer Institute (NCI), not long ago, started a separate institution called NCL (Nanotechnology Characterization Laboratory) headed by a chemist investigating nanomaterials that are below 100 nm on a proposal submission and approval basis (http://ncl.cancer.gov/). Internationally, IBN (Institute of Bioengineering and Nanotechnology) governed by A*STAR (Agency for Science, Technology and Research) in Singapore is an interdisciplinary research park that brings together nanometer scale science with control over biological system (http://www.ibn.a-star.edu.sg/). IBN is headed by a materials scientist which is a sign that the institution has an emphasis more in the materials they make which will help to alleviate transfer of nanotechnology to be implemented in biotechnology.

In essence, a fundamental understanding of nanomaterial toxicology (nanotoxicology) is highly desirable both from the material's stand point as well as from the biological system's point of view. With the increase of commercial products from cosmetics to tennis balls, toxicology evaluations of nanoscale materials should receive greater attention than ever before whether it is the general public, the government, or the personnel involved in the development of nanomaterials (Colvin, 2003; Maynard et al., 2006; Nel et al., 2006; Oberdorster et al., 2005). For the field of neuroscience, the lessons learned from these nanotoxicology studies should help researchers to better choose the type of nanomaterial that can be utilized for studying, for instance, the synaptic plasticity of a neuron. In hopes of doing this, we will review the literature of how nanotoxicology has developed and provide few tables to ease the selection process of materials. With current data, however, it is often difficult to ascertain the toxicity of specific nanomaterials because, as with any small molecule (e.g. pharmaceuticals), toxicity is dose, exposure and pathway dependent. In addition, nanotoxicology studies on animals or cultured cells alone cannot predict in a good manner the effects it might have on human beings.

### 3.2. Nanotoxicology

Various types of engineered nanomaterials exist now thanks to the extraordinary and highly focused efforts from both industry and academia in recent years. The number of published papers dealing with just the synthesis of nanostructured materials has grown exponentially (both 2006 and 2007 exceeds 3200 papers) (Fig. 3). Owing to this explosive increase in publications, hundreds of *in vitro* toxicological studies have been reported (Derfus et al., 2004;Gurr et al., 2005;Oberdorster, 2004;Ramires et al., 2002;Soto et al., 2005;Suh et al., 2006b;Yoshida et al., 2003), as well as numerous reviews and perspectives (Balbus et al., 2007;Borm and Kreyling, 2004;Colvin, 2003;Dobrovolskaia and McNeil, 2007;Garnett and Kallinteri, 2006;Handy and Shaw, 2007;Hardman, 2006;Maynard et al., 2006;Medina et al., 2007;Nel et al., 2006;Oberdorster et al., 2005). *In vivo* toxicology, on the other hand, which probes toxicity (i.e. $LD_{50}$, pathology) by inhalation, injection, and oral digestion, involves the test subject to internalize the test sample whether it is a small mice or a large mammal such as a dog or a monkey. It is, however, troublesome to test nanomaterials' toxic effects on whole animals since all of the synthetic engineering (Cushing et al., 2004;Dai, 2002;Huber, 2005;Jeong et al., 2007;Lee et al., 2006b;Lu et al., 2007a;Medintz et al., 2005;Michalet et al.,

2005) is donevery specifically by individual research groups and proprietary information on synthesis is hard to get especially from the industry. In addition, preparing/conducting/regulating an *in vivo* test is ethically and administratively challenging and individual research efforts have to work in partnership with the institutional approval organization(s) such as IACUC (Institutional Animal Care and Use Committees).

**3.2.1. In vitro nanotoxicology—**The easiest simple solution in assessing nanomaterial toxicology is utilizing various mammalian cells to test for viability or increase/decrease in a designated inherent biological pathway against chosen engineered nanomaterials. For instance, tetrazolium salt based assays (e.g. MTT (Mosmann, 1983) or WST (Ishiyama et al., 1996; Tominaga et al., 1999) are readily available commercially (i.e. Dojindo, Roche) and straightforward to use. Inorganic oxides (Gurr et al., 2005; Ramires et al., 2002; Soto et al., 2005; Suh et al., 2006b; Yoshida et al., 2003) such as $TiO_2$, $SiO_2$, $Fe_2O_3$, carbon-based materials (Jia et al., 2005; Oberdorster, 2004; Sayes et al., 2005; Soto et al., 2005; Zhu et al., 2006) such as nanotubes (Cui et al., 2005a; Donaldson et al., 2006; Garibaldi et al., 2006; Heller et al., 2005; Lam et al., [2004], [2006]; Liopo et al., 2006; Manna et al., 2005; Maynard et al., 2004; Monteiro-Riviere et al., 2005; Shvedova et al., 2003; Singh et al., 2006b), $C_{60}$, and other nanoparticulates (Derfus et al., 2004; Soto et al., 2005; Yoshida et al., 2003) such as semiconductor quantum dots (Chang et al., 2006; Lovric et al., 2005a,b; Tsay and Michalet, 2005; Voura et al., 2004), metal nanoparticles have been evaluated by various research groups (excerpts given as Tables 1–5). The current biggest challenges which have been mentioned in previous papers (Maynard et al., 2006; Nel et al., 2006) might be establishing standard protocols (e.g. particle preparation and growth condition) and producing a reproducible and credible database, such as MSDS (Materials Safety and Data Sheet) for small molecules and effectively linking the toxicological information with physicochemical properties. It is, however, easy to identify a fairly non-cytotoxic material from seriously cytotoxic ones since materials like $TiO_2$ show very little overall cytotoxicity regardless of method or choice of laboratory (Gurr et al., 2005; Ramires et al., 2002; Soto et al., 2005; Suh et al., 2006b; Yoshida et al., 2003). Of course, there are different results arising from different types of assay conditions, the nature of the nanomaterial synthesis, and differences in physicochemical properties.

Another factor to consider is the fact that all of these nanomaterials are not exposed to a biological system in its pristine state (Fig. 4). Consider the DMEM (Dulbecco's Modified Eagle's Medium) liquid cell media and its contents which contain various inorganic salts, amino acids, vitamins and few other components. At least, six components have molar concentrations over 1 mM while fifteen components (mostly amino acids) have concentrations between 0.1 and 1 mM. On top of this, there is approximately 0.1 M of sodium chloride present and the overall molar concentration of small molecules is approximately 0.2 M (or 2 wt%). And this does not even include the various proteins in the serum that is usually supplemented in 5–10% fractions to the cell media. Realistically, when nanoparticles are added to a biologically relevant liquid medium their surface physicochemical properties will change over time depending on their physical conditions such as temperature (37 °C, the incubation temperature), light, and some form of agitation. In fact, several research groups have investigated adsorption of proteins and small molecules on nanomaterials and their effects on biological activity (Chan et al., 2007;Dutta et al., 2007;Wang, 2005;Wiesner, 2006;Yang et al., 2006b). Adsorption chemistry and physics of small molecules and biomolecules onto metal oxides have traditionally been a research topic in the physical sciences (Campbell, 1997;Diebold, 2003;Freund et al., 1996;Hofer et al., 2001;Lavalley, 1996;Rajh et al., 2002) so expanding on such work should greatly aid in the process of assessing nanomaterial toxicology. For instance, Mrksich and Whitesides (1996) wrote a review which dealt with how cells interact with small molecules adsorbed onto surfaces.

**3.2.2. The cell—nanoparticle interface—**Eventually, expanding the toxicity studies to mammals should be done but since it is practically impossible to test on a human subject it will be difficult to assess nanomaterials' effects on human beings with just animal studies alone. In addition, as mentioned previously, nanostructured materials will be in contact with some biologically relevant entity once it enters a biological system. This makes any biochemical assay or structural analysis irrelevant just on its own.

Biological effects of nanomaterials with a focus on toxicity have to be addressed since consumer products as well as medical tools increasingly utilize them one way or another (Maynard et al., 2006). Neuroscience has been linked to nanotechnology previously (Silva, 2006) so instead of repeating things from that particular review we would like to focus on biological effects of nanomaterials with a focus on toxicology and excerpts from recent advances that can potentially be beneficial to the neuroscience community. First, we would like to focus on several nanomaterials and show how researchers around the world have tried to assess their toxicity. Fig. 5 shows eight representative schemes of how a cellular organism can be affected by a nanoparticle: the cell—nanoparticle interface.

Reactive oxygen species (ROS) products whether it is inside or outside of the cell can be key factors in nanostructured materials toxicological effects (Nel et al., 2006). Event 1 represents a nanoparticle smaller than a cell (red particle) producing ROS which ultimately will affect cell membrane stability and cell survivability. If this nanoparticle is internalized, ROS production (event 2) (Nel et al., 2006), particle dissolution (event 3) (Borm et al., 2006), and mechanical damage to sub-cellular units (event 4) (Yamamoto et al., 2004) such as the nucleus will be very important events to monitor and analyze. In addition, different functional groups and surface electronics of the nanostructured materials will determine the level of interaction between the nanoparticles and their surroundings (event 5) (Karakoti et al., 2006; Kostarelos et al., 2007). Furthermore, overall size of the particle can play an important role since large particles can potentially induce permanent damage to the cell membrane while small particles can pass through the membrane and do harm inside the cell (event 6) (Yoshida et al., 2003). Non-spherical particles, on the other hand, might have a different biological response compared to the spherical nanoparticles (event 7) (Geng et al., 2007). Dissolution characteristics of the nanomaterials (whether it is outside the cell or inside) can affect the cell in various ways (event 8) (Borm et al., 2006). Limiting the interaction between a nanoparticle and a cell to eight events is an over simplification and the details of actual phenomena that are happening at the interfaces are very difficult to understand. In addition, the size differences among a 1 nm small molecule, a 4 nm protein, and a 10 nm nanoparticle are huge as shown in Fig. 2. Interaction parameters between these three entities coupled with various other molecules, ions, and particles will make the system highly complex (Fig. 4) to account for in a simple manner so applying systems biology (Ideker et al., 2001; Kitano, 2002a,b) approach could be an interesting option as a long-term research project.

On top of these eight nanotoxicology events, nanomaterials interaction with microbial organisms (Moreau et al., 2007) will be an interesting aspect to consider since biologically contaminated nanostructured materials will have detrimental effects on their utilization in biomedical applications (Fig. 6). For instance, mycoplasmas (Razin, 1978; Razin et al., 1998) have a size range below few hundred nanometers and they have become a rising concern in mammalian cell cultures including stem cells (Chen and Chang, 2005; Cobo et al., 2005, 2007; Rottem and Barile, 1993; Simonetti et al., 2007; Ware et al., 2006). If such microbial organisms integrate themselves readily with engineered nanomaterials their toxic potential as a nanocomposite material could increase which makes probing and understanding nanomaterial's role in controlling and affecting cellular level biological processes (events 1–8 in Fig. 5) very important to investigate and understand. Toxicology arising from such nanobiocomposites will give new meaning to nanotoxicology and, in fact, will be key issues

to consider for neuroscientists wanting to use nanotechnology with focuses on neuronal cell systems, brain implantations, and dementia research such as Alzheimer's disease since mycoplasma detection is not trivial and implications have been made on their possible role in human disease action including CNS diseases (Candler and Dale, 2004; Casserly et al., 2007; Daxboeck, 2006; Daxboeck et al., 2003, [2005]; Narita et al., 2005; Pellegrini et al., 1996; Tsiodras et al., 2005; Waites and Talkington, 2004).

**3.2.3. Titanium dioxide ($TiO_2$)—**Titania ($TiO_2$) has received much attention in materials sciences and engineering due to its optoelectronic properties (Hashimoto et al., 2005). For example, $TiO_2$ has been utilized as photocatalysts for photochemical hydrogen production and for self-cleaning windows. In the cosmetic industry, titania is the main ingredient in many commercial sunscreens along side ZnO due to its property of UV absorption.

The phase mainly responsible for titania's photocatalytic properties is anatase. Other known phases are rutile and brookite. Evaluating and comparing $TiO_2$ toxicology has been the theme of many research groups and the investigations involved assaying for size, content and ROS production. Recent efforts have been focused on engineered nanomaterial toxicology and here we represent few excerpts within the past several years. Yoshida et al. (2003) have reported that LDH (lactate dehydrogenase) assay revealed $TiO_2$ to be the least toxic material from sub-100 nm up to 1 μm. According to their studies toxicology assessed using cell membrane damage assays, metal oxides are toxic in the following order: $TiO_2 < Al_2O_3 < SiO_2$ regardless of size under 1 μm. This study, however, does not probe different types of $TiO_2$. For an overview study of cell toxicology in relation to $TiO_2$ particle size and crystal phase, Sayes et al. (2006) and Warheit et al. (2006) have done studies with dermal fibroblasts and human lung epithelial cells as well as with rats which suggest that photoactivation of anatase $TiO_2$ will increase cytotoxicity but concentrations over 100 mg/mL will be significant enough to cause any ill effects. Soto et al. (2005, 2007) have also done a correlation study between particle size, aggregation and toxicology using cellular experimental protocols. In these studies TEM is extensively used to analyze the particle sizes and the results suggest that $TiO_2$ are much less cytotoxic compared to other types of nanomaterials such as carbon nanotubes and $SiO_2$. In a unique synthesis, Suh et al. (2006b) have produced anatase phase $TiO_2$ microspheres that have nanometer features and also showed that $TiO_2$ is biocompatible. The cause for concern in $TiO_2$ toxicity studies are in the cases where researchers showed genotoxicity (Turkez and Geyikoglu, 2007; Wang et al., 2007a) associated with titania and with particles that are non-spherical (Yamamoto et al., 2004). Table 1 summarizes $TiO_2$ nanotoxicology in recent years with a minimum focus on *in vivo* inhalation toxicology and a focus on cellular level toxicity studies. Utilizing nanotechnology in neuroscience will likely not involve inhalation of particles compared to injection and installation of the nanostructured materials either as injectable devices or implantable machines and tools.

Prosthetic devices including neuroprosthetics require well-defined device characteristics such as mechanical and chemical properties. Titanium based materials have been the choice of many for implants. In a recent study, Palmieri et al. (2007) have investigated into comparing the effects of nano-sized synthetic anatase $TiO_2$ (prepared via the sol—gel route surface) coated onto surfaces against osteoblast-like cells (MG63) for their role in gene regulation using microRNA (miRNA) microarray analyses. miRNAs are small 19–23 nucleotide noncoding RNAs and play a crucial role in the post-transcriptional regulatory process. miRNAs regulate the expression of other types of genes by repressing or cleaving translation of their messenger RNA targets and they have been shown to be an intricate part of neurobiologically important pathways (Kosik, 2006; Kosik and Krichevsky, 2005). The number of known miRNA's are limited to approximately 500, considering this and the shown roles of miRNA it may be an important molecular level screening method that has become available for any type of nanoscience-related neuroscience projects. Interestingly within the past two years, Gao and

researchers have utilized nanotechnology to electrochemically detect miRNA at the pM to fM range (Fan et al., 2007; Gao and Yang, 2006) and the Corn group used nanoparticle amplified optical detection methods which allowed the detection lower limit to reach attomolar concentrations (Fang et al., 2006). Recent advances involving nanotechnology and miRNA will foster new and exciting interdisciplinary research linking biology and physical sciences.

**3.2.4. Silicon dioxide ($SiO_2$)—**In comparison to $TiO_2$, silica ($SiO_2$) has been studied more widely due to an occupational lung disease called silicosis which is linked to crystalline phase silica (Brunner et al., 2006; Jovanovic et al., 2006). Unlike $TiO_2$, however, research involving $SiO_2$ in the field of nanotechnology deals mainly with amorphous phase silica (Bharali et al., 2005; Chowdhury and Akaike, 2005; Gemeinhart et al., 2005). Here we will introduce few good examples of $SiO_2$ nanostructured materials with a focus on recent synthetic particles that have multifunctionality (see Section 4.2). $SiO_2$ sub-50 nm silica nanoparticles incorporating a fluorophore and an MRI agent were synthesized and cell viability was checked with a one day colorimetric tetrazolium assay using monocyte cells which revealed the non-toxic nature of that particular multifunctional particle (Rieter et al., 2007a). Mesoporous $SiO_2$ spheres have been prepared and utilized in several biological applications in the past few years including drug delivery studies (Slowing et al., 2007). In a recent anti-cancer drug delivery study done by UCLA (Lu et al., 2007b), approximately 130 nm amine group functionalized mesoporous $SiO_2$ spheres were formed and surface modified with alkyl phosphate groups. Cytotoxicity tests on several different cancer cell lines (e.g. PANC-1, AsPC-1) revealed practically no toxicity unless the anti-cancer drug was loaded and subsequently released over time. In another protein, polymer functionalized $SiO_2$, luminescent nanobeads of approximately 20 nm were tested for its cytotoxicity (< 6 h) via apoptosis and necrosis assays (flow cytometry) (Bottini et al., 2007). Organically modified 20 nm $SiO_2$ with an incorporated hydrophobic photosensitizer (e.g. porphyrin) were tested for its toxicity levels with tumor cells and showed no apparent toxicity unless irradiated with light to product ROS (Ohulchanskyy et al., 2007). Generally, amorphous $SiO_2$ nanoparticles are considered highly biocompatible and non-cytotoxic unless engineered to be otherwise.

**3.2.5. Iron oxide—**Iron in the presence of an oxidant (e.g. air) will become iron oxide (i.e. rust). There are several phases of iron oxides which include Haematite ($\alpha$-$Fe_2O_3$), Magnetite ($Fe_3O_4$), Maghemite ($\gamma$-$Fe_2O_3$), $\beta$-$Fe_2O_3$, $\varepsilon$-$Fe_2O_3$, Wüstite (FeO) (Cornell and Schwert-mann, 1996). Among them, magnetite ($Fe_3O_4$) nanoparticles have been the subject of research for many years in hopes of using them for biomedical research (Bulte et al., 2001; Caruthers et al., 2007; Dunning et al., 2004; Gupta and Gupta, 2005; Mornet et al., 2004; Pankhurst et al., 2003; Simberg et al., 2007; Sykova and Jendelova, 2007; Thorek et al., 2006; Weissleder and Mahmood, 2001; Xu and Sun, 2007). Sub-10 nm $Fe_3O_4$ nanoparticles have been particularly useful as a superparamagnetic MRI probe that can be made to target-specific cells and tissues inside the body. It is straightforward to synthesize iron oxides especially magnetite nanoparticles: iron salt, surfactant, base, solvent and heat. Compared to $TiO_2$ and $SiO_2$, iron oxides are partially soluble in acidic media containing chelating agents such as siderophores (Kraemer, 2004).

