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Review Article

Applications and Nanotoxicity of Carbon Nanotubes and Graphene in Biomedicine

Caitlin Fisher,[1,2] Amanda E. Rider,[1,2] Zhao Jun Han,[1,2] Shailesh Kumar,[1,2] Igor Levchenko,[1,2] and Kostya (Ken) Ostrikov[1,2]

[1] *Plasma Nanoscience Centre Australia (PNCA), CSIRO Materials Science and Engineering, P.O. Box 218, Lindfield, NSW 2070, Australia*
[2] *Plasma Nanoscience at Complex Systems, School of Physics, The University of Sydney, Sydney, NSW 2006, Australia*

Correspondence should be addressed to Zhao Jun Han, zhaojun.han@csiro.au

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Owing to their unique mechanical, electrical, optical, and thermal properties, carbon nanostructures including carbon nanotubes and graphenes show great promise for advancing the fields of biology and medicine. Many reports have demonstrated the promise of these carbon nanostructures and their hybrid structures (composites with polymers, ceramics, and metal nanoparticles, etc.) for a variety of biomedical areas ranging from biosensing, drug delivery, and diagnostics, to cancer treatment, tissue engineering, and bioterrorism prevention. However, the issue of the safety and toxicity of these carbon nanostructures, which is vital to their use as diagnostic and therapeutic tools in biomedical fields, has not been completely resolved. This paper aims to provide a summary of the features of carbon nanotube and graphene-based materials and current research progress in biomedical applications. We also highlight the current opinions within the scientific community on the toxicity and safety of these carbon structures.

1. Introduction

Carbon nanotubes (CNTs) and graphene are very promising candidates to form the basis of new biological and medical devices. Carbon nanotubes can be thought of as rolled-up graphene sheets with no overlapping edges [1]. Their diameters typically vary from 1 to 100 nm and their lengths can be several orders of magnitude larger, up to millimeters, even centimeters long [2]. Various orientations of CNTs are shown in Figures 1(a)–1(c): randomly oriented, vertically aligned, and in a "dandelion-like" structure, respectively. The well-documented beneficial mechanical, electrical and chemical characteristics of CNTs and graphene [1, 3–7] as well as their ability to be hybridized with a wide range of organic and inorganic materials make them ideal candidates for many biomedical applications such as biosensing [8–12], tissue engineering [13–15], and drug delivery [16, 17].

In the past two decades, intense efforts have been directed at providing specificity, selectivity, reproducibility, and robustness to these carbon nanostructures in biologically relevant environments [18–22]. However, the issue of toxicity of CNTs and graphene in living biological systems, which is vital for the successful incorporation of these materials into functional biomedical devices, remains unsolved at macroscopic, cellular, and intracellular levels [23–25].

In this paper we will, in Section 2, discuss the role of CNTs in biosensing, tissue engineering, and drug delivery. Aspects of the toxicity of CNTs in living biological systems are then discussed in Section 3 and the emerging graphene-related biomedical applications and associated safety issues are briefly presented in Section 4. Finally, a summary of this work and an outlook for future research is provided.

2. Applications of Carbon Nanotubes in Biomedicine

Due to the chemical inertness of graphitic walls, functionalization of CNTs and graphene is often the key step required in

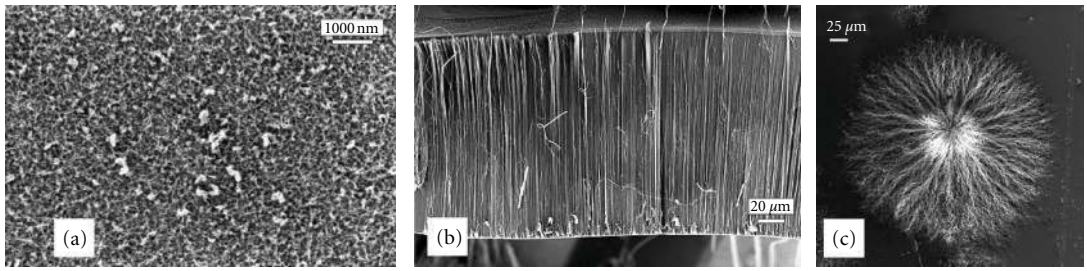

Figure 1: Various orientations of CNTs grown using chemical vapor deposition on Si substrates: (a) entangled, randomly orientated CNTs; (b) vertically aligned CNTs; (c) dense "dandelion-like" CNT structure grown using plasma-enhanced chemical vapor deposition on an etched, catalyst-free Si substrate. Details on the growth of similar structures can be found in [40].

any application of these materials. Let us first briefly consider the possible ways of performing such functionalization.

2.1. Functionalization of Carbon Nanotubes. Successful functionalization should maintain the integrity of CNT's mechanical, electrical, and chemical properties as well as the activity of the biological species being attached. In general, there are two CNT functionalization methods: covalent bonding and noncovalent wrapping [26–28].

Covalent bonding involves chemical attachment of the desirable species to the CNT [26], often at the tube ends or at defect sites [1, 29]. Oxidation processes are often used as a preparation step to create chemically active sites for covalent bonding [30]. These oxidation processes can be performed through wet chemical or dry plasma routes [30], amongst others. A variety of biological species have been covalently bonded to CNTs [26, 31, 32]. However, this often alters the intrinsic structure and properties of CNTs as well as the properties of attached biomolecules [33]. An example of a covalently functionalized CNT is shown in Figure 2(a), which shows a scanning electron microscope (SEM) image of multiwalled CNTs (MWCNTs) covalently functionalized with ferritin [34].

Noncovalent bonding, or physical adsorption, on the other hand, is the process of wrapping a species around the CNT walls [27]. This method is preferable to covalent bonding in many cases as it causes less structural damage to the CNT and the wrapped species, and the chemical environment required during fabrication is less harsh [28]. Over the years, the noncovalent wrapping of CNTs by polysaccharides [33], DNA [35, 36], proteins, polypeptides [37], and synthetic polymers has been widely reported.

The degree of CNT functionalization is commonly characterized by atomic force microscopy, Raman spectroscopy, SEM, transmission electron microscopy (TEM), ultraviolet-visible light spectroscopy, Fourier-transform infrared spectroscopy, thermal gravimetric analysis, and gel electrophoresis [38, 39]. The bioactivity of the attached biomolecules can be characterized by the immunochemical methods such as enzyme-linked immunosorbent assay (ELISA) [38]. It should be noted that whilst the bioactivity is strongly dependent on the bonding between the biomolecule and the CNT, the stoichiometry and the loading ratio are also important factors that must be considered [32].

2.2. Carbon Nanotubes for Biosensing. The incorporation of CNTs in biosensing devices has made a significant progress in the last decade [39]. By definition, a biosensor is an analytic device which consists of a receptor that interacts with the targeted analyte to be measured and a transducer (or detector) that transforms the signal from the interaction into a form that can be easily measured. The one-dimensional (1D) structure of CNTs allows signals to be transported in a confined space, making them extremely sensitive to electrical and chemical changes in their immediate environment [8]. There are generally two configurations of CNT-based biosensors: CNT field-effect transistors (CNT-FETs) [41, 42] and CNT electrochemical sensors [3, 43, 44]. Here, we concentrate on these two types of biosensors and provide details on the role of CNTs in these devices and the common approaches employed to improve their sensitivity.

