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Carbon Nanomaterials: From Therapeutics to Regenerative Medicine

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Abstract

Carbon nanomaterials, including carbon nanotubes and graphene, are widely studied as new biomaterials for delivering drugs as well as providing scaffolds to regenerate specific tissue/organs. In this review, we summarize the main achievements for novel carbon nanomaterials; surface functionalization, toxicity, cancer targeting, and nerve regeneration. In particular, this review describes different forms of carbon nanomaterials and their fabrication methods as threads or ribbons. Carbon nanomaterials as delivery vehicles are also proposed asefficient tools fortransporting and translocating therapeutic molecules with minimized toxicity. Further, nerve regeneration on carbon nanotube threads is briefly reviewed. We conclude with some speculations and predictions on futureexciting and challenging directions for carbon nanomaterial-based nanomedicineapplications.

Keywords: Carbon nanotube; Graphene; Toxicity; Drug delivery

Introduction

This review is focused on carbon nanomaterials and their unique characteristics, but it is important to note that overall, nanotechnology is being explored and utilized at an unprecedented pace to diagnose and treat diseases [1-10]. Other nanomaterials with specific important characteristics useful for medical applications include: gold nanoshells [10] used for cancer therapy and imaging, and zinc-oxide nanowires [11] used for energy harvesting and biosensing. It may also be advantageous to use combinations of nanoparticles to develop multi-mode approaches to solve medical problems, e.g. imaging or sensing using one type of material or particle and therapy using another. Six different areas of application of carbon nanomaterials are discussed next followed by overall conclusions.

Carbon nanomaterials are being used to develop the next generation of biomaterials for applications in therapeutics and regenerative medicine. Carbon nanomaterials, mainly in the form of nanotubes and graphene, have become the focus of intensive research because of their unique physical and chemical properties such as their hollow structure, their high surface area-to-volume ratio, electrical conductance, thermal conductivity, mechanical stiffness, and the possibilities of functionalizing them to change their intrinsic properties [1]. Functionalization can increase their solubility and biocompatibility under physiological conditions. The nanomaterials can be further conjugated with specific biomolecules such as polymers, peptides, proteins, nucleic acids, and other therapeutic agents, which can target specific types of cells, tissue, and organs. This paper reviews recent advances in the use of carbon nanomaterials in medical applications. In particular, we discuss six important areas of application: (i) different forms of carbon nanomaterials; (ii) functionalization strategies; (iii) drug delivery for cancer treatment [2-5]; (iv) nerve regeneration [6]; and (v) in-body sensing [5-9] (v) toxicity issues. These topic areas individually are the subjects of many publications and books. The purpose of the current paper is to give a concise overview of the areas and point to relevant literature that readers can access for further research. It is hoped that the underlying common thread of carbon nanomaterials in these topics may give rise to explorations of intersecting different carbon technologies to make further advances in the future.

Carbon Nanomaterials

Carbon nanomaterials can be described as sp^2- carbon bonded structure; zero dimensional fullerenes, one dimensional carbon nanotubes, and two dimensional graphene (Figure 1). These carbon nanomaterials exhibit extraordinary electrical and mechanical properties [12].

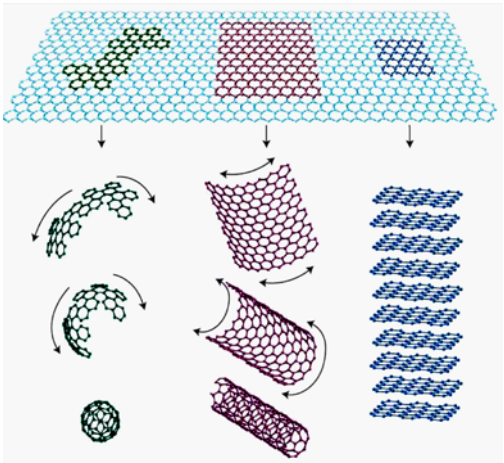

Figure 1: Graphene (2-D) as the source of other dimensional graphitic materials: fullerenes (0-D, left), nanotubes (1-D, middle) and graphite (3-D, right) [16].

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Carbon nanomaterials including carbon nanofibers, fullerenes (C_{60}) [13], single-wall carbon nanotubes, multi-wall carbon nanotubes [14], activated carbons, and graphenes [15], are generally produced by different techniques such as: electric arc discharge, laser ablation, thermal or plasma-enhanced (PE) chemical vapor deposition (CVD), mechanical exfoliation, and epitaxial growth.