For this very reason, *in vitro* neurotoxicity of iron oxides was implicated by researchers from UCSD (Pisanic et al., 2007). In this study, iron oxide nanoparticles affected PC12 cells' ability to differentiate in response to nerve growth factors (NGF) in a concentration dependent manner. For instance, Western blotting revealed that growth associated protein GAP-43 level decreased dramatically when the NGF concentration went from 0.15 to 1.5 mM then 15 mM which alerted the researchers to re-evaluate their efforts in using iron oxide nanoparticles for neurobiological applications. Iron oxides are negatively charged in physiological pH conditions. This good example shows how surface chemistry and its electronic states control bioprocesses in a detrimental manner. Any use of nanotechnology in biological applications should accompany

stringent biocompatibility studies of not only in short-term effects but also effects from chronic exposure. Case-by-case approach to probe nanotoxicology is a must especially when bioprocess control over neurological systems is strongly desired. Table 3 lists several good examples of research groups around the world that have researched into both *in vitro* and *in vivo* toxicology of iron oxides.

On a slightly different note, Ruoslahti and co-workers (Simberg et al., 2007) have utilized 50 nm iron oxide nanopaticles as tumor homing vehicles that has been conjugated to a tumor targeting peptide CREKA (Cys-Arg-Glu-Lys-Ala). CREKA allows the nanoparticle to recognize clotted plasma proteins and bind to vessel walls and tumor stroma. Interestingly, these nanoparticles accumulate in tumor vessels; induce blood clotting which increases binding sites for additional particles to home in to. This type of controlled and targeted toxicity is a new state-of-the-art use of iron oxide nanoparticles in comparison to their sole use as image contrast agents. It will be beneficial for the neuroscience community to bench mark such efforts from the cancer research community and follow the biological target based approaches and implement them to known targets in neurological disorders.

**3.2.6. Cerium oxide: neuroprotecting agent—**$CeO_2$ is a very potent oxidation catalyst which promotes chemical reactions such as CO oxidation in automobile catalytic converters (Guzman et al., 2005; Trovarelli, 1996). In the last few years, several works involving ceria nanoparticles on their ability to offer cellular level protection have been reported (Das et al., 2007; Niu et al., 2007; Schubert et al., 2006; Singh et al., 2006a). Nano-ceria nanoparticles prevented increases in reactive oxygen species (alternatively coined reactive oxygen intermediates) *in vitro* and *in vivo*. Light-induced degeneration of photoreceptor cells leading to vision loss was reduced. These findings suggest that therapeutics developed based on nano-$CeO_2$ may effectively decrease any ill effects arising from ROS related degeneration, diseases and ailments (Chen et al., 2006b). In an earlier study, radiation studies were done and it was found that normal cells pretreated with nano-ceria did not die where as untreated cancer cells did. The nature of these types of protective effect comes from the oxidation—reduction (redox) chemistry between $Ce^{4+}$ and $Ce^{3+}$ and the fact that the inorganic structure of ceria can tolerate defects via oxygen vacancies in $CeO_{2-\chi}$ (Mogensen et al., 2000). Surface charge effects of nano-ceria were investigated in several different pHs and synthesis conditions. As expected, protein adsorption (e.g. BSA) increased as a function of zeta potential increase and negatively charged $CeO_2$ internalized preferentially in cellular uptake experiments. Synthesis methods strongly affected the IEP of nano-ceria: microemulsion method gave 4.5 and hydrothermal method gave 9.5 (Patil et al., 2007). IEP differences arising from synthesis details being different might be a key issue when utilizing nanostructured materials for biological applications. Biological screening of cerium oxide with a focus in nanotoxicology has been conducted only within the last few years and we have summarized those efforts in Table 4.

**3.2.7. Carbon materials—**Among carbon-based materials, carbon nanotubes have been well utilized in recent biological applications. Excellent review papers already exist for CNT's (Dai, 2002; Dai et al., 2003; Harrison and Atala, 2007; Pagona and Tagmatarchis, 2006) and $C_{60}$ fullerenes (Diederich and Gomez-Lopez, 1999; Fiorito et al., 2006; Hirsch, 1995; Jensen et al., 1996; Ke and Qiao, 2007; Prato, 1997; Satoh and Takayanag, 2006) so we will focus on new types of spherical and non-tubular forms of carbon that was developed for biological applications (Fig. 7). The first example is carbon nanohorns by Iijima and co-workers (Ajima et al., 2005; Isobe et al., 2006; Matsumura et al., 2007; Miyawaki et al., 2006; Murakami et al., 2004). Processed in a similar fashion as CNT's, researchers were able to synthesize high surface area carbon materials that have tube-like carbon sticking outward but in a spherical overall shape and are approximately 100 nm in size. Cytotoxic assays show practically no toxicity. The second one is carbon nanodots (sub-10 nm) which were strongly two-photon active and emit in the visible range (Cao et al., 2007). *In vitro* tests suggest that the carbon

nanodots can be internalized into mammalian cells and fluorescent microscopy imaging was possible. A third recent class is (fluorescent) diamond nanoparticles (Fu et al., 2007; Yu et al., 2005) which were found to be noncytotoxic and were used as single-particle biomarkers on mammalian cells.

**3.2.8. Zeolites and clays—**Recent development in utilizing porous zeolite materials for biomedical application has focused on two main areas. One is in hemostatic agents which induces blood clotting upon treatment and the other in antibacterial agent development (Sakaguchi et al., 2005). Quikclot® (QC) developed by Z-Medica has been a key agent utilized by the military to reduce deaths in the field by blood loss. This agent is very effective but also induces local dehydration and causes *in situ* cauterization. Instead of zeolite based porous materials either mesoporous bioglass (Ostomel et al., 2006a,b) or clays (Baker et al., 2007) can be a highly effective blood clotting agent. Both of these materials, in fact, avoid causing burns to the user. A much more recent product, Quikclot Sport® Silver™, which incorporated silver in the matrix alleviated the negative factors in QC and Z-Medica now offers a burn-free, antibacterial dressing for external wounds (Z-Medica). This later examples clearly demonstrates how a single metal ion source can greatly affect the materials' overall interaction with biological systems such as the blood clotting cascade.

Tailoring inorganic nanostructures by their composition and surface electronics might further allow researchers to invent a porous system where one can control the rate of blood clotting by either engineering the isoelectric point (Ostomel et al., 2007; Sakaguchi et al., 2005) or by incorporating biologically relevant entities into the nanostructured base material (Ostomel et al., 2006c). In essence, there is no extensive mammalian toxicology study done on zeolites but their use as blood clotting agents and related clinical studies have proven that their use on animals and human beings are reasonable within the scope of allowed practices of medicine. We expect to see more work on blood clotting and antibacterial agents using zeolite and other types of porous metal oxides. Studying such controllable systems might offer insights into targeting internal head injuries and other types of internal wounds and clots and allow researchers to directly deal with such medical issues.

**3.2.9. Metal and semiconductor nanoparticles—**Utilization of metal and semiconductor nanoparticles in biomedical applications has been demonstrated very well by many research groups (Daniel and Astruc, 2004; Fu et al., 2005; Jun et al., 2006; Medintz et al., 2005; Michalet et al., 2005; Tang and Kotov, 2005). Reviews for these two classes of materials exist in multiples and we do not want to repeat what others have done. For metal nanoparticles such and Au and Ag, however, we would like to introduce molecular imaging via (surface) plasmon resonance coupling (Campbell and Xia, 2007; Haes et al., 2004, 2005a,b).Aaron et al. have shown that 25-nm gold nanoparticles when conjugated with anti-EGF (epidermal growth factor) receptor monoclonal antibodies can be efficiently used as *in vivo* targeting agents for imaging cancer markers, specifically epidermal growth factor receptors. The Au nanoparticles results in a dramatic increase in signal contrast compared to other antibody-fluorescent dye targeting agents.

Semiconductor nanoparticles such as CdSe/ZnS nanoparticles have been utilized heavily for bioimaging applications (Michalet et al., 2005). The biggest challenge with this type of material is the potential of high toxicological effect caused by heavy metal dissociation (Chang et al., 2006; Derfus et al., 2004; Kirchner et al., 2005; Sinani et al., 2003; Voura et al., 2004; Zhang et al., 2006). Many *in vitro* and *in vivo* toxicological studies were conducted and interesting studies have been done and in recent years the effect of nanoparticles on microbial species and in the environment has received notable attention (Adams et al., 2006; Bhattacharya and Gupta, 2005; Dreher, 2004; Guzman et al., 2006; Liu, 2006; Maynard and Kuempel, 2005; Wigginton et al., 2007). It is particularly interesting that certain microbial species interact extraordinarily

with nanomaterials or in certain instances even synthesize nanostructured materials (Gericke and Pinches, 2006; He et al., 2007; Konishi et al., 2006, 2007; Marshall et al., 2006; Moreau et al., 2007; Shankar et al., 2003). Combining efforts from environmental and biological sciences not necessarily related to medicine could eventually help us understand how different biological systems react cooperatively or uncooperatively with certain types of nanostructured materials regardless of their overall size and content. Moreau et al. (2007), for instance, have shown that extracellular proteins from microbial species can promote biomineralization of metal-bearing nanoparticles and suggested that such an event can lead to limiting nanoparticulate dispersion in the environment.

## 4. Nanomaterials for biomedical research: opportunities in neuroscience

### 4.1. Nanowires and patterned surfaces

Patterned surfaces, particularly, created with PDMS (poly (dimethylsiloxane)) elastomer have been of high interest to many for cell attachment studies both for eukaryotic (Aizenberg et al., 1998; Chen et al., 1998, 2005; Kane et al., 1999; Mrksich and Whitesides, 1996; Takayama et al., 1999; Whitesides and Lamantia, 1995; Zhang et al., 1999) and prokaryotic (Weibel et al., 2007) systems (Fig. 8a). Whitesides and co-workers have shown that micro- and nanoscale patterns on flexible substrates can be excellent tools to study cell mechanics and function. In fact, multitudes of projects now involve the use of soft lithography techniques (based on cleanroom microtechnology used to make electronic materials and circuits) which allow facile creation of highly reproducible surface patterns and subsequent systematic analysis of biological systems. Jeon and co-workers at UC Irvine have successfully engineered lab-on-chip systems (made out of PDMS and slide glass) which allow neuronal cell bodies to be spatially separated from the out-growing neurites and axons (Park et al., 2006; Taylor et al., 2005). Microtechnology have also been well utilized by Bhatia and co-workers at MIT to control cellular level microenvironments which allowed three-dimensional cell cultures and high-throughput screening of biomolecules such as extracellular matrix proteins possible (Albrecht et al., 2006; Flaim et al., 2005; Hui and Bhatia, 2007; Khetani and Bhatia, 2008; Underhill and Bhatia, 2007). Lithography techniques also allowed the development of lab-on-chip devices (or platforms) which led to long-term low cell density (nano-liter volumes) postnatal rat primary hippocampal neuron cultures as demonstrated by Millet et al. (2007) at the University of Illinois. The June 2007 issue of Lab on a Chip journal published a special issue on ‘Cell and Tissue Engineering in Microsystems’ which covers a variety of research efforts involving cell biology investigation on microdevices and patterned surfaces (Bhatia and Chen, 2007) and with the advancement of single cell analysis techniques (Jo et al., 2007; Jurchen et al., 2005; Kruse and Sweedler, 2003; Monroe et al., 2005; Northen et al., 2007; Rubakhin et al., 2000, 2003; Rubakhin and Sweedler, 2007), long-term cell culture experiments with precisely controlled microenvironments can be done in a facile manner in conjunction with high resolution real-time analysis of cellular products.

Nanowires with sub-micron diameters have also been utilized to study cell biology. Yang and co-workers at UC Berkeley have recently reported that sub-100 nm (diameter) silicon nanowires (SiNW) can be integrated into live cells without causing detrimental affects (Kim et al., 2007c). Basically, they were allowed to grow mouse embryonic stem cells on the SiNW and also use them as nanoscale needles to deliver biological materials such as GFP (green fluorescent protein) plasmid (Fig. 8b) into cells. At almost the same time, Bertozzi and co-workers have reported the use of a modified nanosized AFM (atomic force microscopy) tip to favorably deliver fluorescent nanoparticles such as CdS (Chen et al., 2007)(Fig. 8c). The diameter of the AFM tip was sub-10 nm and it proved that length scales much smaller than the cell was very important for the survival and subsequent delivery of materials inside the cell. Making sub-micron patterns of biomolecules as well as functionalizing the sub-patterns with

inorganic nanowires and nanopores which can incorporate biological materials will offer additional key functions to any device that may incorporate such sub-units. For neuroscience research, microdevices with sub-cellular (sub-micron) features, patterns, and functional surfaces can eventually aid in carrying out nanosurgeries to cells linked to the CNS and also in studying the interface that is created between neurons and neuronal implants *in vitro* and *in vivo*.

### 4.2. Multifunctional nanoparticle

Recent trends in nanoparticles engineered for biomedical applications involve nanoparticles having multiple components in the nanomaterial (Fig. 9). In most cases, as depicted in the schematic, a multifunctional nanoparticle system (MFNPS) would be comprised of four main components: a matrix which is few hundred nanometers in size or smaller, a magnetic domain (e.g. $Fe_3O_4$) for MR imaging, an optical probe (usually fluorescent such as FITC) for microscopy, and pores or functionality that allows the incorporation of a small molecule (i.e. therapeutic agent) or a biomolecule (i.e. antibody). MFNPSs can have four distinctive types. Type 1 is non-porous but spherical $SiO_2$ based sub-100 nm nanoparticles with two or more components. Type 2 is sub-200 nm spherical nanoparticles that is either porous or can incorporate and, in time, release small molecules such as drug molecules. Type 3 is sub-20 nm nanoparticles with functionalizable ligands or biomolecules stabilized (passivated) onto the nanoparticles and are, in most cases, first synthesized in organic conditions and then phase exchanged. Finally, type 4 is non-spherical nanoparticle systems that have multiple components such as fluorescent tags and antibodies. (Fig. 9) This last type 4 MFNPs will essentially have very different biological responses compared to spherical systems. According to a recent study by Discher and co-workers (Geng et al., 2007) showed that particle flow and subsequent delivery of drugs are affected by shape *in vivo*. Filament (non-spherical) type particles resided approximately ten times longer than spherical particles and due to their prolonged existence drug delivery was more effective as well. Cell uptake efficiencies also differed.

Multiple examples of MFNPS exist that have small molecule therapeutic agents incorporated (Josephson et al., 2002; Kim et al., 2006b, 2007a; Lee et al., 2004b, 2006c; Levy et al., 2002; Lin et al., 2006c; Pellegrino et al., 2005; Rieter et al., [2006], 2007[a],b; Santra et al., 2005a,b,c). The overall theme for MFNPS is very straightforward but finding a balance between rationally designing the system and, at the same time, practically screening will be key issues in the development of MFNPS for biomedical application.

In contrast to inorganic based systems, biodegradable polymers such as poly(L-lactic acid) (PLLA), poly(lactide-co-glycolide) (PLGA), BSA (bovine serum albumin) have been in existence for a while now and is widely used for the controlled delivery of drugs and proteins in the form of microspheres or nanospheres (Giovagnoli et al., 2005; Ibrahim et al., 2005; Langer, 1990; Song et al., 1997; Suslick and Grinstaff, 1990; Wei et al., 2004, 2006; Yeo and Park, 2004). Based on these types of degradable polymeric systems, antibody conjugated magnetic PLGA nanoparticles were reported recently for the diagnosis and treatment of cancer (Yang et al., 2007). The drug molecule incorporated into this PLGA nanoparticle was doxorubicin (DOX) which is very similar in structure with minocycline (Choi et al., 2007)(Fig. 9) which has recently been shown to have potent anti-Alzheimer's disease effect. In fact, although not a multifunctional particle, Huperzine A was encapsulated in PLGA in its microspherical form and was used in the treatment of memory impaired rodents (Chu et al., 2007; Gao et al., 2007). Microemulsion methods have also been used to deliver pharmaceuticals, specifically metal chelators to treat CNS related diseases (Cui et al., 2005b). Veiseh et al. (2005) have reported that multifunctional nanoprobes which contained glioma cell targeting functions were also capable of being detected via MRI and fluorescent

microscopy methods. This multifunctional nanoparticle is made up of iron oxide and poly (ethylene glycol) with dual functional groups.

With just single-component nanoparticles, researchers have used the nanoparticles to aid in their quest to find a cure for dementia related diseases such as Alzheimer's disease and Parkinson's disease. Nanostructured gold materials have been used to promote/suppress local protein aggregations such as Aβ (Kogan et al., 2006). In an earlier study, silver nanoparticles were utilized to study the interaction between amyloid β-derived diffusible ligand (ADDL) and the anti-ADDL antibody (Haes et al., 2004, 2005a).

In summary, tailoring the size, contents, and surface electronic properties through chemistry and physical methods within sub-200 nm nanoparticles will be key factors in the quest of using MFNPS (multifunctional nanoparticles) for the treatment and diagnosis of brain related abnormalities. Many review papers (Cornford and Hyman, 1999; Liu et al., 2005a; Lockman et al., 2002; Roney et al., 2005) have been written in recent years that talk about size being a key issue in drug delivery to the brain past the blood—brain barrier (BBB). That is very true in cases where spherical morphologies are observed in the nanomaterials but it raises a big question about particles of different shapes such as carbon nanotubes (Geng et al., 2007). In addition, although not in the field of neuroscience, lessons learned from blood related research using inorganics (Baker et al., 2007; Boettcher et al., 2007; Ostomel et al., 2006a,b,c, 2007) might help to improve particle design, synthesis and final usage as therapeutic or diagnostic agents in CNS related disorders.

We would like to end this section by providing a table listing various multifunctional nanoparticles (shown in Fig. 9) that have been developed in the past several years. This table is aimed to give a straightforward component and characteristic analysis thus providing unfamiliar neuroscientists (or any other biologist) to pick and choose what they think might improve their current research. In majority of the cases, as outlined in Fig. 9, the particles are comprised of a matrix and two or more sub-components that can be detected using fluorescence microscopy or magnetic resonance imaging. The key structural differences arise from varying formulations among these three main contents but biological functions are more strongly affected by the surface chemistry which is not always straightforward to analyze. The ability to control the size and contents within a multifunctional nanoparticle system seems to have been explored to a much greater extent which focuses on bioimaging rather than actually using them to control specific biological functions. Expanding the state-of-the-art research represented in Table 5 to control bioprocesses involved in various biological systems and functions such as directing neuronal growth and influencing stem cell differentiation seems to be the next logical step in nanobiotechnology utilizing MFNPS.