Carbon nanotube FET biosensors have a current carrying channel connected to a source and a drain, which can be regulated by a gate voltage [3]. A typical CNT-FET setup is shown in Figure 2(b). The current carriers (electrons or holes) running through the channel are highly sensitive to changes in external electric fields and as such can be used to detect electrical signals produced by biological activity or biochemical interactions [45]. The conductive channel in CNT-FET devices can be either an individual semiconducting single-walled CNT (SWCNT) [46] or a randomly distributed bundle of CNTs [8]. The former was first introduced by Martel et al. [47] and has shown superior performance compared to traditional metal-oxide-semiconductor FETs (MOSFETs) [48]. Because of their high sensitivity, CNT-FET biosensors are well suited for the detection of very low analyte concentrations [8, 49]. For example, ultrasensitive detection of DNA at concentrations of 100 fM has been detected with SWCNT-FETs [35, 50].

Semiconducting SWCNTs are often used in FET biosensors as opposed to metallic SWCNTs since their conductivity can be gate-modulated by electrical changes in the external environment [49]. Various purification processes have been reported to separate metallic and semiconducting SWCNT mixtures, such as electrophoresis, centrifugation, chromatography, and solubilisation [55–57]. However, purification of semiconducting SWNTs can add considerable time and resources to the production process [56], and as

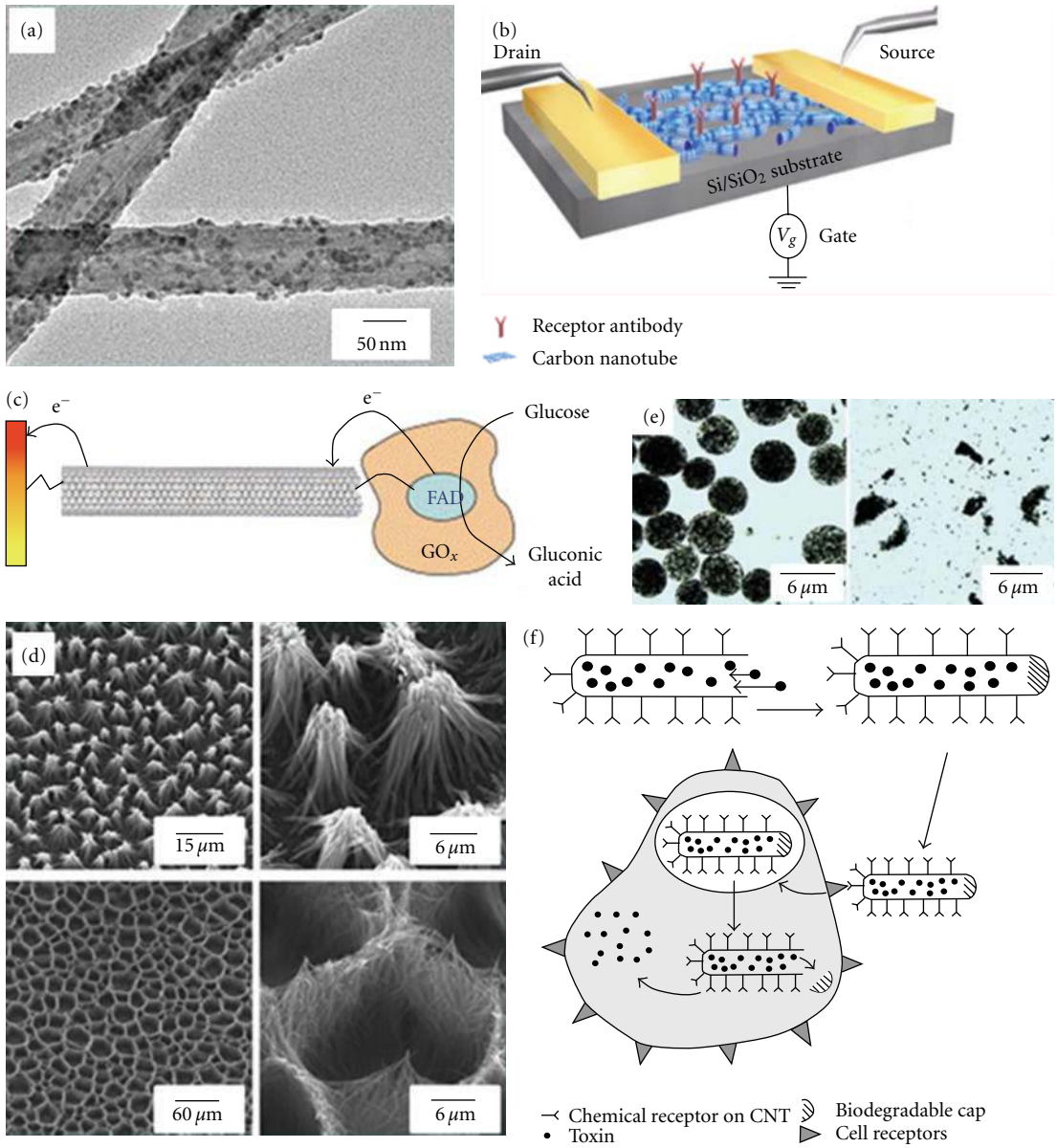

FIGURE 2: (a) Transmission electron microscopy image of ferritin-functionalized MWNT (reproduced with permission from [34]); (b) CNT-FET device for biosensing using antibody receptors (reproduced with permission from [22]); (c) Electrochemical sensor for glucose consisting of an Au electrode bonded to a CNT-GO_x which detects redox reactions between FAD and glucose (reproduced with permission from [51]); (d) "basket-like" periodic MWNT lattices into which mice fibroblast is to be implanted (reproduced with permission from [52]); (e) alginate-polylysinealginate microcapsule destruction by the photoacoustic effect by folate acid—functionalized SWNTs inside the cells (reproduced with permission from [53]); (f) loading and unloading of molecules inside CNTs for drug delivery; drugs are released when a CNT is uncapped within the cytoplasm of the cell (reproduced with permission from [54]).

such should be taken into account when considering the economic viability of CNT device fabrication.

Several approaches have been attempted to further amplify the signals and improve the specificity and sensitivity of CNT-FETs. One of these approaches is to bind specific receptor species, which can undergo selective interactions with the analyte, to the CNT channels. Many types of receptors have been successfully bound to functionalized CNT-FETs, such as aptamers [58], antibodies [59], sugars [60], DNA [50], and proteins [49, 61]. Furthermore, decorating the CNTs with conductive metal nanoparticles (typically Pt and Au) can also amplify the detection signals [62]. Rajesh et al. [63] demonstrated that the sensitivity of DNA detection was 2.5 times greater after the addition of ZnS nanoparticles into CNT-FETs.

Controlling the Schottky barrier effect is another common way to amplify detection in CNT-FETs. Changes in the conductivity of CNT-FETs are mostly due to gate coupling effects and the Schottky barrier effect. The Schottky barrier effect arises from differences between the work functions

of the CNT and the metal contacts [64] and is often hard to predict, and is therefore detrimental to the sensor's performance [8]. Methods such as coating the metal contacts with polymers have been used to minimize this effect and stabilize the response [64]. However, it should also be noted that one can actually amplify the CNT-FET signals for sensing applications by controlling the Schottky barrier effect [3, 65].

Real-time measurement is vital for the monitoring of dynamic systems and is a promising approach for applications in fields such as bioterrorism, food safety, drug testing, and on-the-spot medical diagnosis [65–67]. Carbon nanotube FET biosensors have also been used to monitor biological interactions in real time [8], including interactions involving DNA [35], proteins [64], immunoglobulin [58], morphine [45], and biological processes such as phagocytosis [62]. Again, decoration by metal nanoparticles can be used to improve the performance of CNT-FETs in real-time measurements, as has been demonstrated in the cases of glucose [35] and heroin [45].