Laser ablation and arc discharge are modified physical vapor deposition (PVD) techniques and involve the condensation of hot gaseous carbon atoms generated from evaporation of solid carbon. In arc discharge, carbon vapor is created by electrical discharge between two carbon electrodes with or without a catalyst. Carbon nanotubes are normally produced using these two high temperature PVD methods. Chemical Vapor Deposition (CVD) is a better technique for high yield, high-density and low impurity production of carbon nanotubes which can grow asindividual, free-standing nanostructures. In addition, CVD provides good control over the size, shape, and alignment of the nanotubes. The CVD approach is also used for producing high quality graphene used in numerous electronic and biological applications [16]. Mechanical exfoliation is another simple approach to obtain graphene from graphite. Epitaxial growth on metal and silicon carbide (SiC) substrates is also a well-established technique to produce high quality graphene.

Much work has been done in the post-processing of carbon nanotube arrays into ribbon and yarn forms for specific biomedical applications (Figure 2). The unique electrical and mechanical properties of carbon nanotubes in yarn and ribbon formenable new biomedical applications such as neural prostheses, scaffolds, suture thread, and in-body antennas.

Functionalization of carbon nanomaterials

In order to use carbon nanomaterials in therapeutics and regenerative medicine, as-grown carbon nanomaterials need to be purified to remove amorphous carbon, catalysts, and other impurities introduced during the synthesis process. Typical purification includes high-temperature annealing, plasma oxidation, and chemical treatment. After attaining the requisite purity, the next step is to modify and functionalize the surface of these carbon nanomaterials to immobilize biomolecules. Since as-grown carbon nanomaterials are hydrophobic and are not soluble in biological media, surface functionalization of end- and side-walls of carbon nanomaterials is critical to render solubility, biocompatibility and low toxicity. Surface functionalization can be achieved by wet chemical treatment such as acid reflux and dry treatment such as RF-plasma treatment. In particular, strong acid treatments with HNO_3, H_2SO_4, $KMnO_4$, $K_2Cr_2O_7$, OsO_4, CCl_4, $O_2(g)$, CF_4, and SF_6 are well-established, and can further immobilize specific biomolecules. These methods can create functional groups such as carboxylic, hydroxyl, ketone, alcohol, ester, amine, thiol, and fluorine [17].

Creating functional groups, further, can load small molecules such as chemotherapeutic drugs on to carbon nanomaterials via either covalent conjugation or non-covalent adsorption. Many different conjugation strategies can be applied to immobilize biomolecules with the use of proper coupling agents such as 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC), N-hydroxysulfosuccinimide (NHS), and N,N'dicyclohexylcarbodiimide (DCC) for activated amidation. In the case of noncovalent bonding, coating or wrapping nanotubes with polymers such as poly vinyl pyrrolidone, polypyrrole, poly ethylene glycol (PEGylation), and poly styrene sulfonate makes the nanotubes water soluble and biocompatible. The polymer can also be easily functionalized for conjugating proteins and loading drug such as platinum (IV) complex, paclitaxel [18], doxorubicin, cisplatin, and 10-hydroxycamptothecin (HCPT) [19] (Figure 3).

Drug Delivery in Cancer

The chemotherapeutic agents are still the mainstay treatment for management of advanced cancers. The therapeutic efficacy was, however, less than desired. For example conventional chemotherapies destroy cancerous cells as well as normal cells, causing significant unfavorable side effects. Great efforts have been devoted to develop cancer-targeted drug delivery, which would reduce systemic toxic side effects. Carbon nanotubes have unique hollow structure, large surface area, and chemical functionality on the surface. Functionalized carbon nanomaterials through oxidation, non-covalent bonding, coating and wrapping nanotubes with polymers, become soluble in aqueous solutions. These functionalized carbon nanomaterials will be engulfed into cells through energy-dependent endocytosis pathways. Two endocytosis pathways, clathrin-mediated endocytosis and caveolae were suggested for cells to engulf smaller functionalized-carbon nanomaterials for 50-200 nm single wall carbon nanotube. During the endocytic processes, the membrane compartments move carbon nanomaterials from the plasma membrane into cells and recycle them back to the surface (early endosomes) or deposit them into the late endosomes and lysosomes for degradation [20-28].