### 4.3. Nanoscale imaging

Imaging techniques have improved dramatically over the years, especially the ones that involve nanometer level resolution. Electron microscopy (EM) have been well utilized in many science and engineering fields but such techniques involve the samples to be highly dehydrated since the imaging can only be done under vacuum (Allen et al., 2007; Graham and Orenstein, 2007; Kiseleva et al., 2007). Atomic force microscopy, however, has been the more sample-friendly technique for imaging nanoscale biological and bioinspired materials which is done under atmospheric pressure (Dufrene, 2008; Friedbacher et al., 1991; Hansma, 2001; Hansma et al., 1992, 1996, 1997). Another instrument that biologists and environmental scientists have increased usages of is the ESEM (environmental scanning electron microscope) which can analyze hydrated samples (Bogner et al., 2007; Muscariello et al., 2005; Priester et al., 2007) and is now frequently used to analyze biofilms. Fig. 10 shows characterization tools categorized by type of analysis based on composition (elemental), size (resolution) and type of biological sample analysis which can be linked to contents in Fig. 1. It is important to note that most of

the high resolution instrumentation techniques require the samples to be under high vacuum which complicates the sample preparation process especially for biological and wet-samples; hence AFM is the method of choice when relatively unaltered (excluding the fixation process) sample imaging analysis is desirable. For instance, studying protein interactions on surfaces can be best done using AFM and when coupled with time and optical data, the dynamics of protein folding and unfolding can be imaged, tracked and analyzed. In fact, physical scientists have developed analysis platforms that couple together an AFM with a confocal microscope which is now commercially available (Blow, 2008).

Protein misfolding and formation of aggregations have been linked to several neurodegenerative diseases which include Parkinson's, Alzheimer's diseases and Down's syndrome (Bross and Gregersen, 2003). Research efforts focused on understanding the structural variables dictating the ultimate abnormalities linked with such diseases have been done using imaging techniques including AFM (Braga and Ricci, 2004). Suh and co-workers have recently shown that Aβ peptide agglomeration characteristics influence the proliferation and differentiation of murine adult neural stem cells (Heo et al., 2007). The nanoimaging technique which the researchers utilized was AFM as shown in Fig. 11a and d and under atmospheric pressure morphologically distinctive forms of Aβ peptide are formed; oligomeric or fibrillar. Various other groups have utilized AFM to conduct morphological characterization studies related to amyloid beta peptide and other proteineous species linked to neurological disorders such as α-synuclein and tau (Lyubchenko et al., 2006). Not only in biology but also synthetic inorganic nanomaterials can have distinctive morphologies as shown in Fig. 11b and e which are made up of essentially the same material (i.e. Ti and O). This is why associating structural factors to understand different outcomes in biological systems will be highly important when nanotechnology and biotechnology are adjoined together. For direct cell imaging, Lal et al. (1995) used AFM to image neurite outgrowth and cytoskeletal reorganization in realtime using rat fibroblast cells (NIH/3T3) and rat tumor cells (PC-12) *in vitro*. More recently, efforts of cell imaging using AFM have extended to other eukaryotic and prokaryotic species to reveal nanoscale features under ambient conditions (Dufrene, 2008; Kada et al., 2008).

Analyzing and understanding the toxic potentials of nanostructured beta amyloids vs. similar proteineous structures in microbial organisms (i.e. bacterial toxins) have been one of the latest developments in the efforts to understand the nature of structural and functional factors giving rise to unique but detrimental properties in the CNS (Fowler et al., 2007; Lashuel and Lansbury, 2006). Whether it is the fibrillar or oligomeric or porous (channel like) forms of Aβ or α-synuclein, the underling theme is that different nanostructures at different time-domains will affect neurogenesis in a dynamic and complex manner. As mentioned above, nanomaterials of metal oxides (Fig. 11b and e) can be engineered to mimic the structures of Aβ (as shown in Fig. 11a and d) and have well-defined isoelectric points by utilizing constituent engineering via synthetic chemistry methods.

Biochemical and molecular biology analyses can be performed to further elucidate and understand the structural effects that different nanoparticles will have on living system (i.e. cells) at the sub-100 nm domain which is at a length scale where important cellular functions (i.e. transcription, translation) are carried out. However, as mentioned in Section 3.2, the level of understanding of association between cytotoxicity and structural and physicochemical properties of nanomaterials is still not well established. On top of this unresolved complexity, there are various examples and forms of protein aggregation and misfolding that occurs naturally that is linked with neurodegeneration so a step-wise and systemic (high) throughput approach (Shaw et al., 2008; Weissleder et al., 2005) will be helpful. Cellular level activities involving small ion and molecular trafficking (i.e. $Ca^{2+}$ signaling and gene imaging *in vivo*) have received much attention as of late which focuses on nanometer level resolution and

manipulation (Atanasijevic and Jasanoff, 2007; Atanasijevic et al., 2006; Palmer et al., 2004). As mentioned in Section 2.3, gene transcription has been imaged in the brain of mice after delivery of antisense nucleic acid decorated 15–20 nm superparamagnetic iron oxide nanoparticles (also fluorescent) *in vivo* using magnetic resonance imaging (Liu et al., 2007b; Masotti et al., 2008). Specific sequences for the antisense single-stranded phosphorothioate-modified oligodeoxynucleotides (sODNs) were complementary to *c-fos* and *β-actin* mRNA and avidinbiotin complexation method was crucial in the formation of the imaging probe. Coupling multiple analysis tools (Fig. 10) to establish a well-defined understanding of sub-100 nm activities associated with cell biology will be invaluable in the further development of nanobiotechnology.

### 4.4. Gene delivery

**4.4.1. DNA based nanotechnology—**DNA based nanotechnology, in many ways, has been one of the most heavily studied fields that involves the use and the creation of bioinspired materials for highly selective biosensing, nanoarchitecture engineering and nanoelectronics (Ito and Fukusaki, 2004; Lu and Liu, 2006, 2007; Seeman, 2005; Shamah et al., 2008; Stoltenburg et al., 2007; Wernette et al., 2008). Biologically, nucleic acid delivery *in vitro* and *in vivo* has been well studied and lipid based gene delivery has become a common and essential methodology for neuroscientists and biologists. Transfection techniques, for mammalian cells, are primarily divided into non-viral and viral techniques and for many nanotech research groups investigating gene and drug delivery methodologies, the focus is on the non-viral particle based systems (Dobson, 2006; Labhasetwar, 2005; Li and Szoka, 2007) but increasing number of nanotech projects are investigating and manipulating viruses (Kovacs et al., 2007; Loo et al., 2007; Radloff et al., 2005; Sun et al., 2007).

For DNA delivery and utilization of DNA to study the dynamics of nanostructures, Au nanoparticles (Daniel and Astruc, 2004) and silica nanoparticles have been the choice of materials since there surface chemistries, physicochemical and optoelectronic properties are well established (Hench and West, 1990; Livage et al., 1988; Yan et al., 2007). Nucleic acid hybridization via base pairing (hydrogen bonding) and Au-thiol chemistry (Bain et al., 1989; Laibinis et al., 1991; Love et al., 2005), for the most part, offered a unique opportunity for investigating assembly of DNA functionalized gold nanoparticles which lead to the development of novel sensing technologies (Sassolas et al., 2008) for detecting small molecules (Liu and Lu, 2004b, 2006b; Liu et al., 2006), biomolecules (Cao et al., 2002; Hill et al., 2007; Lee et al., 2004a; Tansil and Gao, 2006) and metal ions (Liu and Lu, [2003], 2004a, 2005, 2006a; Lu and Liu, 2007; Wernette et al., 2008) and nanoassembly/architecture projects (Mirkin, 2000; Park et al., 2004, 2008). Gene delivery using Au nanoparticles have well been demonstrated by Mirkin and co-workers on several occassions (Rosi et al., 2006; Seferos et al., 2007). Surface modified (multifunctional) silica nanoparticles have also been well utilized to deliver or detect DNAs (Bharali et al., 2005; Fuller et al., 2008; Gemeinhart et al., 2005; Klejbor et al., 2007; Kneuer et al., 2000a,b; Radu et al., 2004; Torney et al., 2007).

**4.4.2. RNA interference—**RNA interference (RNAi) and targeting the translation process which occurs in the cytosol, in rapid manner, paved the way to developing novel pathways to alter protein synthesis by the break down of mRNAs using small interfering RNAs (siRNAs) (Hannon, 2002). Along with siRNAs, microRNAs (miRNAs) are used by the genome of various organisms to carry out similar regulatory assignments which stops the translation process and recent research shows that miRNAs play critical roles in various neuronal pathways and stem cell biology (Hebert and De Strooper, 2007; Kosik, 2006; Kosik and Krichevsky, 2005). The use of chemistry and nanotechnology based tools in discovering new types of therapeutics based on non-viral carrier systems to deliver oligonucleotides into the cytosol to control the translation process have increased over the years (Baigude et al., 2007; Guo,

2005; Heidel et al., 2007; Howard et al., 2006; Schiffelers et al., 2004; Yuan et al., 2006). In this section we would like to review some of the latest developments in the area of RNA interference and DNA delivery using synthetic nanomaterials from polymeric systems to inorganic systems (Fig. 12). The basic scheme, to highlight the state-of-the-art, is to penetrate the cell membrane, deliver binding agents, stop the target gene expression pathway but without damaging or killing the target cells.

Keller and researchers thoroughly investigated several different lipid based carrier systems (liposomal systems as mentioned in the paper) in relation to their protein downregulation efficiency and overall *in vitro* cell toxicity (Spagnou et al., 2004). Variety of commercially available lipid based nucleic acid delivery methods were investigated and compared for silencing the β-Gal reporter gene in two cancer cell lines (HeLa and IGROV-1). The conclusion was that cationic lipid based delivery of plasmid DNA vs. siRNA have distinctive differences which warrant optimization of formulation for increased delivery efficiencies with low toxicities. Related research efforts involving the use of inorganic nanomaterials as gene delivery vehicles can readily utilize the nanotoxicology information reviewed (and tabulized) in this review in Section 3.

Rana and co-workers used a non-toxic and cationically charged poly(lysine) based dendrimer (spherical and oligomeric) nanoparticle with unsaturated hydrocarbon side chains (Baigude et al., 2007). The target gene was apoB and the mRNA expression silencing efficiency was, first, investigated *in vitro* using mouse liver cells (FL83B) and the results were comparable to Lipofectamine 2000 which is an industrial standard for gene delivery into cells. The *in vivo* silencing efficiency was highest at 1 mg/kg (reasonable dosage to be used in a therapeutic application) but did not increase past that concentration. Results of this study suggest that using both the cationically charged dendrimer and the chemically modified siRNA most efficiently silences the oligonucleotide.

Amine terminated or functionalized nanocarriers with PEGylated sub-units within the polymeric species were previously designed for complexation and delivery of siRNA to a human hepatoma cell line (HuH-7 cells) to knockdown transfected luciferage genes as well as the endogeneous Lamin A/C gene with excellent efficiencies (Itaka et al., 2004). Three amine variations were tested and compared; the dipropylene triamine moiety instilled supramolecular nanocarrier provided the best gene silencing ability. The other two were poly(L-lysine) and poly(3-dimethylamino)propyl aspartamide containing nanocarriers. The carrier with the dipropylene triamine has pKa values of 9.9 and 6.4 which allow facile siRNA complexation and sufficient buffering capabilities inside the endosome. In addition, the PEG unit within the dipropylene triamine nanocarrier allowed stable complexes to form with siRNAs even under 50% serum conditions and, in fact, the siRNA-nanocarrier complex even suppressed the endogeneous gene of Lamin A/C, a cytoskeletal protein abunduntly expressed in the cell. Kataoka and co-workers, furthermore, introduced a bioconjugate which covalently links siRNA with lactosylated PEG via an acid-labile linkage (size between 90–145 nm with approximately 36 PEG repeats) based on the fact that endosomes have a pH of about 5.5 and internalization of the conjugate will release the siRNA (Oishi et al., 2005, 2007). It is worth noting that PEGylation provides prolonged circulation time *in vivo* (Ogris et al., 1999) and has since emerged as one of the key functionalization tools for developing pharmaceuticals and nanobiocomposites for biomedical usages (Ballou et al., 2004; Brocchini et al., 2006; Harris and Chess, 2003; Kostiainen et al., 2007; Mishra et al., 2004; Petersen et al., 2002; Tang et al., 2003; Tu and Tirrell, 2004).

Inorganic based nanoparticles have also been utilized successfully for siRNA delivery and analysis. Bakalova and Ohba with fellow researchers utilized a synthetic inorganic core—shell and fluorescent nanoparticle made out of CdSe/ZnS (quantum dots; QD) to multifunctionalize

and screen for siRNA sequences. FRET (fluorescence resonance energy transfer) was the main tool for RNA analysis which was done after hybridizing the prepared QD-siRNA probe with Cy5 labeled target mRNA (isolated from K-562 leukemia cells) (Kubo et al., 2008). In an earlier study by Bhatia and co-workers, commercially available QDs that were PEGylated were further functionalized with tumor-homing peptides and siRNA and then used to silence gene (s) after targeting a specific cell (Derfus et al., 2007). Calcium phosphate nanoparticles (approximately 100 nm in size) were also effective in silencing the EGFP gene in HeLa cells in conjunction with siRNAs (Sokolova et al., 2007). In addition, gold nanoparticle (sized approximate 13 nm) decorated with thiol-modified oligonucleotides (i.e. antisense and locked nucleic acid) were also shown to be very effective in entering the target cell and stopping a specific translational process in a non-toxic and controlled manner by the Mirkin group (Rosi et al., 2006; Seferos et al., 2007).

McKnight and co-workers have demonstrated a non-particle based system for RNA interference by using vertically aligned carbon nanofibers to deliver multiple genes (i.e. small hairpin RNA (shRNA) vector and YFP marker gene) which will silence the cyan fluorescent protein (CFP) synthesis in the presence of tetracycline in Chinese hamster ovary cells (CHO-K1) (Mann et al., 2008). Previously, similar platform of materials were utilized to delivery DNA into living cells with good efficiency (McKnight et al., 2003; McKnight et al., 2004). This is very similar to the approach mentioned earlier in the review which highlights the work by Kim et al. (2007c) where GFP plasmid DNA is delivered using silicon nanowires.

RNA dumbbells or nanocircular RNAs (Fig. 12) consisting of 23 base pairs (firefly luciferase gene) and two 9-mer loops were designed and utilized as siRNA precursors after they were processed by the Dicer enzyme inside the cell (Abe et al., 2007). The stem-loop (design) combination allows the RNA dumbbells to be resistant to nucleases and provide a slow-acting RNAi profile. Design concept of this kind will allow the development of well-defined RNAi systems that will effectively silence gene expressions in a highly controllable and non-toxic manner.

## 5. Conclusions

Size means everything in linking nanotechnology together with biotechnology. Much biotechnology relies heavily on biomolecules such as proteins and DNA. Research in the field of neuroscience will definitely benefit with the advent of chemical and materials synthesis (e.g. multifunctional nanoparticle systems) that allows incorporation of these biomolecules to nanostructured inorganic and organic materials. The foremost areas are likely to involve bioimaging, biomedical-diagnostics, drug delivery, tissue engineering, and neuronal (network) systems studies. Most particularly, studies involving stem cell differentiation and transplantation, neural implants, targeted drug delivery with real-time monitoring capabilities, *in vivo* RNAi will prove very attractive. Multidisciplinary approaches will allow these sorts of projects to be successful research efforts and eventually lead to innovations that will ultimately help mankind. Close collaborations among researchers with different backgrounds will succeed best when nanostrutures are created and characterized by chemists and materials scientists and implementation of nanomaterials in specific biomedical applications are done by neuroscientists and clinicians. Most importantly, the roles of scientists trained and having experience working at the interface of biotechnology and nanotechnology will play increasingly important roles in the new wave of biomedical research and application. The scientific language and the way research is conducted, valued and evaluated between scientific disciplines have subtle differences which can slow down and even act as sources of deterrents in the road to a successful collaboration. Nanobiotechnology (or bionanotechnology) has advanced significantly now that synthesis and implication of applications need to be followed by practical and realistic usages. New advances, especially in neuroscience, will arise from

systematic investigations starting from synthesis to application where the central efforts are probing and understanding events occurring at the nano—bio interface.