On the other hand, CNT-based electrochemical biosensors have been used to detect chemical redox interactions [39, 68]. In this sensing mode the electrical properties and small size of each CNT is preferred, as it allows them to act as tiny electrodes with direct contact to biological systems. For example, a SWCNT with a diameter of ~1 nm is comparable to the size of DNA and the active sites of proteins [69]. The 1D structure of CNTs also allows them to interact with one species at a time, ideal for single-species biodetection and biosensing [62, 70]. Carbon nanotube electrochemical biosensors have been used to detect DNA [68], glucose [71, 72], proteins [49], enzymes [72], RNA [73–75], H_2O_2 [76], and many other biomolecules. Analogous to the case of CNT-FET biosensors, functionalization of CNTs is important to increase the specificity of the electrochemical biosensors.

Figure 2(c) shows an example of an electrochemical biosensor, a gold electrode-CNT-glucose oxidase (GO_x) biosensor for detecting redox reactions between glucose (i.e., the analyte) and the redox active center of the GO_x, flavin adenine dinucleotide (FAD) [51]. The orientation of the CNTs on the electrode has been found to be important for sensing performance, with several studies showing that using aligned CNTs increased the sensitivity of the device [18, 69]. Other biosensors rely on an array of CNTs perpendicular to the electrode where the properties of the biosensor sensitivity are dependent on the spatial distribution and relative diameters of the CNTs in the array [50, 77]. Recently, spun CNT fibers have also been attached to electrodes for biosensing [78] and CNT fiber sensors have been reported to detect glucose with greater sensitivity than traditional Pt-Ir sensors [44].

Many different methods have been used to improve the sensitivity of CNT electrochemical biosensors. The most common way has been to combine metal nanoparticles with CNTs to increase the conductivity and redox activity of the sensor [64, 71, 72, 78]. Other methods include gas treatment [79], oxidation, and plasma etching [80, 81], which can add extra functional groups (e.g., –COOH, $–NH_2$) to the CNTs. These functional groups act as active reaction sites for analyte binding [82]. Lastly, optimizing the ratio of semiconducting and metallic CNTs can also improve the sensitivity [50] and even the response speed [78] of CNT electrochemical sensors. For example, it has been shown that biosensing devices using a mixture of metallic and semiconducting CNTs performed better than those using pure semiconducting CNTs alone [50].

Since many of these electrochemical biosensors are used in real biological environments, it is often necessary to prevent nonspecific binding of proteins, which can interfere with the measurements. Polymer coatings such as poly(ethylene glycol) (PEG) and poly(ethylene oxide) (PEO) are often used to reduce nonspecific binding [8, 49, 83, 84]. However, care must be taken to choose the correct polymer which does not distort the CNT and the biological receptor [36].

It should be noted that there are many nanostructures already used in biosensors, for example, Au nanoparticles [85]. Au nanoparticles are gold clusters ranging from 1 to 100 nm in diameter [86] and are easily functionalized with biomolecules such as DNA, enzymes, proteins, peptides, oligonucleotides, glucose, and RNA [85, 86]. Biosensing with Au nanoparticles is quite well established, especially by enhanced surface plasmon resonance [86] and enhanced Raman spectroscopy [86]. The toxicity of Au nanoparticles is currently deemed minimal compared to CNTs [85, 87]. The main advantage of using CNTs in biosensors instead of Au nanoparticles is that CNTs have many more parameters that can be varied, which potentially allows a wider variety of biosensors to be produced.

2.3. Carbon Nanotubes in Tissue Engineering. Tissue engineering aims to repair, regenerate, and replace diseased or damaged tissue. In tissue engineering, scaffolds are often used to promote cell adhesion, growth, differentiation, and proliferation in a three-dimensional (3D) matrix. These scaffolds also provide mechanical strength and add some degrees of control over location and orientation of the attached cells. Using CNTs as scaffolds has attracted great interest due to their mechanical strength [13], chemical stability [14], and biological inertness [52, 88]. Typically, carbon nanotubes are grown into a 3D porous structure, or else coat an existing 3D porous structure, for example, collagen [89] and then seeded with cells [90]. The cells are allowed to grow over the scaffold until they become self-supporting [90]. Carbon nanotube scaffolds can be fabricated into many different structures [91] with dimensions comparable to biological cellular scaffolds [88, 92], which allows them to support a wide range of biological species.

To promote cell growth and adhesion, CNTs are often functionalized with, for example, carboxyl groups, polymers, and sugars [13–15]. It has been shown that surface charge, functional groups, and hydrophilicity are important in determining cell adhesion and growth [93, 94]. For example, in a study by Zhang et al., hydrophilic, neutrally charged amylose-CNT hybrid matrices supported cell growth and proliferation as compared to chitosan-CNT, sodium alginate-CNT, or chitosan-sodium-alginate-CNTs [33].

The periodicity, size, and structure of the CNT scaffolds can also affect the cellular interactions with the scaffold [52, 95]. Vertically aligned MWCNTs can be fabricated into 3D scaffold matrices of periodic "basket-like" cavities, where the cavity size and density depend on the dimensions of the original array as shown in Figure 2(d) [52]. Mice fibroblast cell lines L929 were successfully cultured on these periodic matrices [52]. Patterns of CNTs can be fabricated by lithography and used to direct the growth of cells such as human mesenchymal stem cells (hMSCs) and neurons [96, 97]. In particular, hMSCs have been found to grow and differentiate well on 3D matrices of fibronectin (FN) functionalized CNTs [98], but their growth was inhibited when seeded on carboxylated CNT scaffolding [99]. The polarization of neurons is also extremely sensitive to their environment; hence CNTs could be used to direct neural connections and interactions, potentially for *in vivo* applications [100].

Apart from using CNTs solely to construct scaffolds, they can also be added to other scaffolding materials to produce heterostructures. For example, porous polymer composites can be produced by dispersing CNTs into PEG or poly(propylene fumarate) (PPF) [101–103]. The addition of CNTs allows the polymer composites to be electrically conductive, which is useful for stimulating cell growth [104]. These composites have generally been used to promote osteoblastic cell growth *in vitro* for bone regeneration research [104–107] and also for neural regeneration [108, 109]

We also note that another carbon nanostructure that has recently emerged as a potential scaffold material for tissue engineering is nanodiamond. For example, a monolayer of nanodiamonds has been shown to support neuronal cell growth [110]. Nanodiamond crystals range from 2 to 10 nm in diameter [111], are mechanically stable [110, 112], have a large surface area [112], and are nontoxic [111]. However, like the Au nanoparticles mentioned in Section 2.2, nanodiamonds have significantly fewer tunable characteristics compared to CNTs, thus offer fewer possibilities for tissue scaffold designs.

2.4. Carbon Nanotubes in Drug Delivery. In delivering drugs, the aim is to use a carrier molecule functionalized with a receptor to carry a drug around the body until it attaches to the problematic site, only then releasing the drug [113]. Receptor-functionalized CNTs have been suggested as targeted vehicles for drug delivery, where they are perceived to have several advantages. Firstly, the nanometer size of CNTs allows them to permeate into cellular membranes, making them ideal for inserting drugs directly into cells [16, 114, 115]. Secondly, each CNT can be functionalized to detect and interact with a single cell, improving the delivery efficiency and reducing the drug dosage [17, 116]. It has been demonstrated that 5 million species can be bonded to an 80 nm long CNT [54]. The combination of size and ease of functionalization allows CNT to deliver drugs to cells, such as neurons and cardiomyocytes, which are difficult to reach by traditional drug-delivery methods [117]. Lastly, drugs can be encapsulated into CNTs [54, 118–120], where release of the drug in the desired cell compartment requires the chemical disintegration of the CNT cap, as illustrated in Figure 2(f) [22]. Successful examples include anticancer drugs and IR-emitting molecules for direct heat treatment *in vivo* [121].

