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Recent Patents on Single-Walled Carbon Nanotubes for Biomedical Imaging, Drug Delivery and Tissue Regeneration

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Abstract: Single-walled carbon nanotubes (SWCNTs) have been under investigation during the past decade for an array of applications due to their unique and versatile properties. Recent advances have facilitated the development of numerous SWCNT-based biomedical technologies. Consequently, there has been a worldwide surge in published patent applications and issued patents on SWCNTs. The focus of this review is to summarize the recent patent applications covering the development of synthesis methods, new compositions and utility of SWCNTs for various biomedical applications.

Keywords: Single-walled carbon nanotubes, biomedical imaging, tissue regeneration, synthesis, delivery, contrast agent, therapeutic, pharmaceutical carrier.

1. INTRODUCTION

Since the discovery of fullerenes, carbon molecules in cage-like hollow-sphere conformations, by Smalley, Kroto, Curl and co-workers in 1985, numerous ground breaking advances have been made in the field of carbon nanotechnology [1-3]. Carbon nanotubes (CNTs) are classified as members of the fullerene family with a cylindrical nanostructure. Single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) are the two primary types of CNTs. Seminal work by Ijima and other scientists has lead to significant breakthroughs and resulted in CNTs emergence as one of the most widely studied nanomaterials [2, 3]. SWCNTs, with a single layer of uniform graphite carbon (termed graphene) in a cylindrical conformation, typically have diameters between 0.5 nanometers to 2 nanometers and lengths greater than 1 µm Fig. (**1**) and are considered the most important type of CNTs due to their unique physical properties. Numerous publications have detailed the optical, mechanical, electrical, thermal and magnetic properties of SWCNTs that can be manipulated by varying the diameter, chirality, and functional groups linked to SWCNTs. There are now a number of excellent reviews that detail these advances [4-9].

Advances in the synthesis of SWCNTs for large-scale production and characterization of their unique physical properties have resulted in increased translational research towards their development for biomedical applications. Since the year 2000, the number of scientific articles related to SWCNTs for biomedical research have nearly doubled each year [5]. Similarly, the number of published patent applications and issued patents (biomedical and non-biomedical) involving SWCNTs has also shown a steady increase annually from 2001-2008 Fig. (**2A**). The number of US and international patent applications filed in 2008 was approximately 60 compared to approximately 10 in 2001 showing more than a six-fold increase during this period. The most prevalent patent applications have focused on novel methods of synthesizing SWCNTs, as well as new compositions of matter, comprising of approximately 27% of all US patent applications and 27% of foreign filings (Fig. **2B, C**). Patents that document the unique electrical properties of SWCNTs account for ~24% and ~21% of all US and foreign patent filings, respectively. Furthermore, recent advances in SWCNT biomedical research has lead to an influx of utility patents (approximately 35%) that describe novel applications using SWCNTs for biosensing, bioimaging, therapeutics and tissue regeneration.

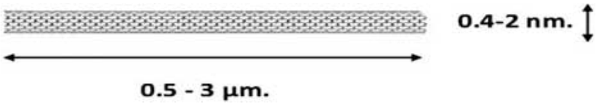

Fig. (1). Depiction of a Single-walled carbon nanotube.

This review focuses on current patents involving SWCNTs in the field of biomedical research. Herein, we will summarize patent applications covering the development of synthesis methods and new compositions of SWCNTs. Next, we will review several key patents related to the biomedical applications of SWCNTs. These patents will include the novel uses of SWCNTs for targeted drug delivery and biomedical imaging. Additionally, we will review method of use, and utility patents describing new uses for SWCNTs in the field of cell and tissue regeneration. Finally, we will summarize the emerging commercial biomedical applications of SWCNTs.