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## Abbreviations

| | |
|---|---|
| 3T3 | derived from primary mouse embryonic fibroblast cells, 3-day transfer, inoculum $3 \times 10^5$ cells |
| A-431 (or A431) | human epithelial carcinoma cell line |
| A549 | human lung epithelial cell line |
| Ab | antibody |
| Aβ | amyloid beta |
| AD | Alzheimer's disease |
| ADDL | amyloid β-derived diffusible ligand |
| AFM | atomic force microscopy |
| AM | alveolar macrophages |
| APP | amyloid precursor protein |
| AsPC-1 | human pancreatic cancer, epithelial cell line |
| A*STAR | Agency for Science Technology and Research |
| ATP | adenosine triphosphate |
| BAL | bronchoalveolar lavage |
| BBB | blood—brain barrier |
| BD-AM | primary alveolar macrophages from beagle dogs |
| BEAS-2B | human bronchial epithelial cell lines |
| BET | Brunauer, Emmett and Teller |
| β-Gal | β-galactosidase |
| bipy | 2,2′-Bipyridine |
| BRL 3A | rat liver derived cell lines |

| | |
|---|---|
| BSA | bovine serum albumin |
| BV2 (or BV-2) | murine brain microglia |
| C57BL/6 | C57 black 6, most common inbred lab mouse |
| CAT | catalase |
| CBEN | Center for Biological and Environmental Nanotechnology |
| CFP | cyan fluorescent protein |
| CFU | colony forming unit |
| CNS | central nervous system |
| CNT | carbon nanotubes |
| Colon-26 (or Colon 26) | murine rectum carcinoma cell line |
| CREKA | Cys-Arg-Glu-Lys-Ala |
| CRL8798 | normal breast epithelial cell line |
| CRP | C-reactive protein |
| DHED | dehydroevodiamine hydrochloride |
| DLS | dynamic light scattering |
| DMEM | Dulbecco's Modified Eagle's Medium |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| DOX | doxorubicin |
| EC | endothelial cell |
| $EC_{50}$ | half maximal effective concentration |
| EGFP | enhanced GFP |
| EM | electron microscopy |
| ESEM | environmental SEM |
| FITC | fluorescein isothiocyanate |
| FRET | fluorescence resonance energy transfer |
| GAP-43 | growth associated protein-43 |
| GAPDH | glyceraldehyde-3-phosphate dehydrogenase |
| GFP | green fluorescent protein |
| GPX (GPx or GSH-Px) | glutathione peroxidase |
| GR | glutathione reductase |
| GSH | glutathione |
| H&E staining | hematoxylin and eosin staining |
| HA | hydroxyapatite |
| HAEC | human aortic endothelial cell |
| HEK293 | human embryonic kidney 293 cells |

| | |
|---|---|
| HeLa | human cervical cancer cell line derived from Henrietta Lacks |
| HER | human epidermal growth factor receptor |
| hMSC | human mesenchymal stem cell |
| HPRT | hypoxanthine-guanine phosphoribosyltransferase |
| HRTEM | high resolution transmission electron microscope |
| HT-1080 (or HT1080) | human fibrosarcoma cell line |
| HT-22 (or HT22) | mouse hippocampal nerve cell line |
| IACUC | Institutional Animal Care and Use Committees |
| IBN | Institute of Bioengineering and Nanotechnology |
| ICON | International Council on Nanotechnology |
| ICP-MS | inductively coupled plasma mass spectrometry |
| IEP | isoelectric point |
| IMN | immuno-magnetic nanoparticle |
| ISI | Institute for Scientific Information |
| IUPAC | International Union of Pure and Applied Chemistry |
| J774A.1 | murine macrophage |
| Jurkat | human T lymphocyte cell line |
| K-562 (or K562) | human myelogenous leukemia cell line |
| L929 | murine fibroblast |
| LBNL | Lawrence Berkeley National Laboratory |
| LDH | lactate dehydrogenase |
| $LD_{50}$ | lethal dose for 50% of population |
| LPO | lipid peroxidation |
| MCF | mesocellular siliceous foam |
| MCF-7 | human breast carcinoma cell line |
| MCM-41 | Mobil Catalytic Material number 41 |
| MCP-1 | monocyte chemoattractant protein |
| MDA | malondialdehyde |
| MFNPS | multifunctional nanoparticle system |
| MG63 | osteoblast-like cells |
| miRNA | microRNA |
| MN | micronuclei |
| MOF | metal-organic framework |
| MR | magnetic resonance |
| MRC-9 | human lung fibroblast |
| MRI | magnetic resonance imaging |

| | |
|---|---|
| mRNA | messenger RNA |
| MDA-MB-231 | human metastatic breast cancer cell |
| MSDS | Materials Safety And Data Sheet |
| MSTO | human mesothelioma |
| MTT | (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay |
| MWCNT | multi-walled carbon nanotube |
| N/A | not available |
| NCI | National Cancer Institute |
| NCL | Nanotechnology Characterization Laboratory |
| NGF | nerve growth factor |
| NIH | National Institute of Health |
| OECD | Organisation for Economic Co-operation and Development |
| ORMOSIL | organically modified silica or silicate |
| PAA | poly(aspartic acid) |
| PANC-1 | human pancreatic carcinoma cell line |
| PBS | phosphate buffer saline |
| PC12 | cancer cell line derived from a pheochromocytoma of the rat adrenal medulla |
| PDMS | poly(dimethylsiloxane) |
| PEG | polyethylene glycol |
| PEI | polyethyleneimine |
| PLGA | poly(lactide-co-glycolide) |
| PLLA | poly(L-lactic acid) |
| PM | particulate matter |
| ppb | parts per billion |
| ppm | parts per million |
| QC | Quikclot® |
| QD | quantum dot |
| RAW164 | murine macrophage cell line |
| RAW 264.7 | mouse leukemia macrophage cell line |
| RBC | red blood cell |
| RIF-1 | murine fibroblastic sarcoma cell line |
| RNA | ribonucleic acid |
| RNAi | RNA interference |
| ROS | reactive oxygen species |
| SBA-15 | Santa Barbara Amorphous 15 |

| | |
|---|---|
| SBF | simulated body fluid |
| SCE | sister-chromatid exchange |
| SEM | scanning electron microscope |
| SH-SY5Y | a third generation human neuroblastoma derived from SH-SY5 |
| SiNW | silicon nanowires |
| siRNA | small interfering RNA |
| SMMC-7721 | human hepatoma (liver cancer) cell line |
| SOD | superoxide dismutase |
| SPIO | superparamagnetic inorganic or iron oxides |
| SPION | superparamagnetic inorganic or iron oxide nanoparticle |
| SRB | sulforhodamine B assay |
| SWCNT | single-walled carbon nanotube |
| TEM | transmission electron microscope |
| TEOS | tetraethyl orthosilicate |
| THB-1 | human alveolar macrophage |
| THP-1 (or THP1) | human acute monocytic leukemia cell line |
| TNF-α | tumor necrosis factor-alpha |
| TUNEL | terminal uridine deoxynucleotidyl transferase dUTP nick end labeling |
| U297 | human lymphoblast |
| UF | ultrafine |
| USPIO | ultrasmall superparamagnetic iron oxide |
| UV | ultraviolet |
| VMD | visual molecular dynamics |
| WIL2-NS | human B-cell lymphoblastoid cell line |
| WSIO | water-soluble superparamagnetic iron oxides |
| WST-1 | water-soluble tetrazolium number 1, (2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium) assay |
| WT | wild type |
| XPS | X-ray photoelectron spectroscopy |
| XTT | (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) |
| YFP | yellow fluorescent protein |

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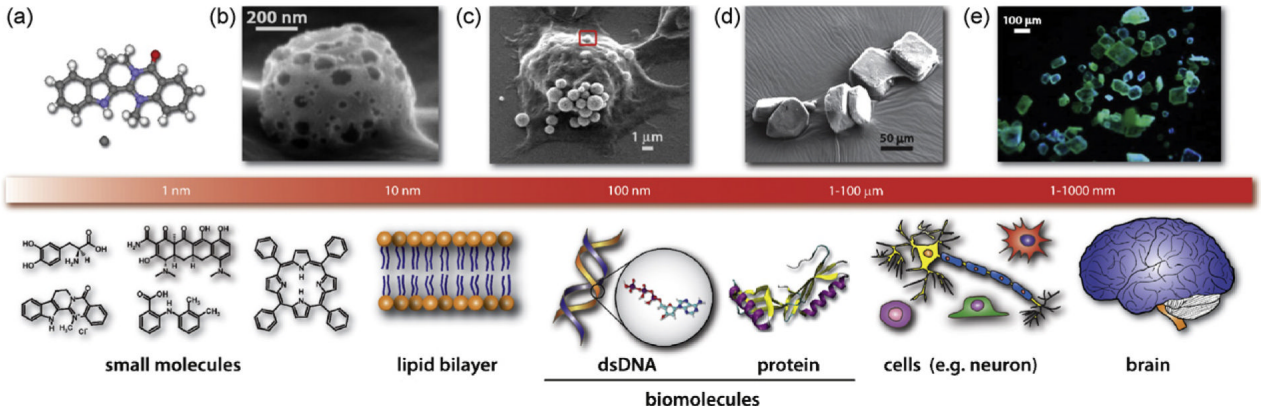



**Fig. 1.**

The sizes of biologically relevant entities. (Top row above scale bar) From left to right: (a) Potent Alzheimer's disease candidate drug, dehydroevodiamine HCl (DHED) X-ray crystal structure, (b and c) porous metal oxide microspheres being endocytosed by BV2 microglia cell (close-up and low magnification) SEM images, (d and e) SEM and fluorescence micrograph of DHED microcrystals (DHED is blue-green luminscent). (Bottom row below the scale bar) Left to right: Small molecules, such as dopamine, minocycline, mefenamic acid, DHED, and heme, are ~1 nm or smaller. The lipid bilayer is a few nanometers thick. A biomolecule such as a (22 bp) microRNA and a protein is only a few nanometers in size. A single cell or neuron is tens or hundreds of microns in size. Illustration of a human brain which is tens of centimeters in size.

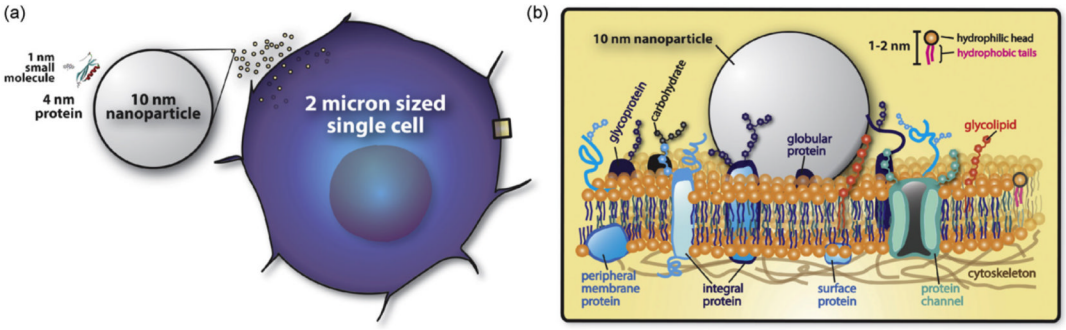



**Fig. 2.**

Size matters. (a) Compared to a 10 nm nanoparticle, proteins (e.g. APP; X-ray crystal structure obtained from www.pdb.org (Berman et al., 2000), protein ID 2FKL; visualization done by Accelrys Discovery Studio Visualization 1.7 software) and small molecules (e.g. DHED) are small in size and volume. A mammalian cell which is made up of proteins, nucleic acids, and other small to large molecules is thousand times larger in volume and size compared to a 10 nm nanoparticle. (b) Cell membrane incorporating various proteins and a single 10 nm nanoparticle.

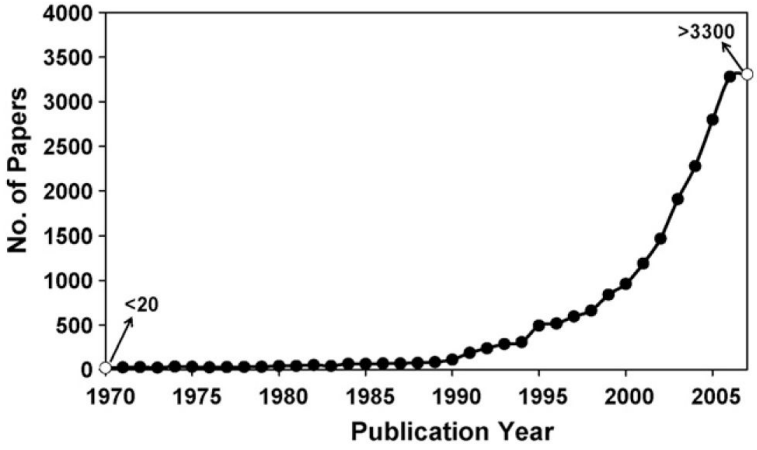



**Fig. 3.**

Published papers in nanomaterials synthesis papers published in 1970–2007. Number of publications was obtained from ISI Web of Science (one of Thomson Scientific databases and part of Web of Knowledge) using a combination of search terms that represent nanomaterial and synthesis.

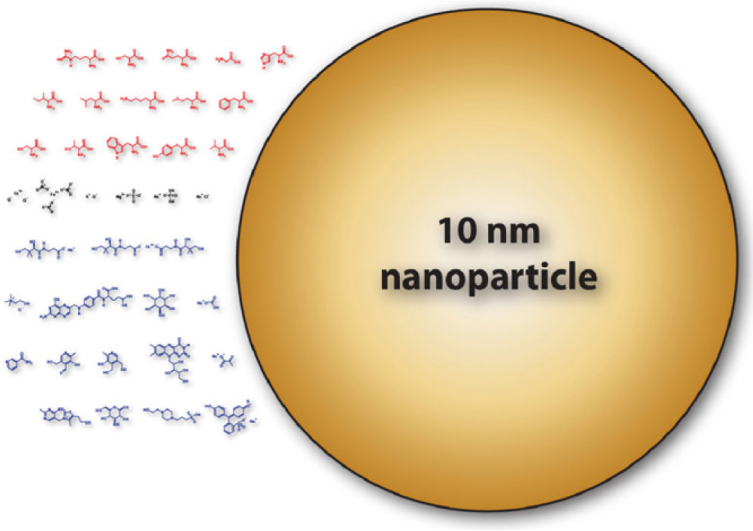



**Fig. 4.**

Contents of DMEM vs. 10 nm nanoparticle. Red chemical structures (first three rows) represent amino acids, black chemical structures (fourth row) represent inorganic salts, and blue structures (rows 5–8) represent vitamins and other small organic molecules. The contents information of DMEM (Dulbecco's Modified Eagle's Medium) were readily available on-line at various biochemical vendor websites such as HyClone and Sigma—Aldrich.

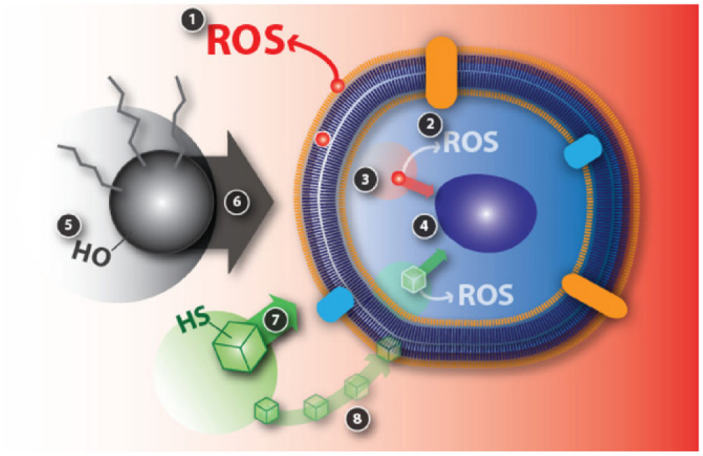



**Fig. 5.**

Cell and particle interactions. Toxicological effects of nanomaterials can be simplified into eight events as shown in the illustration above but limiting the interaction between a nanoparticle and a cell to eight events is an over simplification and the details of actual phenomena that are happening at the interfaces are very difficult to analyze and understand. (1) Reactive oxygen species products such as superoxide ($^{\bullet}O_2^-$) and hydroxyl radical ($^{\bullet}OH$) whether it is inside or outside can be key factors in nanostructured materials toxicological effects (Nel et al., 2006). Cell membrane integrity leading to cell survivability will be affected by ROS produced by a nanoparticle smaller than a cell (red particle) as shown. (2) Event 2 represents the situation where a nanoparticle is internalized and then creates ROS products (Nel et al., 2006). (3) Particle dissolution affecting cellular function after nanoparticle internalization is event 3 (Borm et al., 2006). (4) Event 4 represents any mechanical damage to sub-cellular units such as the lysosome, endoplasmic reticulum, and nucleus (Yamamoto et al., 2004). (5) Different functional groups and surface electronic structures arising from different nanostructured materials will determine the level of interaction between the nanoparticles and their surroundings which is represented by event 5 (Karakoti et al., 2006; Kostarelos et al., 2007). (6) Overall size of the particle can play an important role as represented by event 6 since large particles can potentially induce permanent damage to the cell membrane while small particles can pass through the membrane and do harm inside cell (Yoshida et al., 2003). (7) Non-spherical particles, on the other hand, might have a different biological response compared to the spherical nanoparticles which is shown as event 7 (Geng et al., 2007). (8) Event 8 represents dissolution characteristics of the nanomaterials outside the cell which can affect the cell in various ways (event 8) (Borm et al., 2006).

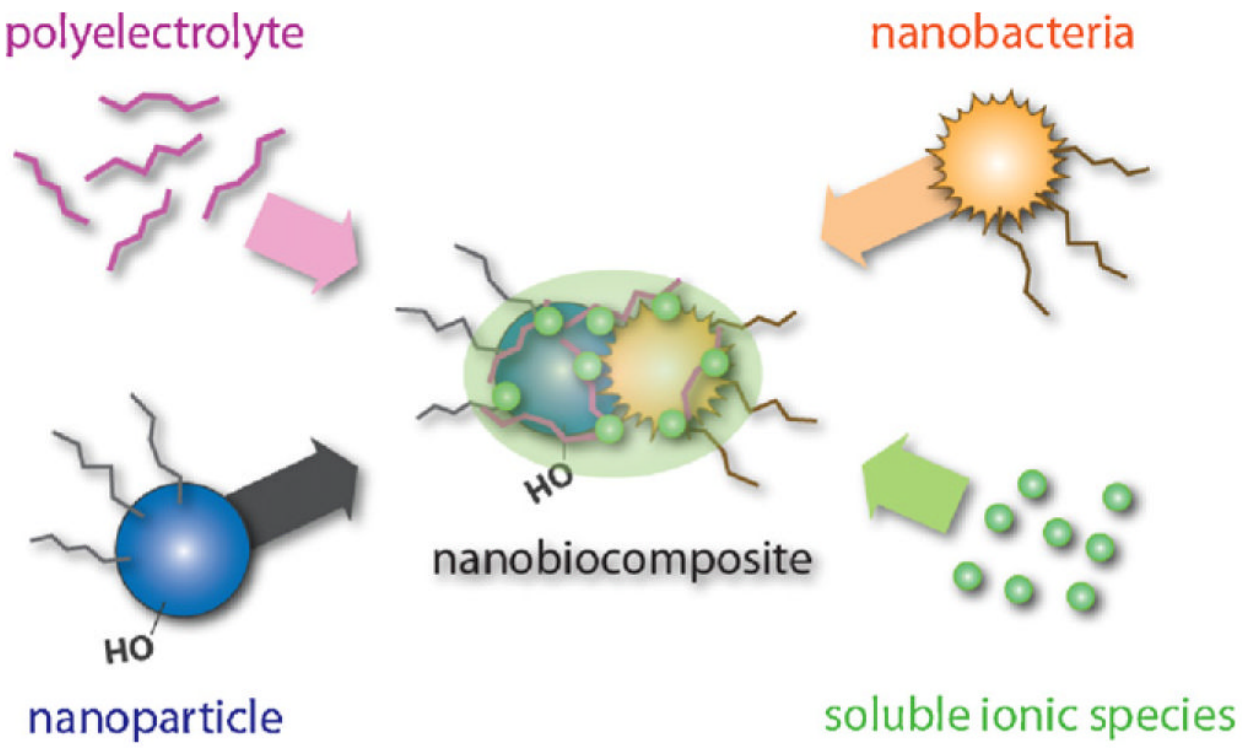



**Fig. 6.**

Nanobiocomposite formed from a nanoparticle (sub-micron) and a nanobacteria (e.g. mycoplasma; sub-500 nm). This event is probable to happen under biogenic conditions where polyelectrolytes (e.g. peptide) and soluble ionic species (e.g. $Ca^{2+}$, $Na^{+}$) are readily available. Sub-micron engineered nanoparticles can form new composite materials with mycoplasma and the new nanobiocomposite material can have vastly different chemistries and physical properties which will lead to different biological properties.