The CNT must have a drug-unloading mechanism for the drug delivery to function effectively [122]. Drug unloading from CNT carriers can by triggered by environmental changes, such as changes in temperature and pH [54]. For example, intracellular pH is lower than extracellular pH; and CNTs, which cross the membrane, can be activated to release their drug load and influence intracellular processes [123]. This allows gene delivery straight into the nuclei of cells, possible by "injection" of CNTs into cells [124]. Drugs may also be released by optical stimulation using near-infrared (700–1100 nm) wavelengths, which are not absorbed by most biological structures, in particular skin [125].

Apart from delivering specific drugs, CNTs can also be functionalized for therapeutic applications. For example, CNTs functionalized with folic acid can bind to cancer cells, which can be killed by using infrared radiation to induce vibration, that is, forming cellular "bombs" [53]. Similar research has been carried out in other studies [125–128]. Figure 2(e) includes two images showing folate-functionalized SWCNTs inside alginate-polylysine-alginate microcapsules [53]. The first image shows the microcapsules before IR irradiation and the second image shows the obliterated microcapsules after irradiation [53]. This specific targeting of cells reduces damage done to surrounding biological systems and is more effective at destroying malignant cells.

3. Nanotoxicity of Carbon Nanotubes

3.1. Background and Motivation. The diagnostic and therapeutic applications of CNT-based materials mentioned above will only be trialed clinically after detailed information on their environmental and health and safety effects in host biological systems is obtained [129–131]. A few preliminary tests have showed that CNTs are biologically benign to certain cells, tissues, and organs under limited conditions [132–134], while further studies have indicated that CNTs are potential hazards that can cause both acute and chronic adverse effects to many living systems [4, 24, 135]. Nevertheless, at this stage, it appears that the biological effects of CNTs are sample specific and must be assessed on a case-by-case basis. The nanotoxicity of CNTs, therefore, requires continuing and extensive investigations and, indeed, this will be required by regulatory bodies before CNTs can be used in clinical environments as functional biomaterials and biomedical devices.

Despite several years of research, definitive findings regarding the extent of toxicological risks arising from using nanotubes are far from complete. Continuing research is required to determine, for example, how CNTs enter cells, where CNTs are internalized, which the cytotoxic mechanisms are relevant, and how the nanotoxicity is affected by a variety of physicochemical characteristics, such as diameter, length, presence of impurities, surface functionalization, and surface wettability. In this section, we give a brief overview of the progress made to date on understanding

the nanotoxicity of CNTs, including the exposure, cellular uptake, subcellular localization, and intracellular trafficking, as well as mechanisms that may result in the mitigation and inhibition of nanotoxicity.

3.2. The Production of and Exposure to CNTs. Despite their relatively recent discovery [136], production of CNTs had already reached 4000 tons by 2010 and could exceed 12000 tons by 2015 [137]. Such large-scale production has inevitably led to exposure risks for both animals and human beings. The most common ways for CNTs to enter the host include inhalation, ingestion from food and water, and absorption through skin wounds or scars [138]. In laboratory-related exposure experiments, intravenous injection [4, 139, 140], intratracheal administration [141], and abdominal implantation [142], are often employed to study the nanotoxicity of CNTs in different organs including the lungs.

3.3. The Cellular Uptake of CNTs. The uptake of CNTs into cells plays a critical role in determining their cytotoxicity and genotoxicity. The outermost layer of the cell, the cellular membrane, consists of a phospholipid bilayer [129], which serves to segregate the subcellular compartments from the external medium, and to regular the transport of foreign materials, including CNTs, into cells [143].

Experimental results indicate that CNTs can be internalized by a variety of cells. Although systematic knowledge is still lacking, it is in general considered that there are two possible pathways for CNTs to cross the cellular membrane and enter cells [129]. One pathway is passive transport, which includes diffusion, membrane fusion, and direct pore transport [24, 144]. Individually dispersed CNTs in aqueous solutions have been experimentally demonstrated to be able to enter the cytoplasm of cells by directly crossing the membrane [145, 146], despite recent modeling showing that the energy cost of entering the cellular membrane via rupture and diffusion was high compared to that of the energy of thermal motion of CNTs [147].

A more common pathway for the cellular uptake of CNTs is active transport via *endocytosis*, which includes phagocytosis and pinocytosis [129, 143, 148]. Endocytosis involves the enclosing of foreign objects in vesicles or vacuoles pinched off from the cellular membrane. In general, long CNTs (>1 μm in length) were taken up by *phagocytosis*, which was mainly conducted by macrophages, monocytes, and neutrophils [143]. Shorter CNTs of length from a few to several hundred nanometers, on the other hand, were mainly internalized by *pinocytosis*, such as macropinocytosis, clathrin-mediated endocytosis, and caveolin-driven endocytosis [129, 143]. Endocytosis is an energy-dependent process, and the orientation of CNT entry can be controlled by the interplay between the tip recognition through receptor binding and the rotation driven by asymmetric elastic strain at the nanotube-phospholipid bilayer interface, as demonstrated recently by numerical modeling [149]. In the most common case, a near-perpendicular orientation resulted in a minimum energy barrier [147].

The exact cellular uptake pathway of CNTs is complex and depends on many experimental parameters, such as the size, length, hydrophobicity, surface chemistry, and the cell culture medium. For example, the uptake of functionalized SWCNTs in phagocytotic cells was found to occur via endocytosis if they were longer than 400 nm and via diffusion-controlled internalization if smaller than 400 nm [150]. Lee and Geckeler [129] have also shown that individual MWCNTs entered cells through direct penetration *in vitro*, whereas bundled MWCNTs entered via endocytosis.

Surface chemistry of SWCNTs also influences the cellular uptake pathway [151]. It was demonstrated that when SWCNTs were grafted with folate using PEGylation and linked by phospholipid bilayer, they could enter HeLa cells bound with the folate receptor (FR, a specific tumor marker) but not those without FR. Similarly, when SWCNTs were grafted with $\alpha_v\beta_3$, they could enter integrin- (a receptor of $\alpha_v\beta_3$) positive U87-MG cells but not integrin-negative cells [152]. If non-cell-targeting molecules were grafted, the entry mode of CNTs will depend on the properties of the conjugated molecules, for example, large molecules such as bovine serum albumin (BSA) enter cells only through endocytosis [152].

Additionally, the hydrophobic surface of CNTs can interact with components in cell growth medium and affect the cellular uptake. Serum proteins in the cell growth medium can bind to CNT walls through π-π interactions or electrostatic attractions, forming a protein coating [129]. The "screening effect" of such protein coatings, known as the "protein corona," allows functionalized CNTs to experience a similar cellular uptake pathway [129, 153].

Finally, the culture medium itself can affect the cellular uptake of CNTs. For example, single-walled CNTs grafted with fluorescein isothiocyamate (FITC) were found to be taken up by cells in a pH 5.8 medium, but the uptake was inhibited in a slightly alkaline medium (pH 7.2) [154]. It was suggested that under the alkaline condition, the anionic form of FITC could dominate the neutral form and hamper the cellular uptake of CNTs [154]. If properly exploited, this property may facilitate the removal of the internalized SWCNTs, though much more research is required.

3.4. Subcellular Localization and Intracellular Trafficking of CNTs. Once taken into the cell, CNTs are often localized in one of a number of different subcellular compartments, for example, cytoplasm, cytoskeleton, mitochondria, lysosomes, endoplasmic reticulum, vesicles, and nuclei and can be translocated between these compartments [143]. Because of their small size and the weak contrast between these cellular components and CNTs, it is often difficult to characterize the subcellular distribution of internalized CNTs. Over the years, techniques, such as confocal and fluorescent microscopy, TEM [4, 24], SEM with focused-ion beam (FIB) [155], Raman spectroscopy [4, 140], and laser and photobleaching [154], have been developed. For example, TEM is a very effective tool to see CNTs (and any other nanoparticles) inside frozen cells. It was utilized by Porter et al. [24] to show that SWCNTs were localized within lysosomes after 2 days,

whereas after 4 days, bundles of SWCNTs were localized in endosomes, translocated across the nuclear membrane, and localized within the nucleus.