It was shown that carbon nanomaterials can be successfully delivered into nucleus and other organelles [23]. The diameter, length, dispersion, and coating are important factors that determine whether

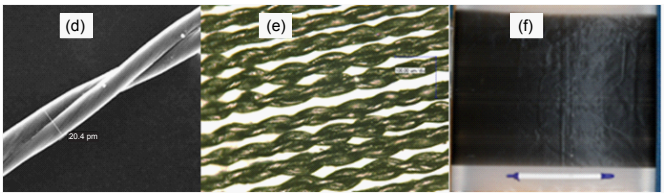

Figure 2: CNT arrays synthesized at UC: (A) 12-mm long, non-patterned; and (B) patterned CNT arrays grown on 4-inch wafers; (C) SEM image of a CNT array; and (D) HRTEM image of DWCNTs; (E) CNT yarn made of two threads; (F) CNT 4-end micro-braid (braid from Atkins & Pearce Inc.); (G) CNT sheet produced from the forest.

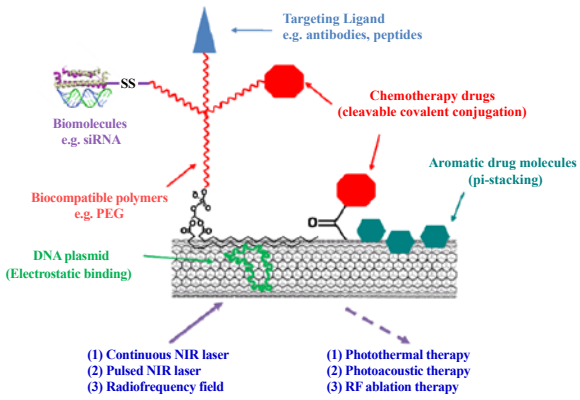

Figure 3: Schematic drawing showing various approaches for CNT-based drug delivery and cancer therapies [20].

carbon nanomaterials will be kept inside of a cell or discharged from a cell by exocytosis pathways. The intracellular transportation ability and hollow structure properties of carbon nanomaterials make them ideal to load and deliver drugs to cancerous cells. In addition to the traditional chemotherapeutic agents, such as toxoid, doxorubicin, cisplatin, and paclitaxel, the functionalized nanomaterials can be used to deliver antisense oligonucleotides, RNA interference, antibodies, and small molecule inhibitors [24-28]. Carbon nanomaterials were successfully conjugated by PEGylation or other polymer conjugation with these therapeutic agents [24-28].

There is a report of successful delivery of drugs without causing cytoxicity into a cell using systems based on endocytotosis pathways *in vitro* [25]. However, *in vivo* targeted delivery of drugs to a tumor is still difficult to achieve in terms of efficiency and clinically relevance. The most challenge task for delivering carbon nanomaterials into tumor tissue is to keep them in circulation and to release them into a tumor lesion through the abnormally leaky tumor blood vessel. In addition, the carbon nanomaterials must be prepared so that they will not be cleared from the blood and taken up by various organs especially kidney and liver for rapid renal and fecal excretion. Blood compatibility, with minimum foreign body reaction, is necessary for prolong circulation of carbon nanomaterials in blood vessels, which eventually increases their uptake in the tumor. Yang et al. [26] reported high *invivo* tumor uptake and efficient photothermal therapy using graphene.

On the other hand, because of permeability and retention effect of local tumors, Honjie Dai et al. [18] deliver drug-carbon nanotube complex to the site of the tumor and inhibited the tumor growth. And specific anti-tumor coated carbon nanotube also successfully localized to the tumor. Multiwall carbon nanotubes are conjugated with quantum dot and visualized in mice.

Carbon nanomaterials were also functionalized with MRI contrast agents such as gadolinium and iron, which eventually image nanoparticles in the body. Also fluorescence nanoparticles such as quantum dots (Figure 4) were conjugated with carbon nanomaterials to target tumors [27]. Antibodies which act against cancer, were covalently immobilized on the functionalized carbon nanomaterials and circulated in the body until they found the tumor. Remarkable physicochemical properties were used for thermal cancer therapy. For example, exposure to radiofrequency (RF)-heated carbon nanomaterials eventually destroyed the tumor. Yang et al. [26] demonstrated that carbon nanomaterials are efficient in *in vivo* photothermal therapy by intravenous administration and suggest the great promise of graphene.