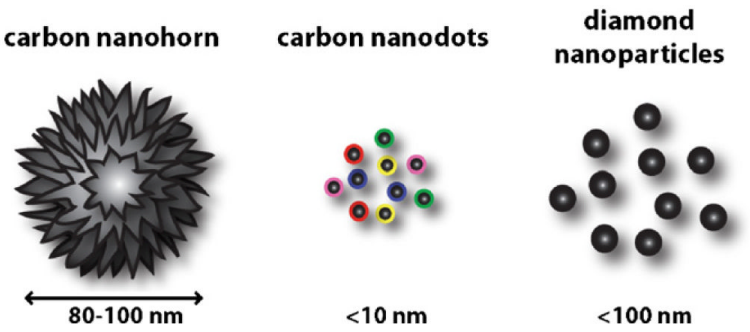



**Fig. 7.**

Spherical and non-tubular carbon nanomaterials. Sub-100 nm carbon nanoparticles that are other than $C_{60}$ or carbon nanotubes will offer another set of tools for neuroscientist as well as other biologists. Illustrations were prepared based on data, schemes, and figures appearing in the references with permission from the publisher.

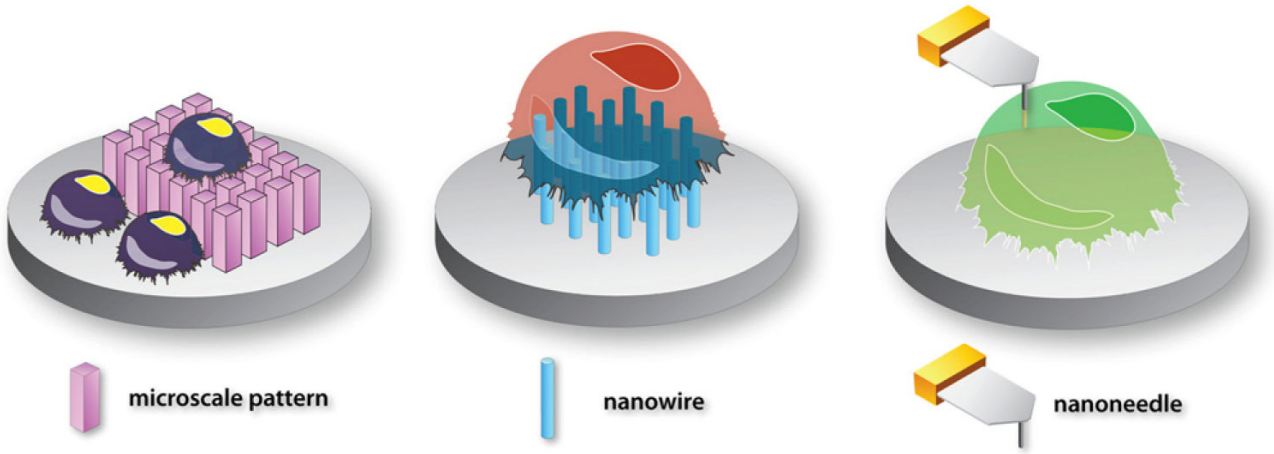



**Fig. 8.**

Controlling cell function by microscale patterns and nanowires. Details are provided for the top three illustrations in the maintext. Making sub-micron patterns as well as functionalizing the sub-patterns with unique nanostructures such as wires and pores will be very interesting to utilize in neuroscience, especially studying interacting neurons and neuronal implants *in vivo*.

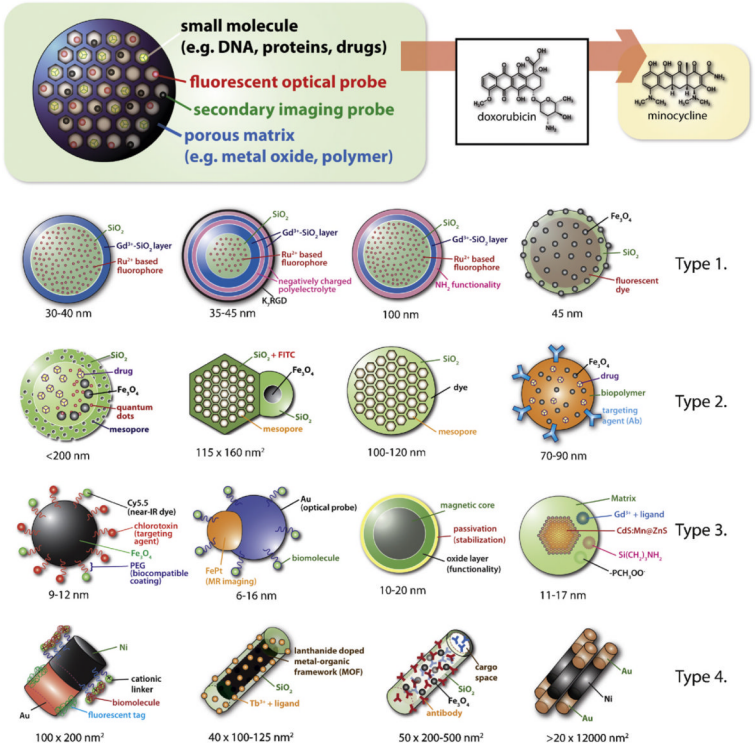



**Fig. 9.**

Multifunctional nanoparticle systems (MFNPS) for biomedical applications. MFNPSs can be divided into four distinctive types. Type 1 is non-porous but spherical $SiO_2$ based sub-100 nm nanoparticles with two or more components. Type 2 is sub-200 nm spherical nanoparticles that is either porous or can incorporate and, in time, release small molecules such as drug molecules. Type 3 is sub-20 nm nanoparticles with functionalizable ligands or biomolecules stabilized (passivated) onto the nanoparticles and are, in most cases, first synthesized in organic conditions which offer good size control and then phase exchanged to become dispersable in aqueous media. Finally, type 4 is non-spherical nanoparticle systems that have multiple components such as fluorescent tags and antibodies. Illustrations were prepared based on data, schemes, and figures appearing in the references of Table 5 with permission.

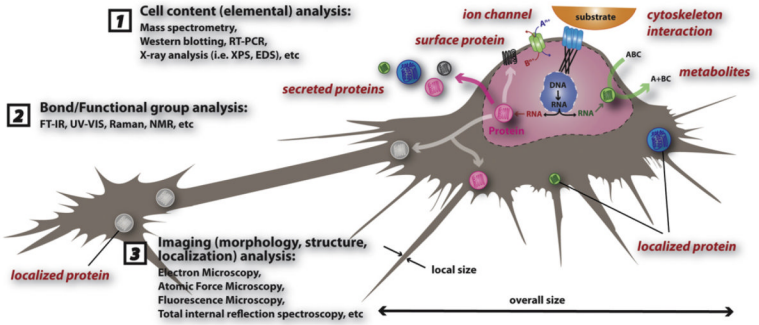



**Fig. 10.**

Analysis of a cell. Sub-components of a cell include (but not exclusive) nucleic acids, membrane fractions, proteins (e.g. secreted, surface displaying, localized), ion channels, and cytoskeletal components. Considering the nature of such sub-cellular components and products three categories of analyses can be drawn: (1) cell content (elemental) analysis, (2) chemical bond/functional group analysis, (3) imaging (morphology, structure, localization) analysis.

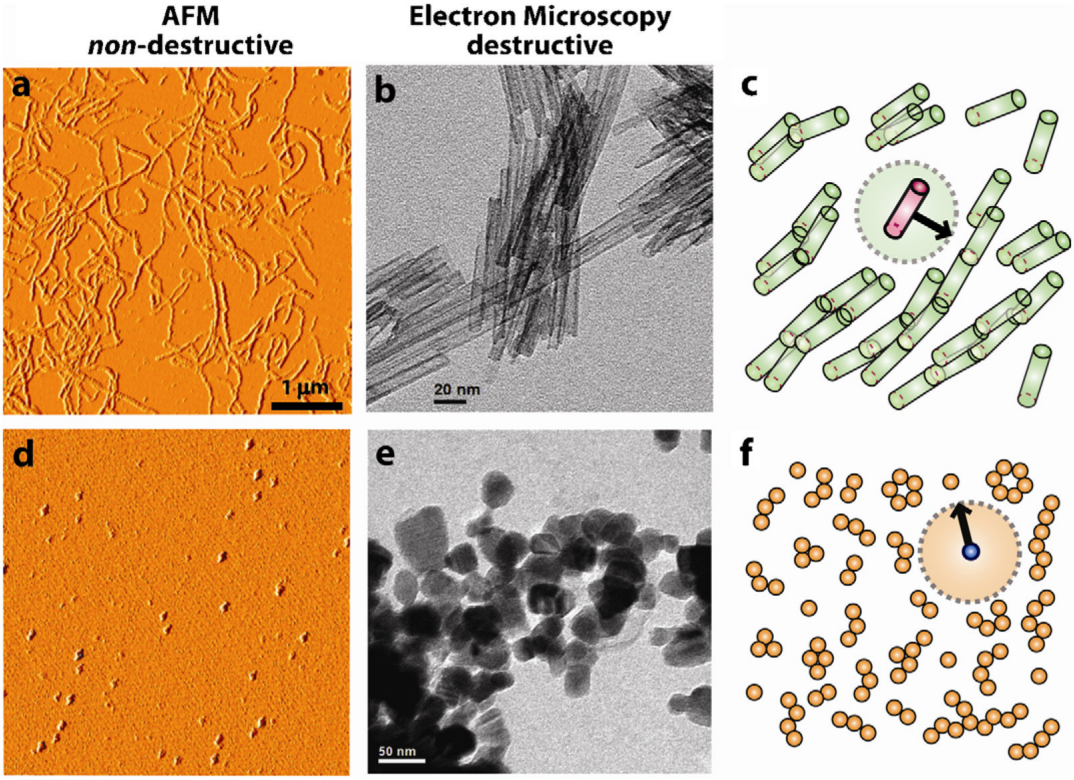



**Fig. 11.**

Nanoscale imaging of biomolecules and inorganic materials. (Top row) high aspect ratio nanomaterials (e.g. fibrillar, tubular, and rod shaped); (bottom row) low aspect ratio nanostructures (e.g. oligomeric, spherical, and sub-100 nm nanoparticles). (a) AFM image of Aβ, tubular form. (b) TEM image of titanium oxide nanotubes. (c) Illustration representing crystallization schemes for high aspect ratio nanomaterials. (d) AFM image of Aβ, oligomeric form. (e) TEM image of titanium oxide nanoparticles. (f) Illustration representing crystallization schemes of spherical nanomaterials. (a) and (d) (the AFM data) were adapted from reference Heo et al. (2007) with permission from the publisher.

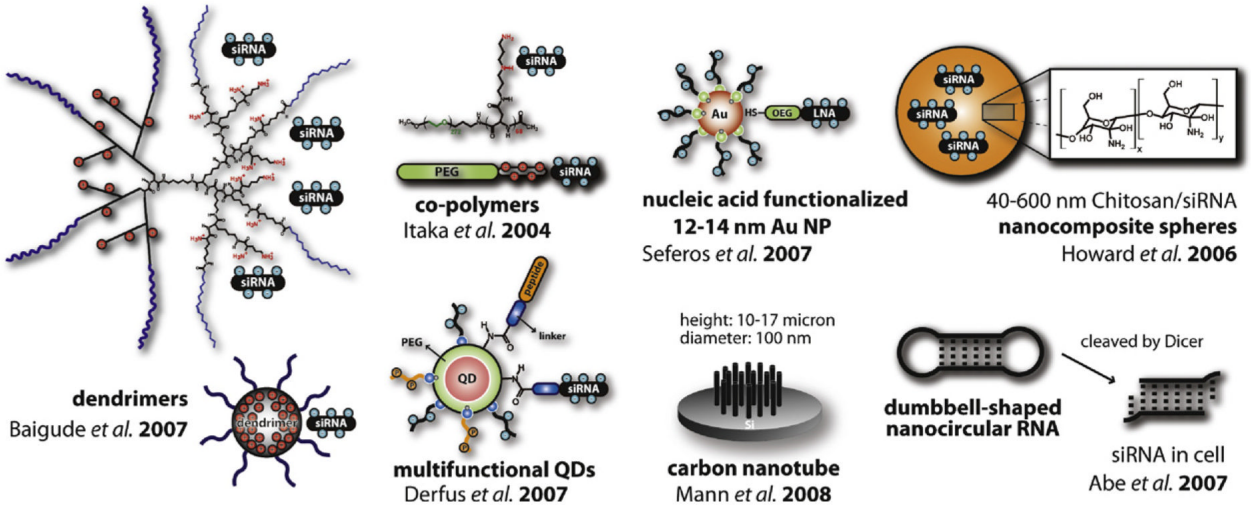



**Fig. 12.**

RNA interference vehicles. Various shapes and forms are used as tools to deliver RNA that will selectively silence gene translation; examples include dendrimers, copolymers, nucleic acid decorated Au NPs, nanocomposite spheres, multifunctional QDs, carbon nanotube arrays, and nanocircular RNAs. Illustrations were prepared based on data, schemes, and figures appearing in the references with permission from the publisher.