One of the major findings made in recent years in this field is that the subcellular localization of CNTs depends on how CNTs enter the cells. When functionalized CNTs directly crossed the cell membrane, they were localized exclusively inside mitochondria, whereas if being endocytosized, they were located inside the lysosomes and phagososome [144, 148, 150]. Small CNTs that entered the cellular membrane through diffusion were found mainly in the cell cytoplasm [129, 150]. These preliminary findings have shed light on the selective translocation and localization of SWCNTs to desired subcellular components.

Figure 3 illustrates the main uptake pathways, the subcellular localization, and the intracellular trafficking of differently functionalized CNTs [129]. It is noted that the internalized CNTs may be translocated between different subcellular components through carrier-mediated transport [154]. For example, endocytosized MWCNTs accumulated in the endosomes could be transported to the endoplasmic reticulum, from which they translocated into the cytosol [148]. Intracellular trafficking can also be effectively controlled by attaching a suitable functional tag on the CNTs. For instance, FITC-SWCNTs were taken up in vacuoles through carrier-mediated transport, but when functionalized with an inhibitor of the carrier-mediated transport, they mostly accumulated in the cytoplasm [154]. Further trafficking of functionalized SWCNTs into nucleoplasm and the nucleus were also observed [129].

3.5. Nanotoxicity Mechanisms in the Lungs. One of the earliest concerns over the toxicity of CNTs arose from the similarity of their structure (i.e., a fibrous shape and a high aspect ratio) and biopersistence to asbestos, an infamous carcinogenic material known to cause mesothelioma [141, 156, 157]. Asbestos has a fibrous structure of 20 to several hundred nanometers in diameter. The toxicity of asbestos in the lungs is thought to be mediated through the generation of reactive oxygen species (ROS), which can induce the activation of antioxidant defenses, causing the release of proinflammatory and profibrotic cytokines from inflammatory and epithelial cells, and activation of the apoptotic (cell death) pathway [141, 158].

Carbon nanotubes in the lungs are often considered less toxic than asbestos [141]. However, many experiments have confirmed that they indeed show many asbestos-like behaviors, although it is still unknown if they can cause mesothelioma. The characteristics of cell deaths were observed when lung cells were exposed to CNTs [24]. When CNTs were inhaled, they were able to reach the subpleura and cause subpleural fibrosis in mice [135]. Chronic exposure to SWCNTs was also shown to cause the malignant transformation of human lung epithelial cells, which is evident for CNT-induced carcinogenesis [156].

Besides the ability to generate ROS in lung cells [4, 159], other cytotoxic mechanisms of CNTs also include blocking ion channels, regulating the intracellular calcium level, binding to subcellular organelles and proteins to stop their functions, and attacking the nucleus and damaging DNA, which can induce apoptosis or necrosis cell deaths and/or mutational cellular events [24, 160, 161]. These effects are in turn strongly influenced by the type, size, shape, surface chemistry, and the route of administration of CNTs [162].

The cytotoxic effect of size and shape of CNTs is best represented by their high aspect ratio, which results in incomplete phagocytosis by the mononuclear cells because the CNTs are too large [129]. This induced incomplete or frustrated phagocytosis can result in macrophage activation and granulomatous inflammation. In fact, it has been hypothesized that the failure of resident macrophages to clear CNTs is the main reason for the activation of proinflammatory pathways that induce lung fibrosis, lung cancer, and malignant mesothelioma [149]. In addition, the aggregation of CNTs by van der Waals' interactions could also affect profibrogenic cellular responses and contribute to the pulmonary toxicity of CNTs *in vivo* [141, 163].

In vivo studies using a mouse model also showed that the pathological origin of CNTs was dependent on the route of administration [164]. For the case of intratracheal instillation, the agglomerates of CNTs with different size and morphology were observed in bronchi of mice, which led to inflammation in 24 days. On the other hand, when CNTs were inhaled, aggregation of CNTs was observed on the lining wall of the bronchi but no inflammation was induced [164].

Surface wettability is another factor that affects the cytotoxicity of CNTs. When macrophages are in contact with hydrophilic CNTs, less inflammation was observed compared to those in contact with hydrophobic CNTs or titanium (a biocompatible metal) [165]. It was found that less proinflammatory cytokines (e.g., tumor necrosis factor-alpha, or TNF-alpha) and interleukin-6 (IL-6) were secreted from macrophages containing hydrophilic CNTs. As a result, hydrophobic CNTs are more toxic than their hydrophilic counterparts.

A final remark on the pulmonary toxicity of CNTs is that many nanoparticle impurities (e.g., Ni, Fe, and Co) carried by CNTs are highly toxic. Removing these nanoparticle impurities is necessary to show the intrinsic toxicity of CNTs [129, 135, 166]. However, conventional purification routes for removing these impurities may generate a high density of functional groups or defects on CNTs, which in turn influences the cytotoxicity. As demonstrated in a recent study, purified CNTs have been shown to have the strongest adverse effects among pristine CNTs, carbon graphite, active carbon, and carbon black.

3.6. Biodistribution and Nanotoxicity of CNTs in Other Organs. Many *in vivo* studies have shown that CNTs delivered to a specific area in the body are not confined to that area [139]. For example, intravenously injected CNTs were shown to be taken up both by the liver and the spleen and then excreted rapidly through the kidney [139, 140]. In contrast, SWCNTs injected into the bloodstream of mice persisted within liver and spleen macrophages (Kupffer cells) [4].

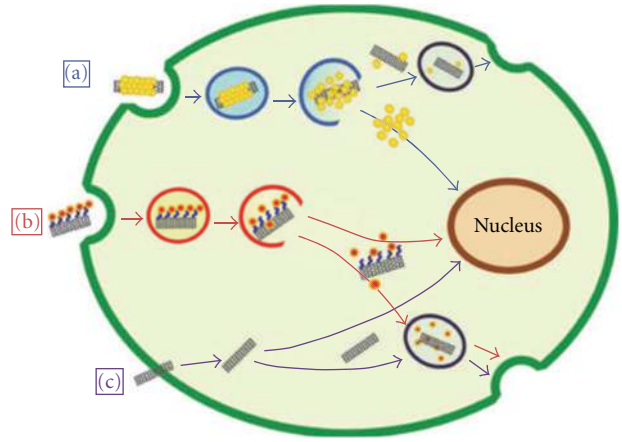

Figure 3: The cellular uptake pathways, subcellular localization and intracellular trafficking of differently functionalized CNTs. (a) Supermolecularly functionalized CNT via endocytosis, (b) covalently functionalized CNT bound with drugs via endocytosis, and (c) individual or specifically functionalized CNT via direct penetration (reproduced with permission from [130]).

Singh et al. [167] also reported that intravenously injected ammonia-functionalized SWCNTs were excreted mainly via the renal route without uptake in the liver and spleen in mice [167].

Because of the migration of CNTs in biological systems, their toxicity to a variety of other organs should also be tested. In many cases, macrophages, which form the first line of defense against foreign materials, will interact with the administrated CNTs [24]. This is why macrophages are one of the mostly studied cells in *in vitro* investigations of CNT toxicity. After CNTs have been ingested by macrophages, they can enter into the blood and lymph circulation at a later stage [24]. Carbon nanotubes can also be dispersed by mucins (glycosylated proteins produced by epithelial tissues) in certain cases and cleaned away in a physiological solution, before they can interact with cells [168].