Nerve Regeneration

Some of the most challenging and disabling issues in the 21st century involve the nervous system, either through injuries resulting from trauma or because of disorders that disrupt function. For example, it is estimated that about 2.5 million people worldwide have spinal cord injuries [29]. Spinal cord injuries occur most often in younger patients, resulting in significant years of disability, costing billions of dollars in supportive services. Other injuries include traumatic brain injury, which influences 1.4 million people in the US, with a 2003 estimated cost per year of $56 billion [30], and traumatic damage to peripheral nerves, which occurs in approximately 2.8% of all trauma patients [31]. In all cases, repairing damaged nervous tissue and in particular, recovering function, remains highly challenging due to the complexity of nervous system anatomy and physiology. Carbon nanomaterials demonstrate several significant features that have promise for use in nervous system repair. Carbon nanomaterials have the type of nanosurface features that have been demonstrated to encourage nervous tissue regeneration, including the physical shape (a linear geometry), the nanoscale surface topology and the high aspect ratio of nanomolecules or larger structures made from carbon nanotubes, like carbon nanotube thread. These closely resemble the microenvironment that nerve fibers migrate along during embryonic development and regeneration. Carbon nanomaterials also offer high mechanical strength to support process outgrowth, and flexibility to avoid further damage of soft surrounding tissues during movement. An additional attractive feature of carbon nanomaterials is their high electrical conductivity, a feature that has been shown to encourage nerve regeneration [32]. Furthermore, they are biocompatible and can be readily functionalized by coating with substances that increase neural cell adhesion, decrease inflammatory responses or stimulate growth. Two applications of carbon nanomaterials of especial interest to neurobiologists are discussed here, their use in scaffolds to repair damaged nervous tissues, and their use as biocompatible electrodes for recording from or stimulating nervous tissues.

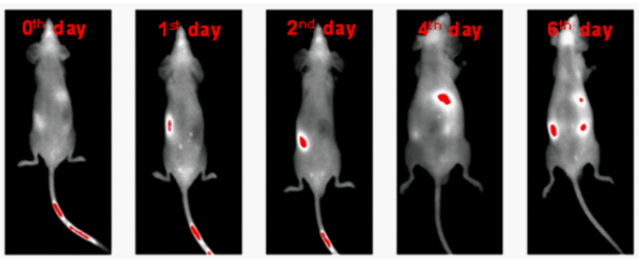

Figure 4: *In vivo* fluorescence images of CNT-QD IV injected into nude mice and imaged after circulation at various time intervals. These pictures show prominent CNT-QD uptake in the liver, kidney, stomach, and intestine [27].

Carbon nanomaterials hold great promise for use in scaffolds to promote nervous tissue regeneration and functional recovery after injury or disease. Towards this goal, carbon nanomaterials, with or without additional coatings or modifications, have been shown, first in culture systems, to promote and improve neural cell attachment, survival, process outgrowth and function, beginning with pioneering work [33] and then continuing [33-37]. A few key examples are that neural cells grown on carbon nanomaterials exhibit enhanced electrophysiological function [38] and that both embryonic and postnatal stem cells can differentiate into neurons [39-42]. An exciting recent development in carbon nanomaterial technology has been the production of thread-like materials from the particulate-like carbon nanotubes [43]. These promote neurite outgrowth from a variety of neuronal cell types (Figure 5) [35,42,44,45] and allow neuronal differentiation from postnatal neural stem cells, (Figure 5(C)) [42]. Studies *in vivo* have begun, focusing on biocompatibility, and are demonstrating promise [46-49]. Thus, the field is poised for further exciting pre-clinical studies of the use of carbon nanomaterials in biomaterial scaffolds for the regeneration of damaged nervous tissues.

Implantable electrodes are used to stimulate the nervous system by electrically activating or inhibiting neural activity in multiple disorders, including Parkinson's [50], epilepsy [51] and chronic pain [52]. Meanwhile, recording electrodes are placed in animals and humans to build brain machine interfaces, which use recorded neural signals to control external devices such as computers, wheelchairs and robotic arms [53-54]. Current neural electrodes are made of chemically inert materials such as platinum, gold, iridium, titanium and stainless steel. Chronic implantation of these microelectrodes leads to glial scar