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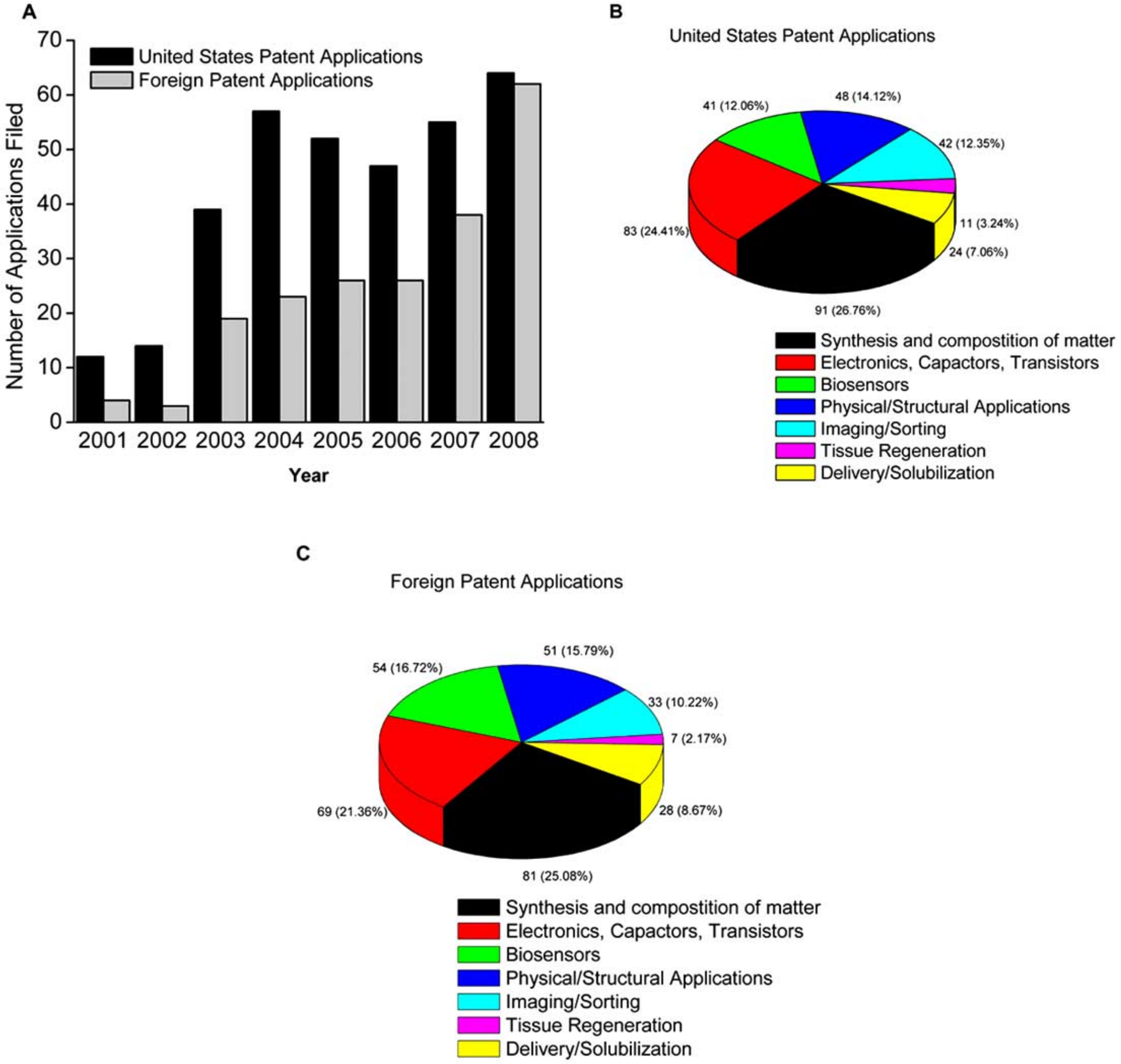

Fig. (2). (**A**) A comparison of the annual number of published United States patent applications with the number of foreign patent filings (WIPO) in the single-walled carbon nanotubes discipline. (**B**) Percentages of total published United States patent filings and issuances divided according to the main application of the invention (**C**) Percentages of foreign patent filings (WIPO) and issuances classified according to the main application of the invention. Please note that although the information here is thought to be reliable, the classifications and search parameters utilized herein are subjective.

2. SYNTHESIS

Despite significant progress, methods of synthesizing SWCNTs in bulk quantities for a variety of biomedical and non-biomedical applications remains an ongoing challenge. Presently, the three main approaches for the synthesis of SWCNTs include the electric arc discharge of graphite rods, the laser ablation of carbonaceous materials and the chemical vapor deposition of hydrocarbons (Table **1**) [10-12]. These methods produce both SWCNTs and MWCNTs. Another research focus is the development of new and improved methods and techniques that purify and sort the semiconducting and metallic SWCNTs present in a typical SWCNT sample allowing researchers to obtain high-quality, purified SWCNTs [9]. Thus, it is not surprising that the largest fraction of SWCNT patents (approximately 40%) describe methods to synthesize, purify and sort SWCNTs Fig. (**2B, 2C**).