The long-term accumulation of SWCNTs in organs was studied by Yang et al., who showed that no apoptosis was induced in the main organs [4]. On the other hand, a low percentage of early miscarriages and fetal malformations was observed in female mice exposed to pristine SWCNTs and ROS were detected in the placentas of malformed fetuses [169]. Carbon nanotubes could also induce actin (fibrous proteins that can form filaments and higher-order network structures of the cytoskeleton and that perform essential functions such as force generation, motility, and division) bundling and reduced cell proliferation, which may cause chronic changes to cellular functions [170]. Inhaled MWCNTs were also shown to be able to suppress the immune function of the spleen through the signals coming from the lungs of the exposed mice [171, 172].

3.7. The Mitigation and Inhibition of CNT Nanotoxicity. In attempting to fully utilize the excellent properties of CNTs without being hampered by their adverse effects, several strategies have been proposed to mitigate or inhibit the toxicity of CNTs. The most common method is through surface functionalization [129, 143]. Noncovalently PEGylated CNTs have been shown to be less toxic than oxidized and pristine CNTs [4, 140, 169]. Repeated administrations of carboxylated (CNT–COOH) and amine-CNTs (CNT–NH_2) in male mice caused only reversible testis damage with no effect on their fertility [173]. Other examples include cell-adhesion peptides bound MWCNTs, which did not interfere with neuronal functionality [174], and amine-functionalized SWCNTs, which even protected the neurons [96].

Another way to reduce the cytotoxicity is through the dispersion of CNTs in a biocompatible block copolymer [141, 175, 176]. *In vivo* experiments showed that SWCNTs functionalized with Pluronic polymers can be gradually cleared from the body by alveolar macrophages through mucociliary clearance, reducing risk of lung fibrosis [141]. Lastly, CNTs have been shown to be biodegradable to certain enzymes, such as plant peroxidases, where the degraded CNT fragments can then be effectively phagocytosized by surrounding cells [177, 178]. It has further been shown that the biodegraded CNT fragments, when aspirated into the lungs of mice, did not generate an inflammatory response [178].

4. Graphene: Biomedical Applications and Nanosafety

4.1. Introductory Remarks. Graphene, a 2D carbon nanomaterial with a honeycomb-like structure, has been the subject of a considerable interest after being the subject of the 2010 Nobel Prize for Physics. Its unique properties, including ballistic electron transport [179, 180] at room temperature, tunable band-gap (for few-layer graphene), high chemical and mechanical stability, low electrical noise, high thermal conductivity, and biocompatibility, have led it to be used in many advanced devices ranging from ultracapacitors to spintronic devices [181–186]. In line with the purpose of this paper, however, we will concentrate on the emerging biomedical-related applications of graphene

and its derivatives (i.e., pristine graphene, graphene oxide, metal nanoparticle decorated graphenes, vertical graphene nanosheets, and many other hybrid structures) in biosensors, biocompatible scaffolds, tumor treatment, and drug delivery. We will first present an overview of how and why graphene is used in these cutting edge applications, followed by a brief discussion of how to make graphene for these applications using plasma-based fabrication and other methods.

4.2. Graphene Biosensing and Biomedical Applications. As noted in Section 2, biosensors consist of two fundamental parts—a biomolecular recognition element (receptor) and a transducer. The former interacts with the analyte, whereas the latter processes the "sensed" information and translates it into a useable signal. Graphene is a particularly versatile material as it can play a role in both of these components, in plasmonic/optical- and electrical-based sensors. For example, the affinity of graphene for aromatic ring containing biomolecules has been utilized in the biomolecular recognition element in surface plasmon resonance (SPR) sensors. Wu et al. [189] demonstrated that a graphene-Au SPR biosensor, shown in Figure 4(d), was more sensitive than a conventional Au-only SPR biosensor due to (1) the greater adsorption efficiency of ring-based biomolecules on graphene and (2) increased sensitivity to refractive index (RI) changes (a 25% increase in sensitivity to RI change for 10 graphene layers compared to the Au only case). This affinity can also be used as the basis for graphene surface-enhanced Raman scattering (SERS) sensors [190]. Ling et al. [187] reported that using a graphene substrate resulted in a SERS enhancement (see Figures 4(a)–4(c)) of common SERS probes including Rhodamine 6G and crystal violet. This enhancement is chemical, rather than electromagnetic, in nature. Specifically, it is due to the π-π stacking that occurs when the ring-containing molecule aligns itself parallel to the graphene basal plane—this stacking means that charge transfer between graphene and the biomolecule occurs easily, resulting in a chemical SERS enhancements of around 2–17 times [187]. This chemical enhancement, however, is markedly less than the electromagnetic SERS enhancement achieved when Ag or Au nanostructures are used as SERS substrates, despite graphene's higher bioaffinity.

Vertical graphenes (such as those in Figures 5(a) and 5(b)) can, however, be used in combination with metal nanoparticles to make 3D metal-graphene nanohybrid SERS platforms. Rider et al. [188] presented a novel SERS substrate consisting of vertical graphenes decorated with Au nanoparticles (see Figures 5(d–g)). Using vertical, rather than horizontal, graphenes provides a markedly higher effective "bookshelf" like area to which Au nanoparticles can attach—a conservative estimate puts the bookshelf nanoparticle density as 224% greater than that for the "flat sensor area" [188]. This means that there is a much greater area to which analyte species can attach, compared to typical horizontal sensor architectures. Gold-decorated graphene composites have also been used in electrodes for electrochemical sensors, due to their high electrocatalytic activity and electrochemical stability [195]. In addition, making use of the high fluorescence quenching efficiency of graphene, Chang et al. [196] constructed a graphene fluorescence resonance energy transfer (FRET) aptasensor, with a reported thrombin detection limit two orders of magnitude lower than CNT-based FRET sensors.

Electrical sensors that have incorporated graphene include electrochemical-impedance based sensors [197], electrochemical sensors (in which graphene-related materials form the electrode) [198], and FET sensors [194, 199, 200]. Wan et al. [197] constructed immunosensors based on electrochemical impedance with reduced graphene sheets as electron conductors [197]. Ohno et al. [194, 201] showed that graphene FETs (such as those shown in Figure 5(f)) could be used for label-free biosensing—specifically, they demonstrated electrical detection (via a change in the drain current) of solution pH, protein adsorption and specific biomolecules (such as IgE). Zhang et al. noted that the hydrophobic interaction between certain proteins and chemically reduced graphene oxide is promising for protein immobilization and as a result could be used in a biosensor [202].

Aside from sensors, the biocompatibility and chemical inertness (the basal plane, not the edges, which are quite reactive) of graphene surfaces have led to their use as biocompatible scaffolds for the growth of human osteoblasts [203] as well as components in drug delivery and tumor treatment routes [193, 204–206]. Use of graphene oxide as a drug delivery vehicle for anticancer drug doxorubicin [207] is shown in Figure 5(e). Due to the strong optical absorbance of graphene nanosheets in the near infrared, they have been used as a crucial component in photothermal treatment [192, 208, 209] with reported efficient tumor ablation; this can be clearly seen in Figure 5(c), where the best tumor ablation was observed in mice treated with PEG-graphene nanosheets, indicated by the star [192]. The passage of single molecules through nanochannels or nanopores is important for many biological diagnosis processes [210] including DNA sequencing [211, 212]—nanopores in graphene have recently been used for single DNA molecule translocation [213].

Diagnostics and therapies do not exist in a vacuum, they are informed by each other—leading to mutual benefits—this is reflected in the emerging term "theranostics," focusing on individualized medical treatments [214]. This is an area in which graphene-related materials, as already indicated by Yang et al. [192, 215], can play a very important role as their properties lend them both to sensing and intervention/treatment methods.