formation and neuronal loss around the electrodes, which interfere with the intended recording or stimulating functions [55]. In recent years, carbon nanomaterials have been investigated as an alternative material for neural electrode because they present superior electrical and mechanical properties compared to the conventional electrode materials. Carbon nanotubes deposited on neural electrodes improve the recording capabilities of the electrodes [56]. Cellot et al. [57] proposed that carbon nanotubes help promote neuronal activity in a cultured network by forming tight contacts with the cell membranes that might favor electrical shortcuts between the proximal and distal compartments of the neuron. Electropolymerization of a biocompatible polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), doped with multiwall carbon nanotubes has been shown to greatly reduce the electrode impedance while increasing the charge injection capacity and chronic stimulation stability [58]. In addition, the PEDOT/CNT substrate supported healthy neuronal attachment and growth, demonstrating excellent biocompatibility. Furthermore, it has also been demonstrated that drug molecules can be loaded into carbon nanotubes and electrically released to treat the inflammatory tissue response around the implanted electrodes [57-60] (Figure 6).

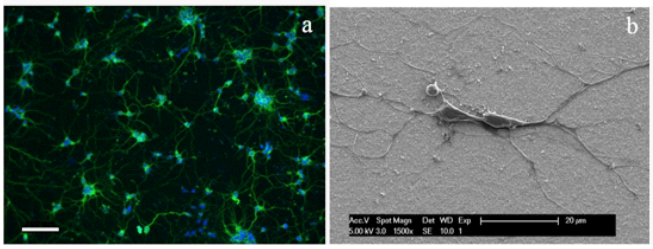

Figure 6: (A) Fluorescent and (B) SEM images of neurons grown on PEDOT/CNT surfaces. For the fluorescent image, the scale bar represents 100 μm [42].

Carbon Nanomaterials for In-Body Sensing

Conventional approaches diagnose and treat illness and diseases by making measurements external to the body or by taking blood or a tissue sample. These conventional methods are accurate and well accepted in medical practice. But they are inspection techniques where the patient must come to the clinic and large equipment is used to perform the testing. There has been limited research into the use of sensors inside the body for real-time biological health monitoring. There are external sensors to monitor biological functions such as heart rate and there are internal temporary sensors such as a temperature sensor pill or inspection camera. Recently, nanotechnology is providing sensors that can be implanted into the human body for real-time human health monitoring. Sensors based on carbon nanomaterials can be placed into the body to continuously monitor biological processes and detect illness and disease. Various types of sensors are being conceptualized and developed. These include carbon nanotube-based orthopedic implant sensors, sensors for monitoring the degradation of biodegradable implants [61], monitoring bone healing [62,63], smart orthopedic implant sensors, anti-infection sensors, contact lens sensors for diabetics, diabetic sensors, inflammation and infection sensors, brain derived self-adapting sensors, implanted neural sensors, nanoporous membranes, tissue healing sensor, brain hemorrhaging sensor, acid reflux sensors, chemical sensors, protein sensors, and others. The future of carbon nanotechnology-based *in situ* sensors is bright, because measuring inside the body can provide more information and continuous information that cannot be obtained using conventional methods. Monitoring multiple variables simultaneously in the body can help uncover disease early and provide understanding of biological processes.

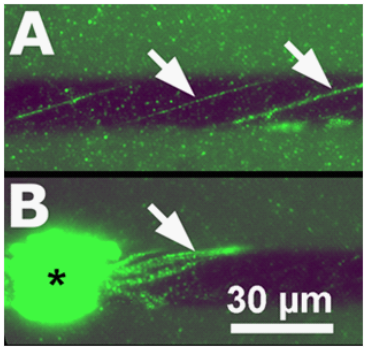

Figure 5: (A - B) Rat DRG neurons grown (for 7 days) on carbon nanotube (CNT) thread (black), immunostained for neuron-specific tubulin (NST). Arrows A point to neurites A) away from the ganglion on the thread and B) extending out of the ganglion (asterisk). C) Mouse CNS neurosphere cells (grown for 5 days in differentiation medium on laminin-coated thread, see (Hopkins et al., 2010) for culture details) differentiated into neurons (green, NST immunostaining) and astrocytes (red, GFAP immunostaining), with blue stained nuclei (DAPI stain) [42].