The arc discharge method, a process reported to permit scalable production of SWCNTs, involves the generation of an electric arc through the passage of electric current across two close-but-non-contacting carbonaceous electrodes in an

Table 1. Summary of Carbon Nanotube Production Methods

	Arc Discharge	**Chemical Vapor Deposition**	**Laser Ablation**
Percent Yield	30-90	20-100	~70
SWNT Characteristics	Short nanotubes. Diameter: 0.5-1.5 nm	Elongated nanotubes. Diameter: 0.5-4.0 nm	Long nanotubes. Diameter: 1.0-2.0 nm
Advantages	Inexpensive. SWCNTs have limited structural defects. Simple protocol.	Scalable production of SWCNTs. Produces long nanotubes. High purity. Controllable diameter.	Produces uniform SWCNTs. Very few structural defects. High purity.
Disadvantages	Short nanotubes. Inconsistent size of SWCNTs. Heterogenous reaction product requires purification.	Best fit for producing MWCNTs.	Cost and labor intensive technique.

inert gas atmosphere Fig. (**3**) [10]. A recent patent by H. Cheng *et al.* describes a method of SWCNT production using the hydrogen arc discharge method [13]. In this technique, the anode, preferably 10-20 times larger in diameter than the cathode, is comprised of graphite powder, a metal catalyst (e.g. Iron) and a growth promoter (e.g. Sulphur). The anode and cathode are contained in a pressurized atmosphere containing primarily hydrogen, which acts as a buffer gas during synthesis. An electric arc is induced facilitating the production of uniform SWCNTs and by expanding the reaction time this technique may facilitate the production of SWCNTs on a larger scale.

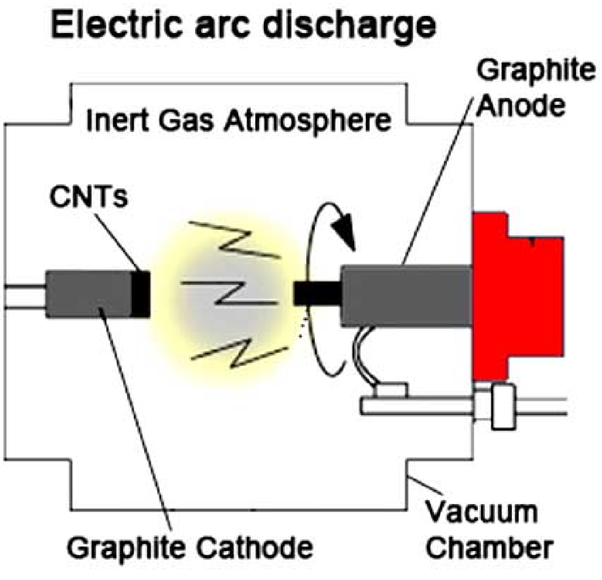

Fig. (3). Electric arc method schematic. This method creates carbon nanotubes through arc-vaporization of two graphite rods separated by approximately 1mm, in a vacuum chamber that is typically filled with inert gas (helium, argon) at low pressure (~50-700 mbar). A direct current creates a high temperature discharge between the cathode and metal catalyst coated anode, vaporizing graphite and causing carbon nanotubes to accumulate on the negatively charged cathode.