4.3. Nanosafety and Nanotoxicity of Graphene. As mentioned in Section 3, for any biological-related application, particularly *in vivo* applications, great care must be taken to ensure that the toxicity of the nanomaterial is well characterized and understood. Whilst this has been extensively done for carbon nanotubes, markedly fewer studies [158, 216–222] are available for graphenes (e.g., an ISI Web of Knowledge topic search on 03/01/2012 gave 59 hits for "graphene" and "toxicity" compared to 1668 hits for "nanotube" and "toxicity"). There is even less consensus as to the sagacity of using this next-generation material as an integral component in *in vivo* applications. Zhang et al. [158] compared the

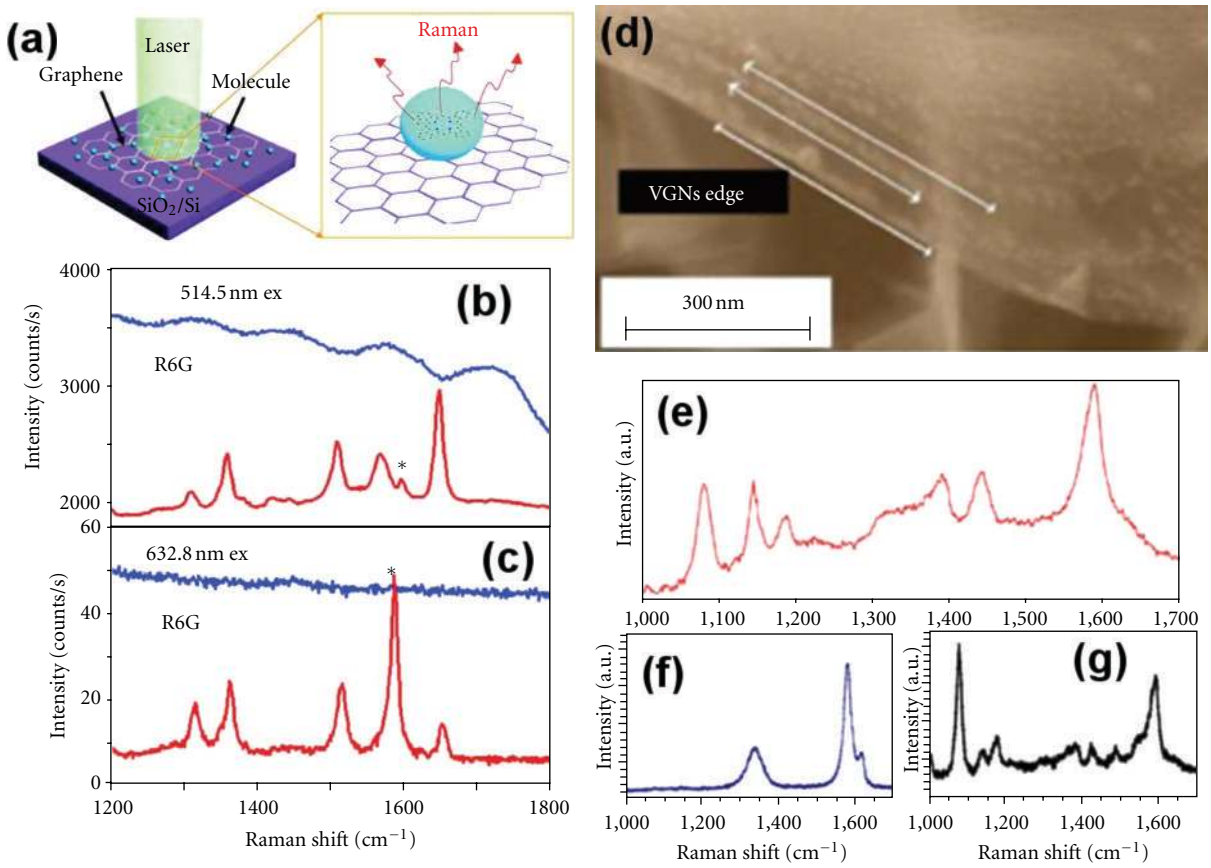

FIGURE 4: (a) Schematic of graphene as a SERS substrate. Graphene as a SERS substrate for Rhodamine 6G detection using (b) 514.4 nm laser and (c) 632.8 nm laser. The blue line is a SiO_2/Si substrate and the red line is graphene. Note that (a–c) reproduced with permission from [187]; (d) a quasi-linear arrangement of Au nanoparticles on vertical graphene nanosheets (VGNs); SERS spectra of 10^{-2} m 4-aminothiophenol on (e) Au-VGNs array, (f) VGNs only, and (g) Au nanoparticles only. Note that (d–g) reproduced with permission from [188].

cytotoxicity level of graphene to that of carbon nanotubes in the case of neuronal PC12 cells. They found that toxicity was shape and composition dependent, with graphene overall having a lower toxicity than CNTs; however the toxicity of graphene was curiously found to be inverse to concentration [223], with graphene exhibiting a higher toxicity than CNTs at low concentrations [223]. Studies on the uptake of PEG-coated graphene nanosheets in mice and subsequent photothermal treatment of cancerous tumors did not show any adverse toxic effects [192, 215]. In other studies, however, sharp graphene nanosheet edges [216] have been shown to cause considerable damage to the cell membrane of bacteria, although this antibacterial property has the potential to be useful. Moreover, hydrophilic carboxyl-functionalized graphenes have been shown to be able to be internalized in cells without any toxic effects, in contrast to hydrophobic pristine graphene [224]. The biocompatibility of graphene oxide has also been studied, with toxicity shown to be dose-dependent in both humans and animals [225], with little to no effect for low and medium doses in mice [225]. Graphene oxide nanosheets were demonstrated to be biocompatible with yeast cells [226]. With the wide range of morphologies, coatings, and hybrid structures available for graphenes, more detailed and longer-term studies are required before serious *in vivo* biomedical graphene applications are implemented.

4.4. Fabrication of Vertically Aligned Graphene Structures. Many different fabrication methods have been used to make graphene-related materials, from the first successful isolation via micromechanical cleavage [227], to chemical reduction of graphene oxide [228, 229], chemical vapour deposition (CVD) [230, 231], thermal decomposition of SiC [232], plasma nanofabrication techniques including plasma-enhanced CVD [233, 234] and arc discharges [235], as well as unzipping of CNTs via a variety of methods (e.g., chemical treatment, plasma etching) [236, 237]. For a detailed description of the relative merits of these fabrication methods, we refer the interested reader to two comprehensive reviews [238, 239]. As noted in Section 4.2, vertically aligned graphene structures have beneficial properties for sensing and other biomedical devices. However, so far there have been limited successes in fabricating these structures. In particular, plasma-based self-organization [240] is a promising way to grow catalyst-free, high-quality vertical graphenes