**Table 1**

$TiO_2$ nanotoxicology

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 1 Manufactured $TiO_2$ | • Anatase<br>• Rutile | • 5–40 nm/1–2 μm aggregate (surf. area = 55 $m^2$/g)<br>• 2–60 nm/0.5–1.5 μm agg. (surf. area = 125 $m^2$/g)<br>• Sizing by TEM | • Murine alveolar macrophage (RAW 264.7)<br>• Human alveolar macrophage (THB-1)<br>• Human lung epithelial cell line (A549) | Up to 10 μg/mL | *In vitro* bioassays<br>MTT assay | • RAW 264.7 murine alveolar macrophage cell line $EC_{50}$ (anatase) = 10 μg/mL $EC_{50}$ (rutile) = non-cytotoxic<br>• THB-1 human alveolar macrophage cell line $EC_{50}$ (anatase) = 5 μg/mL $EC_{50}$ (rutile) = non-cytotoxic<br>• A549 human epithelial cell line $EC_{50}$ (anatase) = 1 μg/mL $EC_{50}$ (rutile) = non-cytotoxic<br>• $TiO_2$ can be considered non-cytotoxic compared to Ag, $Al_2O_3$, $Fe_2O_3$, $ZrO_2$, $Si_3N_4$, asbestos, carbon nanoparticles | Soto et al. (2007) |
| 2 Manufactured $TiO_2$ | • 80% Anatase ($TiO_2$-1)<br>• Rutile ($TiO_2$-2)<br>• Anatase ($TiO_2$-3) | • 5–100 spherules/ 0.5–1 μm agg.<br>• 5–15 nm short fibers/0.5–1.5 μm agg.<br>• 5–40 nm spherules/ 1–5 μm agg.<br>• Sizing by TEM | Murine alveolar macrophage (RAW 264.7) | Up to 10 μg/mL | *In vitro* bioassays<br>MTT assay | • $EC_{50}$ ($TiO_2$-1, 80% anatase) = 10 μg/mL<br>• $EC_{50}$ ($TiO_2$-2, rutile) = non-cytotoxic<br>• $EC_{50}$ ($TiO_2$-3, anatase) = 10 μg/mL<br>• $TiO_2$ can be considered non-cytotoxic compared to Ag, $Al_2O_3$, $Fe_2O_3$, $ZrO_2$, $Si_3N_4$, asbestos, carbon nanoparticles | Soto et al. (2005) |
| 3<br>• DuPont ultrafine rutile $TiO_2$ (uf-1)<br>• DuPont ultrafine rutile $TiO_2$ (uf-2)<br>• Degussa P25 (uf-3)<br>• DuPont rutile R-100 fine-$TiO_2$ (F-1) | • Rutile<br>• Anatase<br>• 80/20 = Anatase/ rutile<br>• Rutile 99%, alumina coat 1%<br>• Crystalline silica | • 2.1–2.9 μm in PBS<br>• 129–382 nm in water<br>• Sizing by DLS<br>• Surface areas: F-1 = 5.8, uf-1 = 18.2, uf-2 = 35.7, uf-3 = 53.0 $m^2$/g | 8-week-old male rats (210–280 g in weight) | • 1 or 5 mg/kg intratracheal instillation<br>• PBS instilled rats were vehicle controls | *In vivo* lung toxicity assessment<br>**1** Bronchoalveolar lavage (BAL) fluid inflammatory marker evaluation<br>**2** Cell proliferation<br>**3** Histopathology | • Toxic ranking: quartz > uf-3 > F-1 = uf-1 = uf-2<br>• uf-3 anatase/rutile $TiO_2$ particles produced pulmonary inflammation, cytotoxicity and adverse lung tissue effects<br>• Inhaled rutile ultrafine- $TiO_2$ particles are expected to have a low risk potential for producing adverse pulmonary health effects | Warheit et al. (2007) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| • α-Quartz particles | | | | | | • Cannot assume that all nanoparticle $TiO_2$ are toxic | |
| 4<br>• Nano-sized $TiO_2$ particles (Hangzhou Dayang Nanotechnology)<br>• Fine $TiO_2$ particles (Zhonglian Chemical Medicine) | N/A | • 25 nm<br>• 80 nm<br>• 155 nm<br>• Sizing by TEM | Adult mice (19 ± 2 g in weight) | • 5 g/kg (due to low toxicity)<br>• Single oral administration (OECD Guidelines, No. 420) | *In vivo*<br>**1** Histopathology of the brain, kidneys, liver, and the stomach tissues (hematoxylin–eosin staining)<br>**2** Blood biomarker assay<br>**3** Titanium ICP-MS | • $TiO_2$ particles showed no obvious acute toxicity in two weeks<br>• Female mice liver affected by 25 and 80 nm $TiO_2$<br>• Hapatic injury observed due to various levels of $TiO_2$ exposure<br>• $TiO_2$ gets retained in the liver, spleen, kidneys, and lung tissues (ICP-MS analysis) | Wang et al. (2007b) |
| 5 Sigma–Aldrich nano-sized or ultrafine $TiO_2$ (UF-$TiO_2$) | 99% $TiO_2$ but no crystal phase given | Sub-100 nm | Human B-cell lymphoblastoid cell line (WIL2-NS) | • 0, 26, 65 and 130 μg/mL<br>• 6, 24, 48 h | *In vitro* bioassays<br>**1** MTT assay<br>**2** Population growth assay<br>**3** Apoptosis assay (flow cytometry)<br>**4** Cytokinesis-block micronucleus assay<br>**5** Comet assay<br>**6** HPRT gene mutation assay | • Significant decreases in viability were seen in the MTT assay at higher doses (130 μg/mL)<br>• UF-$TiO_2$ can cause genotoxicity and cytotoxicity in cultured human cells. | Wang et al. (2007a) |
| 6<br>• Pigment-grade $TiO_2$<br>• Nanoscale $TiO_2$ rods<br>• Nanoscale $TiO_2$ dots<br>• Quartz | • Rutile<br>• Anatase<br>• Anatase<br>• Crystalline silica | • 300 nm (6 $m^2$/g)<br>• 92–233 nm × 20–35 nm (26.5 $m^2$/g)<br>• 5.8–6.1 nm spheres (169.4 $m^2$/g)<br>• 1–3 μm (4 $m^2$/g)<br>• TEM sizing | • 8-week-old rats (240–255 g in weight)<br>• Lung parenchymal cells of rat | • 1 or 5 mg/kg intratracheal instillation<br>• PBS instilled rats were vehicle controls | *In vivo* pulmonary bioassays<br>**1** Bronchoalveolar lavage (BAL) fluid inflammatory marker evaluation<br>**2** Cell proliferation<br>**3** Histopathology | • No significant lung toxicity difference observed for $TiO_2$ nanorods and nanodots<br>• Results not in line with previous studies which link increased surface area to being more toxic<br>• Further study required to address particle size and surface area effects on lung toxicity | Warheit et al. (2006) |
| 7 Sigma Titanium dioxide ($TiO_2$) | N/A | N/A | • Human whole blood cultures from four non-smoking healthy donors | • 1, 2, 3, 5, 7.5 and 10 μM | *In vitro* bioassays<br>• Blood examination (oxidative stress markers) | • DNA damage by oxidative stress observed<br>• GSH-Px, GR, CAT, SOD activity decrease | Turkez and Geyikoglu (2007) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| | | | | • Sterile DMSO stock solution<br>• Dilution in water | **1** Glutathione peroxidae (GSH-Px)<br>**2** Glutathione reductase (GR)<br>**3** Catalase (CAT)<br>**4** Superoxide dismutase (SOD)<br>**5** Sister chromatid exchange (SCE)<br>**6** Micronuclei (MN) | • Sister-chromatid exchanges (SCEs) and micronuclei (MN) frequency increase<br>• $TiO_2$ is a potential genotoxic agent for blood cells | |
| 8<br>• DegussaTiO$_2$<br>• Nanocrystalline synthetic TiO$_2$ (nano-TiO$_2$) | • Anatase/rutile = 80/20<br>• Anatase<br>• Anatase/rutile = 60/40<br>• Rutile | • ~21 nm<br>• 10.1 ±1.0 nm<br>• 3.2 ±0.34 nm<br>• 5.2 ±0.65 nm | Human lung epithelial cell line (A549) | 3 μg/mL to 30 mg/mL | *In vitro* bioassays<br>**1** Viability<br>**2** Live/dead staining<br>**3** LDH release<br>**4** MTT assay | • Cytotoxicity and inflammation observed over 100 μg/mL concentration<br>• Reactive oxygen generation results in increased cytotoxicity<br>• Anatase $TiO_2$ produced the most ROS thus was 100 times more cytotoxic compared to rutile under light conditions | Sayes et al. (2006) |
| 9 $TiO_2$ microspheres | Anatase | • Average 1 μm spheres made up of sub-20 nm $TiO_2$<br>• SEM, TEM sizing | • Murine brain microglia (BV2)<br>• Rat adrenal pheochromocytoma (PC12)<br>• human neuroblastoma (SH-SY5Y) | • <1 μg/μL<br>• 6 h to 6 days | *In vitro* bioassays<br>**1** WST-1 assay<br>**2** Endocytosis | • Non-cytotoxic up to 10 μg per $10^4$ initial cells<br>• Toxicity was observed for Co doped $TiO_2$ | Suh et al. (2006b) |
| 10 Degussa P25 | Anatase/rutile = 70/30 | • ~30 nm/826 nm to 2368 nm aggregates | • Murine brain microglia (BV2) | • 2.5–120 ppm<br>• 6–18 h | *In vitro* bioassays<br>**1** CellTiter-Glo assay<br>**2** ROS assays | • Stimulate microglia to produce ROS<br>• Neurotoxicity implication | Long et al. (2006) |
| 11 NanoTiO$_2$ | Rutile | NanoTiO$_2$ (19–21 nm) microparticles (180–250 nm) | • THP-1 cell lines<br>• A549 cell lines | 0.1 or 0.5 mg (intratracheal) | Immunostaining<br>TUNEL staining | Pulmonary inflammatory response from 20 nm $TiO_2$ | Chen et al. (2006a) |
| 12 Flame synthesized | N/A | 8 nm | • Human mesothelioma<br>• Rodent fibroblast cell lines (3T3) | 30 ppm for 3 days | *In vitro* bioassays<br>MTT assay total DNA measurement<br>DNA Hoechst assay | • Non-toxic up to 30 ppm for fibroblast<br>• Some toxicity shown for mesothelioma cell | Brunner et al. (2006) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 13<br>• Pigment-grade $TiO_2$<br>• Ultrafine $TiO_2$ (Degussa P25) | Rutile PG-$TiO_2$ | • PG-$TiO_2$ (200–300 nm)<br>• Ultrafine $TiO_2$ (10–20 nm) | Rats, mice and hamsters | • PG-$TiO_2$: 0, 10, 50, 250 mg/$m^3$<br>• UF-$TiO_2$: 0, 0.5, 2,10 mg/$m^3$ | Lung burden | High clearance rates (hamsters) | Hext et al. (2005) |
| 14 Ultrafine $TiO_2$ | Anatase, rutile | Anatase-sized (20 nm) | Human bronchial epithelial cell lines (BEAS-2B) | 0.01, 0.1, 1, 10 μg/mL for 3 days | *In vitro* bioassays MTT assay | Induce hydrogen peroxide (rutilesized 200 nm) | Gurr et al. (2005) |
| 15 Commercial (Altair) | N/A | 40 nm | Rat liver derived Cell lines (BRL3A) | 10, 50, 100, 250 μg/mL | *In vitro* bioassays MTT assay LDH assay glutathione levels | • No measurable effect (10–50 μg/mL)<br>• Toxic at high conc.(100–250 μg/mL) | Hussain et al. (2005) |
| 16 Commercial (Neturen, Ishihara Techno Corp.) | Anatase, rutile, mixture | • $TiO_2$-spherical: 30–50 nm<br>• $TiO_2$-spindly: 10–20 nm × 50–100 nm<br>• $TiO_2$-dendritic: 40–70 nm × 200–300 nm | • Murine fibroblast (L929)<br>• Murine macrophage (J774A.1) | Assays probed by varying number, surface area, and volume of the particles | *In vitro* bioassays Colony formation assay | • Macrophage cells predict cytotoxicity better<br>• Non-spherical $TiO_2$ lower cell viability | Yamamoto et al. (2004) |
| 17 N/A | N/A | 1–7 μm (longitudinal length) | Human lymphoblast (U937) | 0.125, 0.25, 0.5, 1, 2 mg/well | *In vitro* bioassays LDH assay | • $TiO_2$ particles are the least toxic<br>• $SiO_2$ > metal alloy > $Al_2O_3$ > $TiO_2$ | Yoshida et al. (2003) |
| 18 $TiO_2$/hydroxyapatite coated titania | N/A | N/A | Primary rat osteoblasts | $TiO_2$/HA ratio: 0.5, 1, 2 | *In vitro* bioassays MTT assay | Non-cytotoxic | Ramires et al. (2002) |
| 19<br>• f$TiO_2$ (Degussa)<br>• uf$TiO_2$ (Degussa) | | • 220 nm<br>• 20 nm | • Primary alveolar macrophages from beagle dogs (BD-AM),<br>• Macrophages (J774A.1) | 10–320 μg UFP/mL/$10^6$ cells up to 24 h | Apoptosis and necrosis | Fine $TiO_2$ did not show any effects (cytoskeletal dysfunction) | Moller et al. (2002) |
| 20 Commercial (Sigma Chemical Co.) | N/A | ~1 μrn | Pulmonary Alveolar Macrophages | 0.1, 0.5, 1, 5 mg/mL | *In vitro* bioassays MTT assay | Significantly lowered cell viability (0.5–5 mg/mL) | Kim et al. (1999) |
| 21 Ultrafine $TiO_2$ | | Sub-20 nm | • Alveolar macrophages (AM)<br>• Peripheral red blood cells (RBC) of rat | 5 mg; single intratracheal | • Lipid peroxidation (LPO)<br>• Glutathione peroxidase (GPx) | • Induction of $H_2O_2$ is maximum with crocidolite followed by chrysotile and minimum with UF-$TiO_2$ | Afaq et al. (1998a) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | | • Comparison to both the asbestos fibers, UF-$TiO_2$ induced far less toxicity | |
| 22 Ultrafine $TiO_2$ | | Sub-30 nm | Rat alveolar macrophages (AMs), cell-free lavage fluid | 2 mg per rat; single intratracheal | Lactate dehydrogenase | • Increased activities of LDH<br>• Induction of antioxidant enzymes by these cells for self-protection is not sufficient to cope against the toxic action of UF-$TiO_2$, which may lead to oxidative stress | Afaq et al. (1998b) |
| 23<br>• Degussa P25(UFl)<br>• UV-TITAN Ml60 (UF2)<br>• Pigmentary $TiO_2$ Kemira AFDC | • Uncoated anatase<br>• Rutile coated<br>• Uncoated anatase | • 20 nm<br>• 20 nm<br>• 170 nm | Rat liver epithelial cell lines | 0, 5, 10, 50, 100, 200 μg/$cm^2$ | Multinuclei assay (measure the inhibition of cell growth) | Ultrafine $TiO_2$ samples not toxic to cells at the concentration range of 5–200 μg/$cm^2$ | Linnainmaa et al. (1997) |
| 24 $TiO_2$-hexachloroethane and Zn-hexachloroethane pyrotechnic mixtures | | N/A | Female rats | • Concentration of smoke was varied (acute inhalation)<br>• Exposed to smoke for 1.25, 2.5, 5 or 10 min | • Histological evaluation<br>• Smoke particle analysis | • The acute inhalation toxicity of $TiO_2$-HC smoke was much lower than the Zn-HC smoke<br>• The animals survived exposure to $TiO_2$-HC smoke, even at relatively high smoke conc. | Karlsson et al. (1986) |

**Table 2**

$SiO_2$ nanotoxicology

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 1 Mesoporous $SiO_2$ | Amorphous | • 130 nm by SEM, TEM<br>• Amine and phosphate functionalized<br>• Hexagonal and 2 nm pores | Cancer cells (e.g. PANC-1, AsPC-1) | • 6.4, 64 mg/mL, 6.4, 64 g/mL<br>• 1 day | *In vitro* bioassays<br>• WST assay<br>• Apoptosis assay<br>• Necrosis assay | • Non-toxic without cancer agent camptothecin<br>• Toxic to cancer cells with cancer agent | Lu et al. (2007b) |
| 2 Mesoporous and luminescent $SiO_2$ | Amorphous | • 100–120 nm by TEM<br>• 780–1050 $m^2/g$ surface area<br>• Rhodamine B incorporated<br>• Hexagonal and 2–3 nm pores<br>• (+) and (-) charged surfaces | • Adipocytes (3T3-L1)<br>• Human mesenchymal stem cells (hMSCs) | • 0.1 mg/mL, 3 h (cytotoxicity)<br>• 0.1 mg/mL, 1 day (proliferation) | *In vitro* bioassays<br>• MTT assay | • Non-toxic regardless of surface charge<br>• Adipogenic and osteogenic differentiation unaffected<br>• Uptake efficient regardgless of surface charge | Chung et al. (2007) |
| 3 Multifunctional and luminescent $SiO_2$ | Amorphous | • sub-50 nm by SEM, TEM<br>• Amine/carboxylate/ Gadolinium functionalized<br>• Luminescent (Ru $(bipy)_3^{2+}$) | Monocyte cell (bone marrow progenitor cells from C57BL/6 mice) | • 0.012, 0.123, 1.23, 12.3, 123 μg/5000 cells<br>• 1 day | *In vitro* bioassays<br>• Cell viability assay | • Non-toxic | Rieter et al. (2007a,b) |
| 4 Polymer and protein functionalized luminescent $SiO_2$ | Amorphous | • 20 nm by TEM<br>• Luminescent (Ru $(bipy)_3^{2+}$)<br>• Polymer and protein coated | Jarkat T luekemia cell | • Concentration enough for fluorescence microscopy<br>• 1, 3, 6h | *In vitro* bioassays<br>• Necrosis assay<br>• Apoptosis assay | • Non-toxic<br>• Apoptotic, necrotic profile same as nontreated | Bottini et al. (2007) |
| 5 Organically modified $SiO_2$ | Amorphous | • 20 nm by TEM<br>• Porphyrin incorporating<br>• ORMOSIL | Tumor cells (e.g. Colon-26, RIF-1) | • 0.5 μM/well<br>• 0–8 $J/cm^2$ irradiation | *In vitro* bioassays<br>• Photosensitization assay | • Non-toxic without light<br>• Toxic to tumor cells with increasing light dosage | Ohulchanskyy et al. (2007) |
| 6 Silicon nanowires | Silicon | • 90 nm in diameter<br>• 6 μm height | • Murine embryonic stem cell | • N/A (grown on Si wafer)<br>• Several days | *In vitro* bioassays<br>• Cell incubation | • Murine stem cells survive for several days interfaced to silicon nanowires with 100 nm diameter | Kim et al. (2007c) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| | | | • Kidney cell (HEK293T) | | | | |
| 7 Synthetic $SiO_2$ | Amorphous | • $SiO_2$ from $Na_2SiO_3$ 15–25 nm (SEM)/177–200 nm (DLS)<br>• $SiO_2$ from TEOS 65–95 nm (SEM)/230–243 nm (DLS)<br>• $SiO_2$-chitosan composite 10–15 nm (SEM)/153–177 nm (DLS) | • Fibroblast cells<br>• Epithelial cells | 0.21–0.667 mg/mL for 2 days | *In vitro* bioassays<br>• MTT assay<br>• LDH assay | • $SiO_2$-chitosan composite has less toxicity<br>• Silica is more lethal to fibroblast cells<br>• Longer the cell doubling time, the more cytotoxic | Chang et al. (2007) |
| 8 Silica shell with quantum dot core | • Amorphous shell<br>• CdSe/ZnS core<br>• Amine termination | • 15–20 nm overall size | • Leukemia cells (Jurkat, K-562)<br>• Lymphocytes | • 5 μM QD core concentration<br>• 0.5, 3, 24, 48 h<br>• $5 \times 10^5$ cell/well | *In vitro* bioassays<br>• Flow cytometry | • Non-toxic up to 5 μM QD core concentration, 2 day, no light exposure<br>• Slightly cytotoxic with UV irradiation (ROS, radical generation probable)<br>• Intracellular delivery possible | Zhelev et al. (2006) |
| 9 Multifunctional silica nanotubes | Amorphous walls | • 50 nm diameter<br>• 200 and 500 nm lengths<br>• No surface modification<br>• Magnetite incorporated and amine functionalized (+ charge) | • Human metastatic breast cancer cell (MDA-MB-231)<br>• Normal human umbilical vein endothelial cells | • 0.005, 0.05, 0.5, 5 μg/mL | *In vitro* bioassays<br>• MTT assay | • Non-toxic only at low concentrations (below 0.5 μg/mL)<br>• Toxicity is length independent but dose-dependent<br>• (+) Charged 200 nm long $SiO_2$ nanotubes are toxic, especially for normal cell lines | Son et al. (2006) |
| 10 Flame engineered $SiO_2$ | • Amorphous<br>• Crystalline | 14 nm | Human mesothelioma rodent fibroblast cell lines (3T3) | 15 ppm for 6 days | *In vitro* bioassays<br>• MTT assay<br>• Total DNA measurement<br>• DNA Hoechst assay | Non-toxic | Brunner et al. (2006) |
| 11 N/A | Amorphous | 0.5–4 μm/1–12 μm | Human leukemic monocyte lymphoma (U937) used differentiated | 0.125–1 mg/well | *In vitro* bioassays<br>• LDH assay | • $SiO_2$ particles are the most toxic<br>• $SiO_2$ > metal alloy > $Al_2O_3$ > $TiO_2$ | Yoshida et al. (2003) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 12<br>• 15 nm $SiO_2$<br>• 46 nm $SiO_2$<br>• Crystalline (Min-U-Sil 5) (Min-U-Sil 5) | • Amorphous (15, 46 nm)<br>• Crystalline (Min-U-Sil 5) | • 15 nm $SiO_2$ (15 ± 5 nm)<br>• 46 nm $SiO_2$ (46 ± 12 nm)<br>• Min-U-Sil 5 (629 ± 272 nm) | Human lung cancer cells (A549) | • 10, 50, 100 μg/mL for 48 h for GSH, MDA, and LDH ($1 \times 10^4$ cell/well; T75)<br>• 10, 50, 100 μg/mL for 48 h for SRB ($1 \times 10^4$ cell/well; 24 well)<br>• 48 h for ROS | *In vitro* bioassays<br>• Sulforhodamine B assay<br>• LDH assay<br>• Intercellular ROS<br>• GSH measurement<br>• MDA measurement<br>• Protein assay | • 15, 46 nm $SiO_2$ particles are toxic which is dose-dependent and time-dependent at 10–100 μg/mL<br>• Amorphous was more toxic than crystalline $SiO_2$ for cultures involving human bronchoalveolar carcinoma-derived cells | Lin et al. (2006a) |

**Table 3**

Iron oxide nanotoxicology.