SWCNT growth by laser ablation is achieved by irradiating a solid graphite target doped with metal by a high-power laser Fig. (**4**) [11]. A patent by Simard *et al.* reports the laser ablation synthesis process to be an advantageous synthesis technique with the ability to control SWCNT size and chirality [14]. The inventors further claim that the laser ablation protocol allows for large-scale synthesis of SWCNTs in a more efficient manner. Additionally, this patent describes a novel method of synthesis involving laser ablation of a bulk metal catalyst within a carbon based solution that produces metallic nanoparticles. The formation of SWCNTs is then facilitated by aerosolizing these particles under high temperatures and their laser ablation. This process is reported to be unique in it's ability to govern the controlled synthesis parameters that modulate the structure and purity of the resulting SWCNTs. For example, the inventors claim that the size or density of the nanoparticles formed during the ablation step can be modified by manipulating the parameters of the laser, stabilizing agents, or catalysts utilized in the reaction, enabling researchers to produce SWCNTs with unique properties and desirable characteristics. Another patent by Phaedon *et al.* reports the development of a novel method for producing SWCNTs

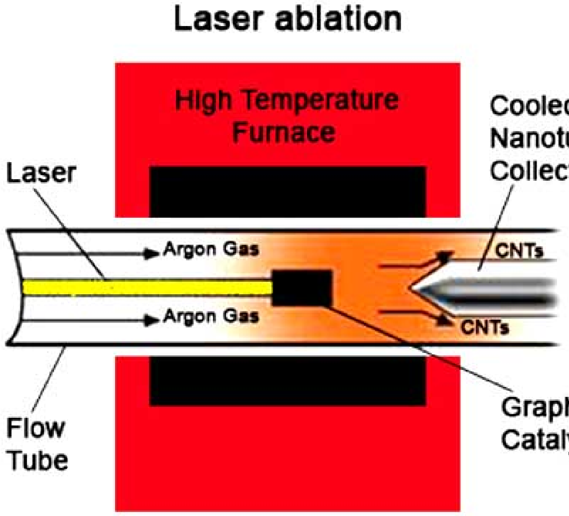

Fig. (4). Laser ablation method schematic. A pulsed or continuous laser source is used to vaporize the graphite substrate in a high temperature environment, typically 900-1200^{o}C for SWCNTs. The reaction is typically carried out in helium or argon gas, under high pressure (~500 Torr). As the vaporized carbon cools, small carbon molecules condense to form clusters, and grow into SWCNTs.

without incorporating a metallic catalyst [15]. The inventors use a carbon dioxide laser to ablate silicon carbide nanoparticles under high temperature and vacuum conditions, leading to the growth of SWCNTs on a silicon carbide surface.

SWCNT synthesis by chemical vapor deposition (CVD) involves the reaction and/or decomposition of one or more volatile carbon precursors on substrates containing catalytic metal nanoparticles to produce SWCNTs Fig. (**5**) [12]. A recent patent by Gimzewski *et al.* describes a method of producing SWCNTs on substrates with structures that form the catalytic pillar for the CVD reaction [16]. Briefly, the pillars are comprised of alternate layers of fullerene molecules (C_{60} or C_{82}), and a second material (a metal catalyst). These two materials are deposited on the substrate by thermal evaporation through a shadow mask, or template, containing one or more openings. Next, the precursor carbon material is evaporated on the catalytic pillar in a high pressure environment at various temperatures creating the SWCNTs. The inventors claim that heating the pillar(s) in the presence of a magnetic or electric field promotes the growth of nanotubes in the direction of the applied field. Additionally, the inventors claim that the SWCNTs synthesized have identical diameters and chirality, properties that can be modulated by varying the deposition rate (of the carbon precursor materials) and altering the density of individual pillar layers.

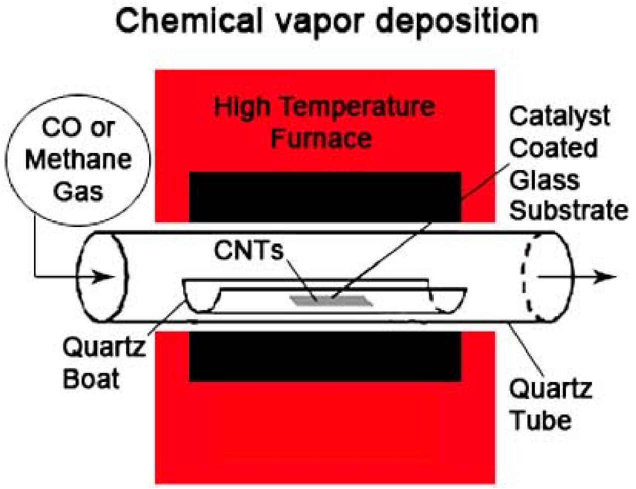

Fig. (5). Chemical vapor deposition method schematic. In this method metal catalysts are deposited on a glass substrate and the specimen is placed in a quartz boat. The boat is positioned in a high temperature (~700-1000^{o}C) CVD reaction furnace where nanometer-sized catalytic metal particles are formed. Typically, carbon nanotube formation is facilitated by catalyst-assisted decomposition of hydrocarbons, usually carbon monoxide or methane gases, under high temperature conditions causing SWCNT growth upon cooling. Figure adapted from [17].