Sensors are used almost everywhere in our environment and society but there is a glaring lack of the use of sensors to monitor the workings of the most important things on earth, humans. The reason for the lack of use of sensors inside the body centers on a few things; the problems of sensors becoming quickly bio-fouled and causing inflammation or other reactions, the difficulty of communicating with the sensors, a conservatism of physicians to explore new technologies, and expensive and long-time procedures needed to gain FDA approval to commercialize sensors. Also, development of *in vivo* sensors is highly interdisciplinary research involving chemistry, physics, materials science, biology, and engineering. There might be two general classifications or types of sensors that can be used inside the body; (i) chemical and protein bio-molecular biosensors, and (ii) physical property sensors. These two types of sensors are discussed next along with other aspects of sensing in the body.

Chemical or protein bio-molecular sensors would measure glucose, dopamine, cancer markers such as PSA or IL-8, bone turnover markers [63], pH, and a huge number of other proteins. The chemical and protein sensors might be the most useful, but face the large problem of biofouling of the electrodes or sensing elements *in vivo*. Also, the sensors often use anti-bodies for selectivity and the antibodies have a limited lifetime and the sensing is difficult to reverse to measure up and downward changes in concentration. Coatings or nano-patterning on surfaces is used to slow down biofouling. Another more complex possible approach to overcome the biofouling problem is to develop telescoping or retractable electrodes, figure 7. A concept *in vivo* biosensor uses a solenoid electrode built using carbon nanotube wire [16].

Physical property sensors would measure temperature, pressure, acceleration, displacement, wave velocity, light, sound, vibration, flow velocity, strain, proximity, magnetic field, or possibly other parameters. Physical property sensors are simpler because they are less affected by biofouling. The sensors can be inert, maybe hermetically sealed, and be biocompatible if their size is small. The greatest enabling feature of nanotechnology is the ability to make the sensors small, which allows

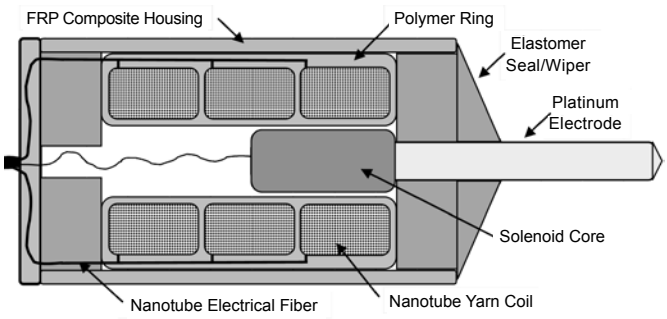

Figure 7: Concept active biosensor with nanotube solenoid retractable electrode.

them to be less invasive and to provide high spatial resolution of the measurand. Many medical behaviors and diseases are related to or caused by small changes in temperature, pressure, damping ratio, strain, or changes in tissue homogeneity. In principle, tiny sensors distributed in the body to measure physical properties could provide continuous and early information on the health of the body. Carbon nanomaterials are poised to provide the sensing mechanisms for several of the physical property sensors. An approach to decide on the most appropriate type of sensor to be used for an application is to make a table of all of the chemical and physical properties of the material or system to be measured. Then the most practical type of sensor can be developed. A problem is that the information, for example on tissue properties for different tissues, is not available. This illustrates that sensors are needed just to characterize the properties of materials *in vivo*. The properties of tissue *in vivo* and *ex vivo* may be different and it may be preferred to measure the properties of biological materials *in vivo* being careful that the sensor does not affect the property of the material being measured.

A challenge with using *in vivo* sensors is communicating with the sensor. Wireless transmission using RF signals requires an antenna in the body, which increases the size of the sensor. Nanotube thread has been shown to be an excellent antenna [64-66] and electromagnetic waves were propagated through biological media using a CNT antenna. Magnetic communication through coils on two sides of the skin is an approach that avoids RF signals but requires close proximity of two coils. Other approaches to communication are being developed but some are proprietary and the subject of intellectual property and details will be released as development proceeds in the upcoming few years.

Toxicity

The number of literature articles concerning the health impacts of carbon nanomaterials is far behind the publications describing their physical and chemical properties, however a few recent reviews concerning carbon nanomaterial toxicology are available [67-76]. The interested reader is encouraged to examine these reviews and the articles referenced there in for a more thorough review of toxicity. There has been limited research into theuse of The analysis of the potential cytotoxicity, oxidative stress, and inflammatory response due to exposure is complicated by the fact that nanomaterials can differ in composition based on the purification and synthetic methodology. Furthermore, much chemistry is available to functionalize carbon nanomaterials, and it is possible that the functionalization can help induce or prevent harmful effects. Care must be taken in interpreting literature results in light of the complexity of variations associated with the materials.