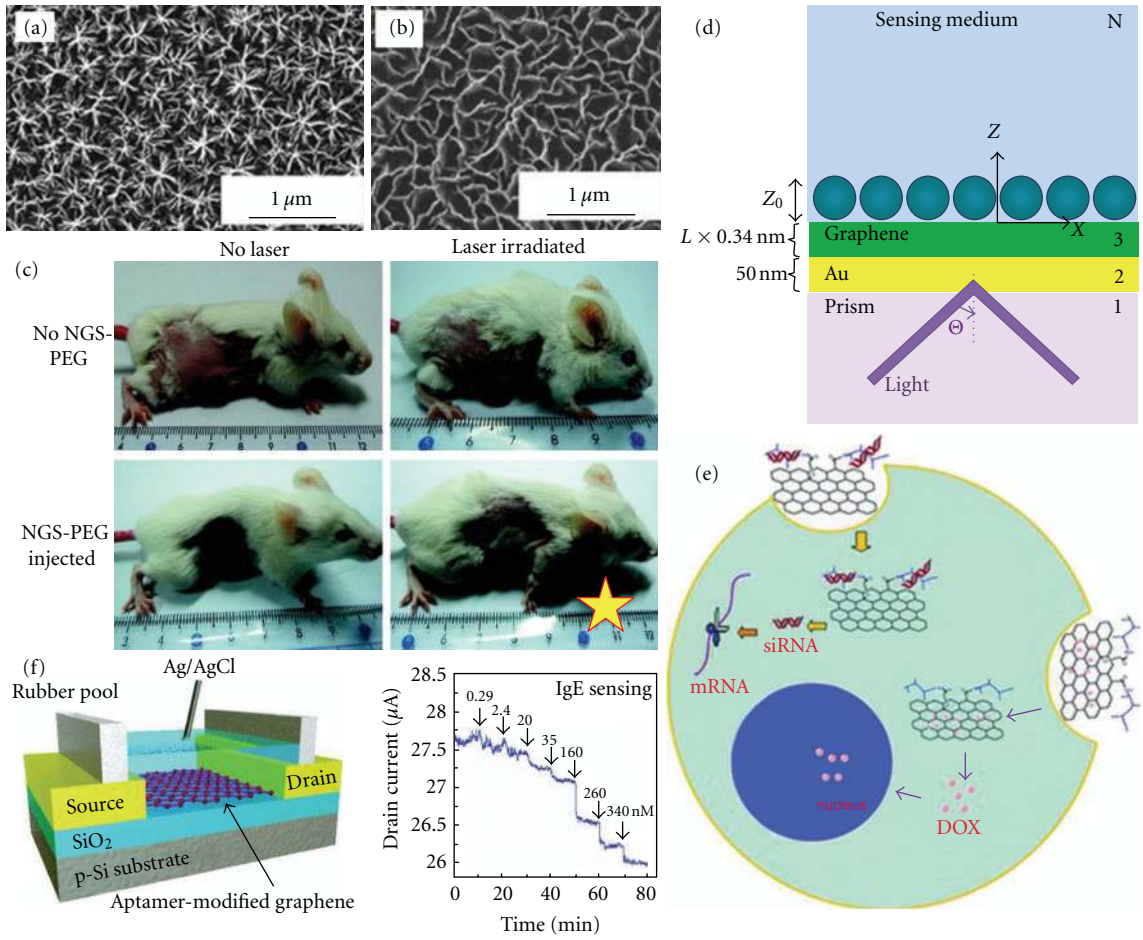

FIGURE 5: (a, b) Turnstile-like VGNs and maze-like VGNs, respectively. Reproduced with permission from [191]; (c) efficient tumor ablation in mice using PEG-graphene nanosheets where the best tumor ablation occurred in the mice injected with PEG-graphene nanosheets and laser treated (indicated by the yellow star). Reproduced with permission from [192]; (d) graphene as a biomolecular recognition element in SPR sensor. Reproduced with permission from [189]; (e) use of graphene oxide as a drug delivery vehicle for anticancer drug DOX. Reproduced with permission from [193]; (f) use of graphene in FRET-based sensor, specifically for detecting IgE; reproduced with permission from [194].

[191, 241]. Papers by Seo and Kumar et al. [20, 191, 241] have shown that it is possible to grow graphene nanosheets with a variety of morphologies (e.g., unidirectional, or see Figure 5(a) for turnstile and Figure 5(b) for maze-like) with different optoelectronic properties by modifying the plasma parameters such as gas composition and the degree of ionization. Plasma-based fabrication routes reduce human exposure to any hazardous byproducts since the growth is conducted under vacuum. Moreover, the nanostructures are typically surface-bound, which means they are less likely to be ingested or inhaled, as discussed for CNTs in Section 3 [131].

5. Summary and Outlook

In this paper, we have discussed the promising future of incorporating CNTs into the field of biomedicine, specifically their current roles in biosensing, drug delivery, and tissue engineering. The benefits of CNTs were presented, together with potential nanotoxicity and harmful effects of CNTs, on biological systems. Also discussed were the potential uses for graphene for similar biomedical applications as well as the problems associated with graphene's toxicity and safety. There are many challenges ahead that must be addressed before CNTs and graphene can be successfully integrated into biomedical devices and technology. The main advances required, in our opinions, include the following.

(i) Advanced techniques and facile methods are needed to increase the sensitivity of CNT biosensors towards single-molecule detection.

(ii) More efficient loading and unloading methods for drug delivery would refine overall performance of CNTs as carriers.

(iii) Further research is required into various CNT hybrid scaffolds to promote cell adhesion, growth, differentiation, and proliferation.

(iv) More specialized coatings and CNT-functionalization to minimize nonspecific bonding are needed.

(v) Protocols and further experiments should be conducted to determine the exact nature of the nanotoxicity of CNT-based and graphene-based materials.

(vi) Innovative ideas and further experiments are needed to further develop the use of graphene in advanced biomedical applications.

(vii) Innovative solutions are required to reduce fabrication and running costs of CNT and graphene biomedical devices to make them economically viable.

The long-term goals associated with incorporating CNTs and graphene into biomedical technology suggest that further research is required before these carbon nanostructured devices reach sufficient performance standards.

Authors' Contribution

C. Fisher, A. Rider, and Z. Han contributed equally to this work.

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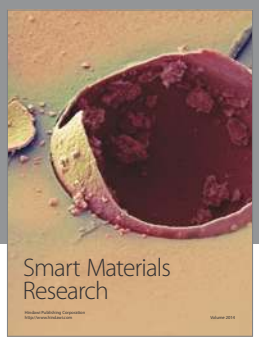

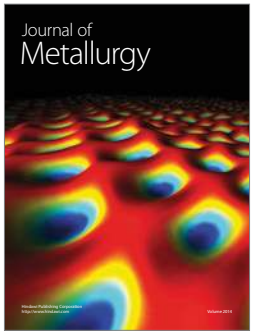

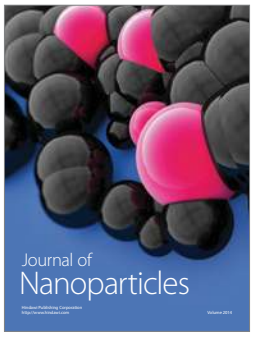

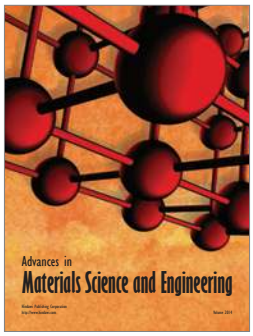

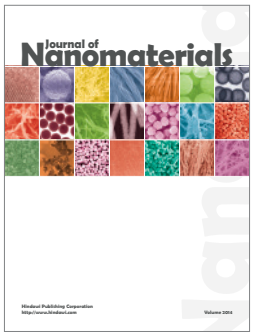

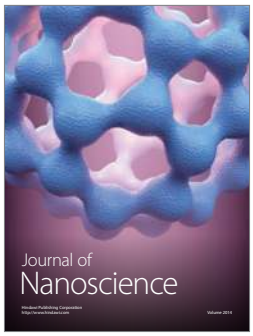

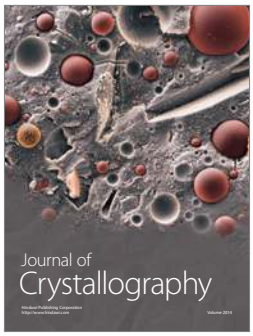

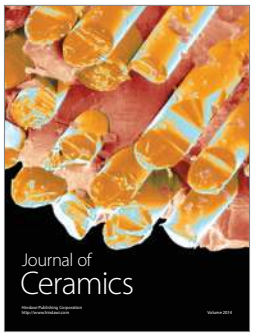

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