To date, the three common methods of production incorporate the use of a metal catalyst. Apart from the nucleation step in the formation of SWCNTs, catalysts are important for their sustained growth, which is an energetically unfavorable process. It is widely believed that the diameter of SWCNTs is closely related to the size of the catalyst nanoparticles used during synthesis. Due to difficulties in controlling the nanoparticle size of the catalyst used, SWCNTs with a wide range of diameters are commonly produced. A number of metal catalysts that allow the growth of SWCNTs have been investigated. For example, metal catalysts such as, iron (Fe), cobalt (Co), nickel (Ni), ruthenium (Ru), rhodium (Rh), palladium (Pd), Osmium (Os), Iridium (Ir), Platinum (Pt), Chromium (Cr), Tungsten (W), Molybdenum (Mo), Manganese (Mn), Nickel (Ni) are among the most common materials used in the field and have been patented [18]. Additionally, support materials for the deposition of the metal catalysts such as wafers or substrates can be formed from alumina (Al_2O_3), magnesia (MgO), silica (SiO_2), $Mg(Al)O_x$, ZrO_2, glass, quartz, clay, hydrotalcite or silicon and have been patented as well [19-21].

Methods that improve the synthesis process of SWCNTs by CVD have also been patented. These synthesis methods claim to enhance and control the quality and quantity of the final SWCNT product. Hartuyunyan *et al.*, have patented a method of producing SWCNTs whereby bulk synthesis of SWCNTs was achieved by selecting metal catalytic salts and supporting substrates that are soluble in the same solvents. This process is claimed to allow for a liquid phase reaction between the catalytic salts and support substrates, resulting in an increased yield of SWCNTs [21]. Other inventors have improved the process of introducing the carbon precursor gas by developing an apparatus that prevents the mixing of a metal catalyst and gaseous or liquid carbon precursors until the optimal pressure and reaction temperature has been achieved. This method allows to control the quantity, chirality and composition of the SWCNTs [22, 23].

Currently, SWCNT synthesis techniques produce a heterogeneous CNT mixture containing various fractions of semiconducting SWCNTs, metallic SWCNTs and MWCNTs. Typically, the application of interest requires one type of SWCNT (semiconducting or metallic) and therefore purification methods are routinely required. Recently, researchers have begun to patent purification techniques whereby the desired SWCNTs can be isolated from the unwanted reaction products. Tulevski *et al.* describes a method by which functional groups are incorporated into a solution that contains a heterogeneous mixture of SWCNTs [24]. In this method, the functional groups only react with a specific subset of SWCNTs to form functionalized (covalently bonded) SWCNT conjugates. Next, these SWCNT conjugates, due to their unique densities, are separated (from the unwanted byproducts of the reaction) *via* high speed centrifugation. Another method developed by McGown *et al.*, uses a patented biogel with an affinity to specific SWCNT chiralities to bind and separate specific types of SWCNTs [25].

3. THERAPEUTICS AND DRUG DELIVERY

The physical and chemical properties of SWCNTs make them useful for a variety of therapeutic and drug-delivery applications. The external carbon sheath of the SWCNTs can be covalently or non-covalently functionalized with biological moieties that target specific cell or tissues types and/or pharmaceutical agents [7]. Covalent and non-covalent functionalization of therapeutic molecules to SWCNTs have attracted significant interest from biomedical researchers. Proteins, polysaccharides, enzymes, nucleic acids and synthetic peptides are examples of molecules that have been functionalized to carbon nanotubes. The ability of functionalized SWCNTs to cross cell membranes make them ideal candidates for intracellular drug delivery. Similarly, the hollow space comprising the interior of the nanotube can be filled with biologically important molecules [26, 27]. Here, the SWCNTs target a specific cell or tissue type and act as biological cargo vehicles to transport and deliver therapeutic agents induced by a biochemical or biophysical stimulus. Furthermore, the SWCNTs themselves can be used as a therapeutic agent by exploiting their unique physical properties [9]. For example, the strong optical absorption properties of SWCNTs in the near infrared range facilitates tumor ablation due to targeted hyperthermia of the cells. Other advantages of using SWCNTs for therapeutic purposes and as delivery vehicles include their nanoscale dimensions which enhance their retention and permeability into diseased tissues (e.g. tumors). Additionally, their large aspect ratio allows attachment of multiple functional groups for the targeted delivery of multiple therapeutic entities [28].