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 1 Iron oxide ($Fe_2O_3$) nanoparticles | N/A | Diameter: 5 and 12 nm<br>• Sized by TEM | Rat pheochromocytoma cell line (PC 12) | 0.15–15 mM | • Fluorescent Live/dead cell staining<br>• Calcein AM and ethylidium homodimer-1<br>• Neurite morphometry<br>• Alterations in cytoskeletal structure | Exposure to increasing concentrations of anionic magnetic nanoparticles results in a dose-dependent diminishing ability of PC12 cells to differentiate in response to nerve growth factor | Pisanic et al. (2007) |
| 2 $Fe_2O_3$ (flame synthesized) | N/A | • Larger mode: 45 nm<br>• Small mode: 5 nm<br>• Sized by SMPS (Scanning Mobility Particle Sizer) and TEM | Human aortic endothelial cells (HAECs) | 0.001–50 μg/mL direct exposure | • Measured mRNA level<br>• Measured protein levels of the inflammatory markers<br>• Trypan blue exclusion assay | $Fe_2O_3$ nanoparticles fail to provoke an inflammatory response in HAECs at any of the concentrations tested | Gojova et al. (2007) |
| 3<br>• β-FeOOH nanorods<br>• Polymercoated β-FeOOH nanorods (four-layers of polyelectrolytes (PAA/PEI/PAA/PEI)) | Akaganeite (β-FeOOH) | • Diameter: 38 ± 5 nm lengths: 480 ± 45 nm (sizing by TEM)<br>• BET surface area: 45.96 $m^2/g$<br>• Pore size distribution: 2–20 nm | Human cervical carcinoma cells (HeLa) | • 0.1 ng/mL and 100 mg/mL<br>• 5000 cells/well | *In vitro* bioassays<br>• WST-1 assay | • As-prepared and polymer coated iron oxide nanorods were non-toxic at the concentrations between 0.1 ng/mL and 100 mg/mL for HeLa cells<br>• Porous nanorods were uptaken within 15 min and dyes were released into the cytosol and then to the nucleus within 1 day | Wu et al. (2007) |
| 4 Amino-functionalized superparamagnetic iron oxide nanoparticles (SPION) | $Fe_3O_4$ | 10–15 nm | Human liver cancer lines (SMMC-7721) | N/A | *In vitro* bioassays<br>• MTT colorimetric assay | • Amine functionalized SPION can be $^{188}Re$ labeled<br>• $^{188}Re$ labeled immuno-magnetic nanoparticles (IMN) can markedly kill SMMC 7721 liver cancer cells with right dosage | Liang et al. (2007) |
| 5 $Fe_2O_3$ (flame synthesized) | | 12–50 nm | • Human mesothelioma (MSTO)<br>• Rodent fibroblast cell lines (3T3) | 30 ppm for 3 days | *In vitro* assays<br>• MTT assay<br>• Total DNA measurement<br>• DNA Hoechst assay | • Cytotoxic for MSTO cells for both MTT and DNA (level was same as asbestos; lethal above 7.5 ppm)<br>• Iron ion concentration coupled with nanoparticle uptake may be the cause of increased toxicity | Brunner et al. (2006) |

| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| | | | | | | • Fairly non-cytotoxic for 3T3 cells (MTT and DNA) | |
| 6 SPIO (Ferumoxtran-10) (or AMI 7227) | N/A | 30 nm | Rats, rabbits, dogs, and monkeys (lymph nodes) | 2, 13, 40, 126, 400 (mg Fe/kg) | • Pharmacokinetic, safety pharmacology<br>• Single and repeated dose study<br>• Reproduction toxicity<br>• Genotoxicity toxicity | • Toxic at high iron conc. with repeated injections<br>• Not mutagenic but teratogenic in rats and rabbits | Bourrinet et al. (2006) |
| 7 $Fe_3O_4$ | N/A | 30, 47 nm | Rat liver derived cell line (BRL3A) | • 10, 50, 100, 250 μg/mL<br>• 24 h | *In vitro* assays<br>• MTT assay<br>• LDH assay | • No measurable toxic effect between 10–50 μg/mL<br>• Toxic at high conc. of 100–250 μg/mL | Hussain et al. (2005) |
| 8 Ferumoxides-poly-L-lysine (PLL) (ferumoxide is commercially sold by Berlex Laboratories which is now Bayer HealthCare Pharmaceuticals as Feridex I.V.) | N/A | • FDA approved iron oxide<br>• PLL = 38.8 kD | • Human mesenchymal stem cells<br>• Human cervical carcinoma cells (HeLa) | 25 μg/mL per 5000 cells (for 96 well assays) | *In vitro* bioassays<br>• MTT assay<br>• ROS measurement<br>• Apoptosis assay | • Long-term viability, growth rate, and apoptotic indices of the labeled cells were unaffected by the endosomal incorporation of SPIO<br>• Nonsignificant transient increase in reactive oxygen species<br>• Magnetic cellular labeling with the ferumoxides-PLL complex had no short- or long-term toxic effects on tumor or mesenchymal stem cells | Arbab et al. (2003) |
| 9 SPIO (AMI-25) | N/A | 80 nm | Rats, beagle dogs | • Acute toxicity: 500 μmol Fe/kg (28 mg Fe/kg) or 3000 μmol Fe/kg (168 mg Fe/kg)<br>• Subacute toxicity: 0–250 μmol Fe/kg (0–14 mg Fe/kg)<br>• Mutagenicity (Ames test): 0–2140 μmol Fe/kg (0.008–12 mg Fe/kg) | • Acute toxicity<br>• Subacute toxicity: mortality, morbidity, body weight, or food consumption; histology<br>• Mutagenicity (Ames test) | • Acute toxicity: no adverse effects<br>• Subacute toxicity: all within normal ranges; no tissue damages<br>• Mutagenicity (Ames test): non-toxic | Weissleder et al. (1989) |

**Table 4**

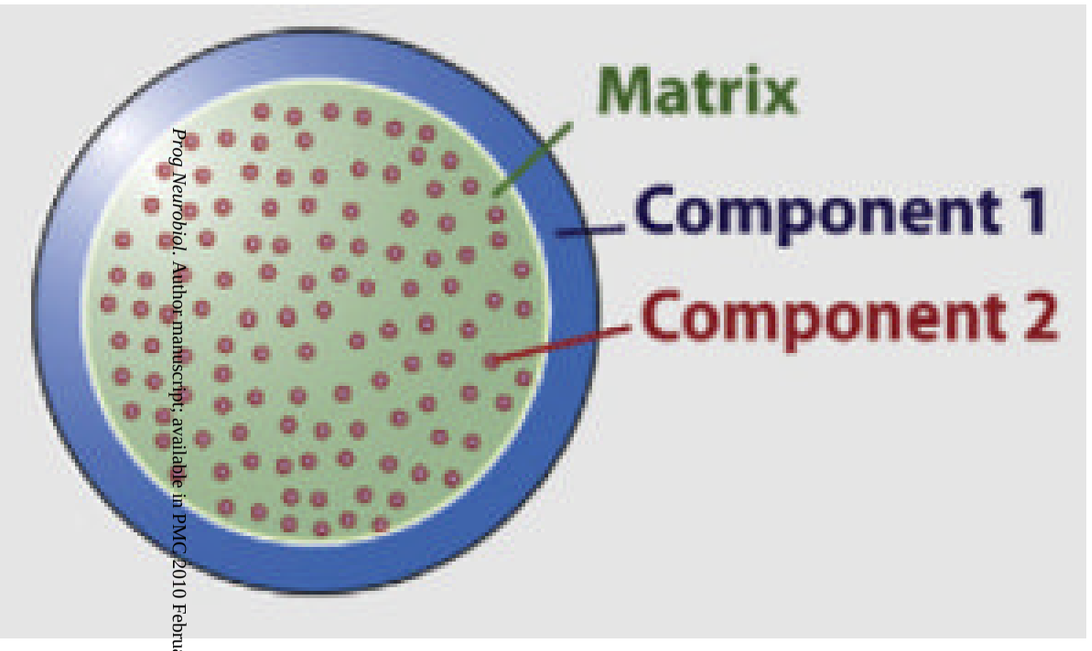
$CeO_2$ nanotoxicology

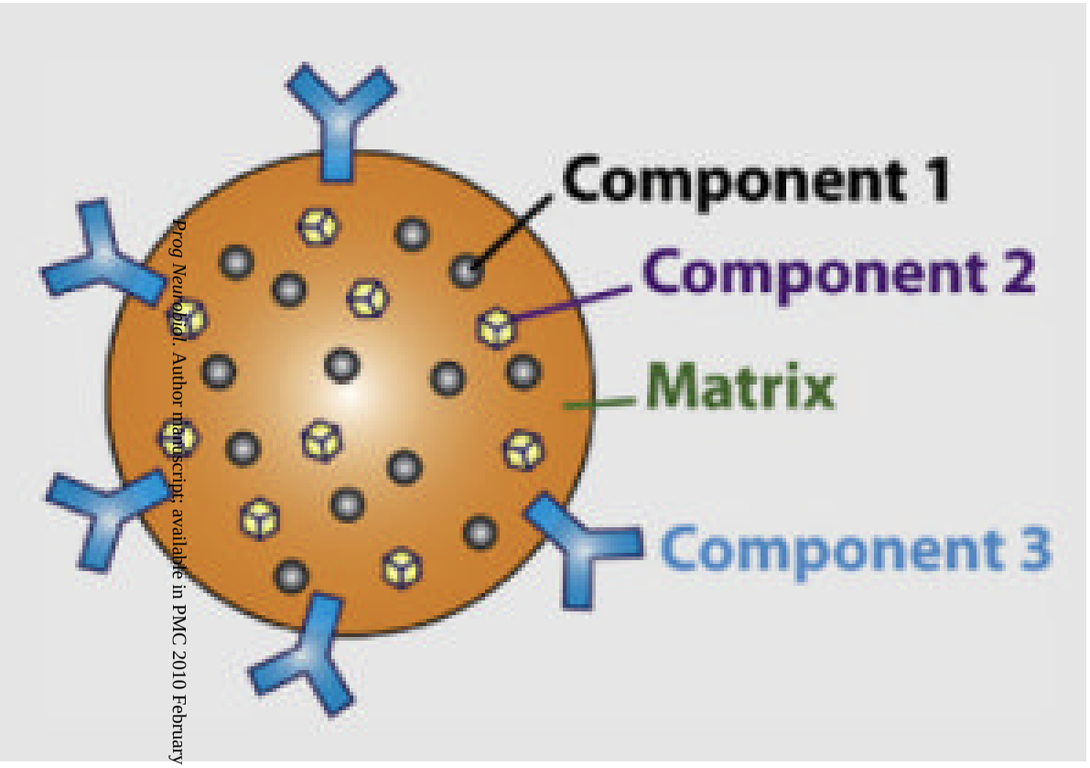
| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| 1 Cerium oxide nanoparticles via microemulsion method | N/A | 2–5 nm | • Neuronal and glial cells from adult rat spinal cord<br>• Isolated spinal cord cells | • 1000 cells (2 cells/ $mm^2$ density)<br>• Single dose of 10 nM<br>• 15 and 30 day cultures for live—dead cell assays<br>• 100 mM $H_2O_2$ for 1 h | *In vitro* assays<br>• Live—dead cell assays<br>• Neuron—glial cell assay<br>• Hydrogen peroxide-induced oxidative injury assay | • Nano-ceria treated cultures lived longer for both 15, 30 days<br>• Neuronal cells survived significantly higher vs. controls<br>• Protection against hydrogen peroxide-induced oxidative injury is observed for nano-ceria treated cultures | Das et al. (2007) |
| 2 Ceria nanoparticles (commercial NanoActive) | N/A | 7 nm in diameter | • MCP-1 transgenic mice (MCP mice)<br>• Wild-type FVB/N mice (WT mice)<br>• 5 weeks old; 20–25 g body weight<br>• Sacrificed at 6 months of age<br>• *MCP = monocyte chemoattractant protein | • 15 nmol via intravenous administration<br>• Twice a week for 2 weeks | *In vivo*<br>• Myocardial histology<br>• Expression of cytokines<br>• ER stress-associated genes evaluation | • Cardiac dysfunction slowed while myocardial oxidative stress and ER stress was attenuated using nano-ceria<br>• Cytokine (TNF-α, IL-1β, and IL-6) production decreased for myocardium in MCP mice via nano-ceria treatment<br>• Circulating MCP-1 and CRP levels reduced (likely due to anti-inflammatory effects of $CeO_2$<br>• Nano-ceria is a potent autoregenerative antioxidant | Niu et al. (2007) |
| 3 Cerium-based compound Envirox™ (commercial catalyst from Oxonica, UK) | N/A | • 70–90 nm<br>• 2% nano-ceria in a mixed aliphatic/cyclo-aliphtic fluid (Envirox™ is a fuel additive to reduce particulate matter (PM) emission in diesel engines | Rat lung slices | N/A | *In vitro* assays<br>• Cell viability (ATP, intracellular Glutathione)<br>• Proinflammatory reaction (TNF alpha)<br>• Anti-oxidant enzyme activity (total GPX, Mn SOD, catalase) | • No impact on lung tissue viability, glutathione dependent metabolism, superoxide dismutase activity, proinflammatory reaction<br>• Cellular defense can take over without harmful consequences | Fall et al. (2007) |
| 4 $CeO_2$ oxide (commercial, Rhodia) | N/A | • 7 nm<br>• 400 $m^2$/g surface area<br>• IEP = 10.5 | Gram-negative bacteria (*Escherichia coli*) | 4, 15 mg/L | Counting colony forming units (CFU) on LB petri dishes | • Adsorption and reduction of ceria nanoparticles lead to significant bacterial cytotoxicity<br>• Nano-ceria adsorbs onto the *E. coli* outer membrane | Thill et al. (2006) |
| 5 $La_{0.7}Sr_{0.3}MnO_3$ (LSMO) nanoparticles doped with cerium | Perovskite | 50–300 nm according to cited paper | • Human skin carcinoma (A-431) | 5–100 μg/mL | *In vitro* assays<br>Tetrazolium salt XTT assay | • Cerium-doped LSMO samples and reduced La/Sr ratios resulted in extremely low cytotoxicity | Kale et al. (2006) |

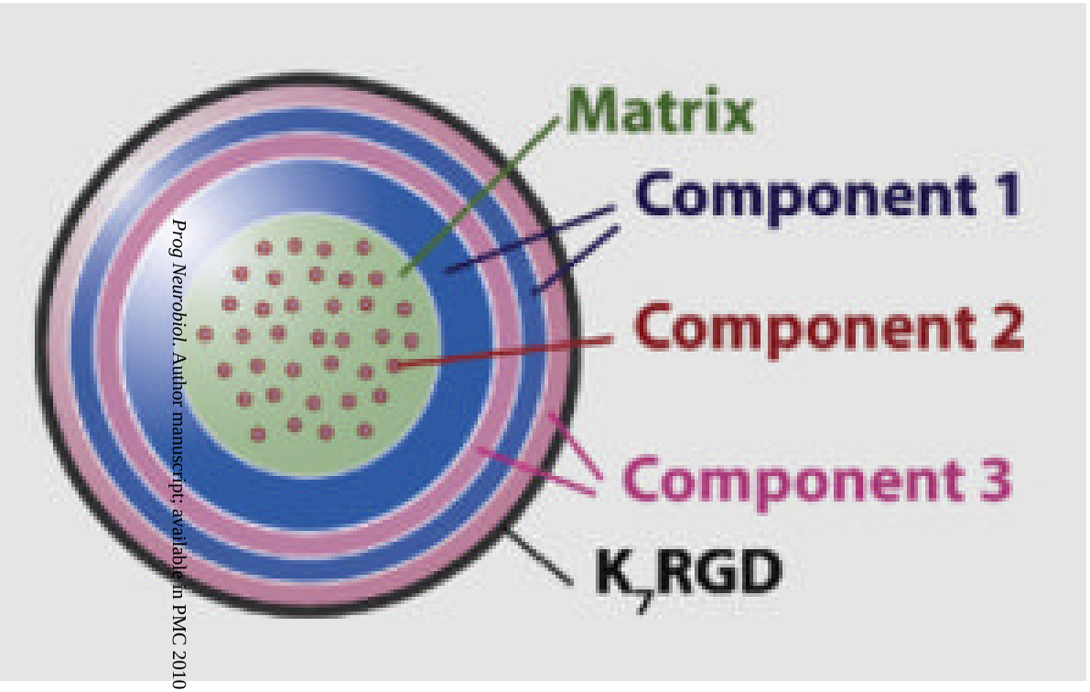
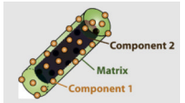
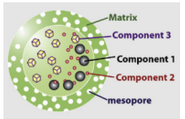
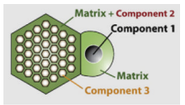
| Type | Crystal phase | Size and characteristics | Animal or cell type | Concentration | Assay | Results | Reference |
|---|---|---|---|---|---|---|---|
| | | | • Human fibrosarcoma cell lines (HT-1080) | | | • Pure LSMO particles are toxic but cerium doping (~3%) reduced the toxicity level | |
| 6 Cerium oxide ($CeO_2$) nanoparticles via sol—gel synthesis | N/A | 6, 12 nm, and 1 μm sizes | • Hippocampal nerve cell line (HT22)<br>• Murine macrophage cell line (RAW164) | 0.01, 0.1, 1, 10, 100 μg/mL per $2.5 \times 10^3$ initial cell seeding | *In vitro* assays<br>• MTT assay<br>• Reactive oxygen species (ROS) measurement | • One micron ceria particles show toxicity over 20 μg/mL<br>• Ceria and yttria show antioxidant properties that promote cell survival under conditions of oxidative stress | Schubert et al. (2006) |
| 7 Ceria nanoparticles via room temperature homogeneous nucleation method | N/A | 17–23 nm (by TEM and gas surface analysis | Human bronchoalveolar carcinoma derived cell line (A549) | • 3.5, 10.5, 23.3 μg/mL<br>• 1–3 days for SRB assays<br>• 1 day for ROS measurement<br>• 3 days for LDH assay | *In vitro* assays<br>• Sulforhodamine B assay<br>• Intracellular ROS measurement<br>• LDH assay<br>• GSH, MDA, α-tocopherol measurement<br>• Total protein concentration assay | • 20 nm ceria particle reduce human lung cancer cell viability<br>• Free radicals are generated to cause oxidative stress and reduce GSH and α-tocopherol levels<br>• Toxicity correlates well to both dose and time exposure<br>• Oxidative stress led to increased LDH, MDA release which are indicators of lipid peroxidation and membrane damage | Lin et al.(2006b) |
| 8 Cerium oxide nanoparticles ($CeO_2$-NP) | N/A | N/A | Neonatal rat brain cell (astrocytes, neurons, microglia) | • 10 nM, single dose<br>• 24 h on day 10 *in vitro* | *In vitro* assays<br>• Cell damage measured by propidium iodide<br>• Inflammatory activation in microglia | • Reduced free radical mediated cell damage<br>• Decreased NO release<br>• Decreased microglial activation | Strawn et al. (2006) (meeting abstract) |
| 9 Ceria nanoparticles | N/A | • 3–5 nm (non-agglomerated) (by HRTEM and XRD)<br>• Mixed valence states of $Ce^{3+}$ and $Ce^{4+}$ (by XPS) | • Human breast carcinoma cell lines (MCF-7)<br>• Normal breast epithelial cell lines (CRL8798) | 0–5 μM | *In vitro* assays<br>• Radiation (0–10 Gy) experiments<br>• MTT assay<br>• TUNEL (apoptosis) staining | • Toxic to cancer cells at concentrations greater than 50 nM<br>• Normal cells are protected against radiation damage | Tarnuzzer et al. (2005) |
| 10 Ceria nanoparticles via flame spray synthesis | N/A | • Size fraction I (20–50 nm)<br>• Size fraction II (40–80 nm)<br>• Size fraction III (80–150 nm)<br>• Size fraction IV (250–500 nm) | Human lung fibroblast (MRC-9) | 100 ng/g and 1 μg/g of fluid (100 ppb to 100 ppm) | Uptake *in vitro* assays Analyzed by different sizes, concentrations, and exposure times | • Ceria particle size dictates toxicity<br>• The biological uptake processes on the surface of the cell are faster than the physical transport to the cell<br>• Particle uptake rate is dominated indirectly by particle size while primary particle number conc. and surface area are minor factors | Limbach et al. (2005) |