The level of toxicity of purified nanomaterials is a function of size, aspect ratio, surface area, functionality, and structure.The high aspect ratio, fibrous nature, and biopersistence of carbon nanotubes, nanorods, and nanofibers have drawn parallels to asbestos in terms of fitting the fiber toxicological paradigm [77-79]. Indeed some studies have demonstrated that MWCNTs have carcinogenic potential, yet the underlying mechanism has not been studied. A further complicating factor concerning application of results is the experimental dosage and its relevance to actual environmental exposures [79-81]. CNTs are generally more flexible than asbestos and the chemistry of highly conjugated carbon materials is different than the silicate-based asbestos.The similarity between these two fibrous materials is not to be under- or over-estimated, and precise toxicity studies are necessitated.

Much research does exist that demonstrates that harmony can be achieved between carbon nanomaterials and the biological systems in which they are used. Medepalli et al. [81] reported that acute response of blood leukocytes to CNTs in *in vitro* sDNA-functionalized SWCNTs did not elicit an acute immune response from blood leukocytes through either direct or indirect interactions. Semberova et al. [82] suggested that CNTs activate blood platelets by inducing extracellular Ca^{2+} influx that could be inhibited by calcium channel blockers SKF 96365 and 2-APB. Thurnherr et al. [83] demonstrates that despite the high potential for ROS formation, pristine MWCNTs can accumulate and persist within cells without having major long-term consequences or inducing adaptive mechanisms.

Another aspect to address before commercializing carbon nanomaterials in the biomedical and pharmaceutical markets is occupational health safety and health issues related to exposure during manufacturing [84]. Carbon nanomaterials can be exposed the body through the various pathways including lung, nose, skin, digestive tract, and eyes. Several studies have focused on the amounts of nanoparticle inhalation during routine working conditions. Maynard et al. [85] have reported ~ 1 mg/kg/day for SWCNTs and Han et al. [86] have shown several mg/kg/day exposure for MWCNTs. The exposure to metal catalyst particles typically involved in carbon nanomaterial synthesis is also an area of concern.The respiratory system is one of the most critical organ systems of the body which acts as the main pathway for nanoparticle entrance [87]. Upon inhalation, carbonnanomaterials can be translocated readily to extrapulmonary sites and reach other target organs such as the lymph node, central and peripheral nerve system, heart, liver, and kidney. More studies targeting relevant exposures to carbon nanomaterials are warranted and will be necessary before large scale production of carbon nanomaterials is undertaken.

The concerns about using carbon nanomaterials for drug delivery and tissue engineering applications are warranted, but appropriate therapeutic and other uses of these materials and their unique behaviors still hold immense possibility. It is clear that further investigation is needed. Also of importance is the need for validated synthesis and purification of carbon nanomaterials to limit the amount of nanoparticulate metals and ensure that the properties of the carbon nanomaterials are the material responsible for bio-response observed. As suggested by Uoet al. [67], at this date the precautionary principle is the best approach when utilizing carbon nanomaterials: these materials should be handled like a hazardous material and unnecessary exposure to humans and the environment should be avoided. Assessing risk factors and determining threshold exposure levels will be a key milestone for carbon nanomaterials before they are utilized in any ventures in pharmaceutical and medical companies.

Conclusion

Carbon nanomaterials have extensively studied over the last two decades for target drug delivery, use as drug carriers, tissue scaffolds, as anti-bacterialagents, MRI contrast agents, and new biosensors, and in regenerative medicine, photothermaltherapy, and electrochemotherapy. Significant advances have been made in technology, engineering, and animal study. The field continues to hold huge potential for the development of more effective therapies for cardiovascular disease, cancer, neuro-disease, musculoskeletal disorder, and diabetes mellitus. This paper reviewed the current status of carbon nanomaterial applications in medicine as new biomaterials for drug delivery and regenerative engineering. The major challenge facing the research community currently is the possibility of long-term toxicity of carbon nanomaterials compared to biodegradable-type organic polymers. Whether and how those carbon nanomaterials affect long-term immune-response to downstream events of foreign body reaction have not yet been systemically demonstrated. More *in vivo* studies and pre-clinical tests are definitely needed before these materials can be translated into the market place.

Acknowledgement

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