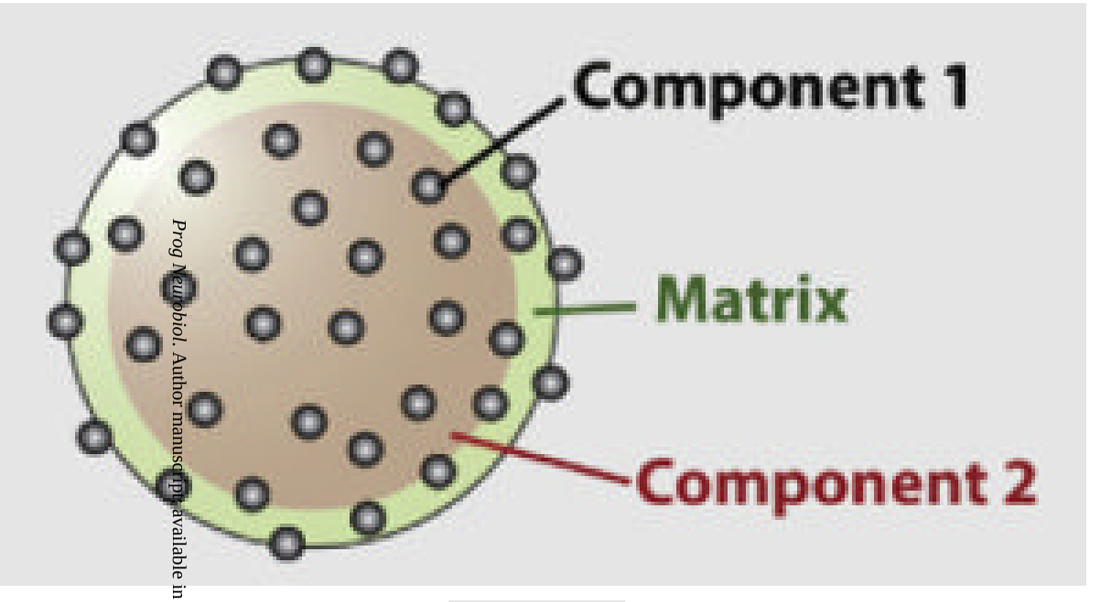
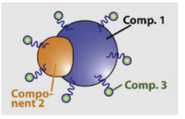
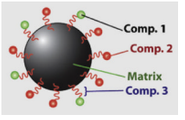
**Table 5**

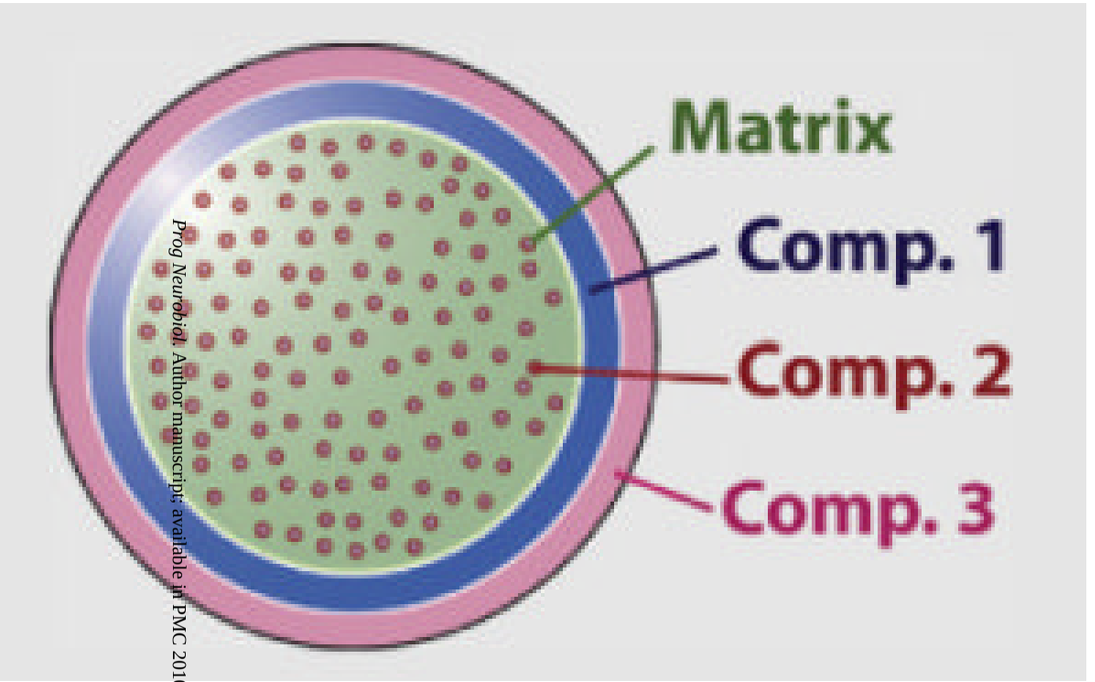
nctional nanoparticle systems (MFNPS)

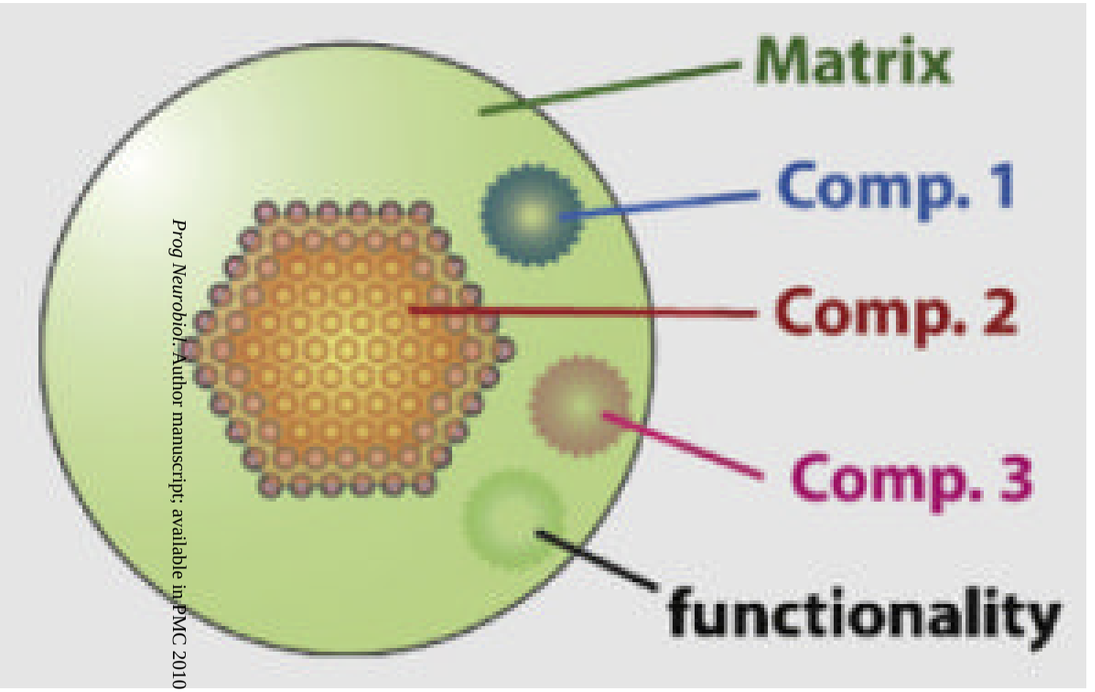
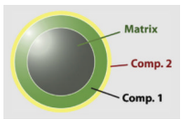
| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|   | 30–40 | $SiO_2$ | $Gd^{3+}$ + ligand (MR agent) | $[Ru(bipy)_3]^{2+}$ (fluorescent) | N/A | Si-OH | Target-specific contrast agents for optical and MR imaging of rheumatoid arthritis in mice | Rieter et al. (2007a); Kim et al. (2007a) |

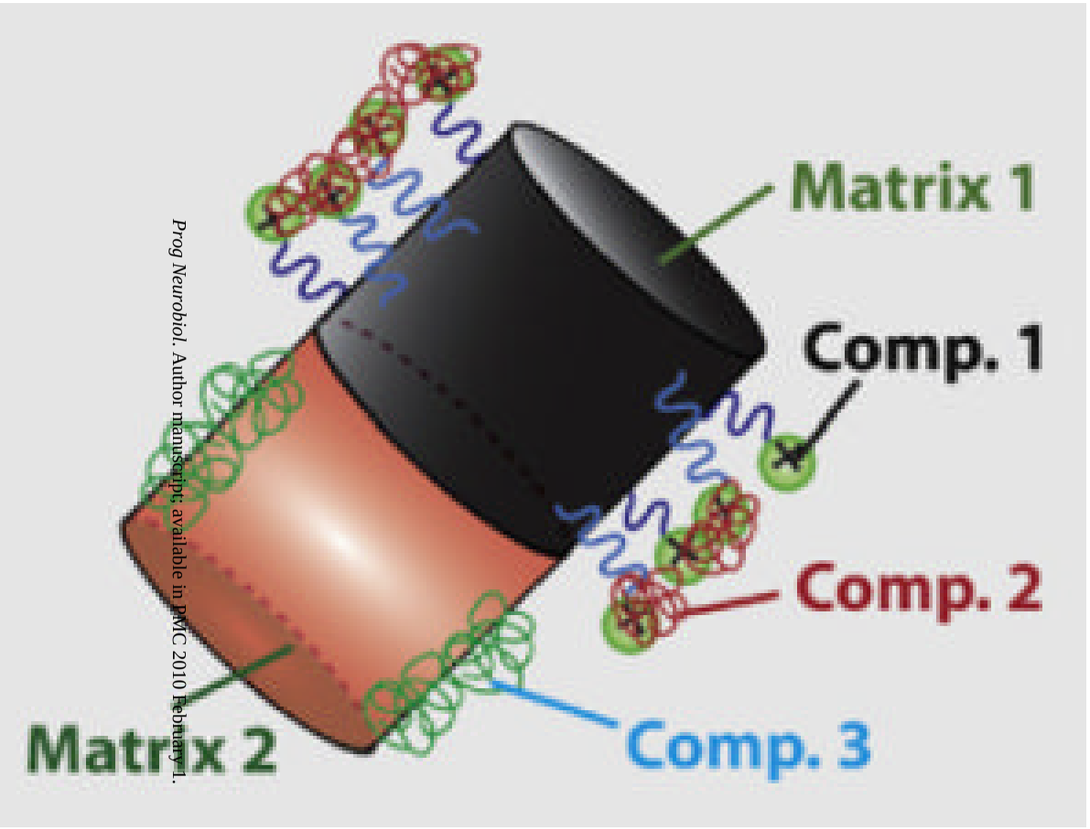
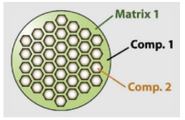
| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 70–90 | PLGA | $Fe_3O_4$ (MR agent) | DOX (drug molecule) | HER (targeting agent) | -OH | Diagnosis of breast cancer; detection and treatment | Yang et al. (2007) |

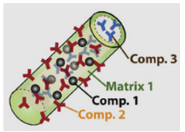
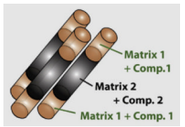
| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 35–45 | $SiO_2$ | $Gd^{3+}$ + ligand (MR agent) | $[Ru(bipy)_3]^{2+}$ (fluorescent) | Negatively charged polymer | $K_7$RGD (positively charged oligomer) | Layer-by-layer assembly method to construct multifunctional nanoparticles; cancer cell targeted imaging | Kim et al. (2007a) |
|  | 40 × (short axis) 100–125 (long axis) | $SiO_2$ | Lanthanide ($Eu^{3+}$, $Gd^{3+}$, $Tb^{3+}$) doped metal-organicframework (MOF) | $Tb^{3+}$ + ligand | N/A | -OH/-COOH/-$NR_2$/ -NHC(O) | Controlled release of small molecules (drug delivery); detection of small molecules; MR imaging | Rieter et al. (2007b); Rieter et al. (2006) |
|  | <200 nm | $SiO_2$ | $Fe_3O_4$ (MR agent) | CdSe/ZnS (fluorescent) | Ibuprofen (drug molecule) | Si-OH | Drug delivery; magnetic susceptibility measurement; fluorescence imaging | Kim et al. (2006b) |
|  | 115 × (short axis) 160 (long axis) | $SiO_2$ | $Fe_3O_4$ (MR agent) | FITC (fluorescent) | Mesopore | -OH | Cell tracking and drug delivery | Lin et al. (2006c) |

| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 45 | $SiO_2$ | $Fe_3O_4$ (MR agent) | Fluorescent | N/A | -$NH_2$/-SH/-OH | Imaging neuroblastoma | Lee et al. (2006b) |
|  | Comp. 1 = 10,<br>Comp. 2 = 6 | N/A | Au (optical probe) | FePt<br>(MR imaging) | Biomolecule (targeting; e.g. antibody) | N/A | Biochip sensing; molecular<br>MR imaging of cancer cells | Choi et al., 2006 |
|  | 9–12 | $Fe_3O_4$ | Cy5.5 (near-IR fluorescent) | Chlorotoxin (targeting agent) | PEG (biocompatible stealth coat) | Biomolecules | MR imaging and fluorescence microscopy<br>on rat glioma (brain tumor) cell and rat cardiomyocytes | Veiseh et al. (2005) |

| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 100 | $SiO_2$ | $Gd^{3+}$ + ligand (MR agent) | $[Ru(bipy)_3]^{2+}$ (fluorescent) | $Si(CH_2)_3NH_2$ (for bioconjugation) | $-NH_2$/$-PCH_3OO^-$ | MR and fluorescence imaging possible; radio-opaque (via X-ray fluoroscopy) | Santra et al. (2005a,b) |

| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 11–17, QD = 3 | $SiO_2$ | $Gd^{3+}$ + ligand (MR agent) | CdS:Mn@ ZnS (fluorescent) | $Si(CH_2)_3NH_2$ (for bioconjugation) | $-NH_2/-PCH_3OO^-$ | MR and fluorescence imaging possible; TAT peptide conjugation and rat brain labeling studies | Yang et al., 2006a; Santra et al., 2005[b,c] |
|  | 10–20 nm | Magnetic core (magnetic attraction) | Oxide layer (functionalization) | Ligand or functionality to bind His (stabilization) | N/A | Stabilizing agent/ bound functional group/unbound-OH | Magnetic separation of Histidine modified biomolecules such as proteins from cell lysates | Lee et al. (2006a); Xu et al. (2004) |

| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 100 (diameter) × 200 (two 100 nm segments) | Matrix 1 = Ni, Matrix 2 = Au | Cationic linker (to harness negatively charged biomolecules) | Biomolecule (e.g. negatively charged plasmid; to bind with cationic linker) | Fluorescent tagged biomolecule with thiol functionality (to bind with Au) | Attached biomolecule | *In vitro* and *in vivo* gene delivery in mammalian systems | Salem et al. (2003) |
|  | 100–120 | $SiO_2$ | Rhodamine (fluorescent) | Mesopore | N/A | (+) and (-) examples | Differentiation of human mesenchymal stem cells or cancer drug delivery | Chung et al. (2007); Lu et al. (2007b) |

| Schematic | Size (nm) | Matrix | Component 1 | Component 2 | Component3 | Surface chemistry | Application(s) | Reference(s) |
|---|---|---|---|---|---|---|---|---|
|  | 50 (diameter) × 200–500 or longer (length) | $SiO_2$ | $Fe_3O_4$ (MR agent) | Antibody (bioconjugation) | Cargo space or Ab | Biomolecules + -OH/hydrophobic interior | Biodetection and controlled release of small molecules | Son et al. (2006) |
|  | >20 nm (diameter) × 12 μm (length) | Matrix 1 = Au, Matrix 2 = Ni | Au (protecting group; functionality via thiol chemistry) | Ni (magnetic domain; His-tag binding domain) | N/A | PEG (thiol linked molecules) | Magnetic separation of histidine tagged biomolecules | Lee et al. (2004b) |

ations were prepared based on the data, schemes, and figures provided in the references in the table with permission from the respective publishers.