Smalley and co-workers, in two patents, claim that malignant cells may be destroyed by prolonged exposure of SWCNTs to a near infrared light source [29,30]. Here, the SWCNTs are either conjugated to targeting moieties such as antibodies that enable the SWCNTs to bind to the harmful malignant cells without non-specific attachment to the surrounding healthy tissue. Once the SWCNTs are in contact with the malignant cells, the tissue is exposed to an external source of electromagnetic energy (typically a light source) causing heating of the bound SWCNTs resulting in localized hyperthermia in the malignant cells, and targeted cell death by thermal necrosis [29, 30].

A number of recent patents discuss the development of SWCNT-drug conjugates. For example, the therapeutic entity is covalently bonded to the exterior aromatic carbon sheath of the SWCNT *via* chemical linkers [31, 32]. Alternatively, the chemical moiety may be bound to the carboxy and/or hydroxy groups formed along the exterior carbon sheath due to oxidation and release of the pharmaceutical occurs *via* cleavage of the linker group due to a biochemical stimulus, such as the presence of an enzyme or pH change [33, 34].

Another method patent uses SWCNTs as delivery vehicles to introduce a biological material into a cell to facilitate the isolation of these cells [35]. The proposed SWCNT-based construct contains externally functionalized nucleic acid groups and internally loaded magnetic materials (iron, cobalt, nickel). The SWCNTs facilitate the delivery of the nucleic acids to target cells which enable the isolation of these cells using magnetic separation techniques. The inventors claim that the isolation of these genetically modified cells may be useful in creating a transgenic animal or novel cell lines capable of expressing the exogenous nucleic acids.

A patent by Chauhan *et al.*, discusses the development of SWCNT-based ocular drug delivery methods to enhance the bioavailability of ocular medications; a limitation of traditional ocular drug delivery methods [36]. Repeated self-administration of topical eye drops for preventive or active inhibition of post-surgical complications is both problematic for the patient and ineffective due to toxicity associated with continued topical or systemic administration. Furthermore, when applied as eye drops most drugs penetrate poorly through the cornea with the rate of corneal uptake, being high initially but declining rapidly with additional exposure, a phenomenon leading to a transient period of overdose followed by an extended period of sub-therapeutic levels prior to the administration of the next scheduled dose. In their patent, Chauhan *et al.*, describes a SWCNT-ophthalmic drug conjugate that promotes diffusion and delivery from its carrier into the surrounding ocular environment. This technology utilizes a contact lens (carrier) containing or perfused with SWCNT-ophthalmic drug (e.g. an antibiotic) conjugates, whereby the conjugates are capable of diffusion through the contact lens into the targeted ocular tissue. Another strategy for controlled ocular drug release using SWCNTs is the patented synthesis of a SWCNT-biodegradable polymer that adsorbs or encapsulates a pharmaceutical entity in the polymer network. Here controlled and sustained drug release is achieved over a period of time as the polymer degrades into smaller macromers or monomers [33].

SWCNTs have also been patented as potential vehicles for precise delivery of fluids into targeted cells or intracellular compartments [37]. Here, the hollow interior space of the SWCNTs has been exploited to permit intercellular delivery of fluids or small molecules. Delivery of fluids to a cell is achieved by inserting one end of a SWCNT into a cell, and the opposite end of the SWCNT to a fluid source. The SWCNT is then used as a conduit to transfer fluid from its source into the cell. This delivery strategy may be suitable for the study of the cellular response to the introduction of exogenous fluids or materials as well as to directly connect two or more cells effectively forming a network of cells that permit researchers to study the transfer of specific molecules between different cell or tissue types.

Recently methods to harness acoustic energy have been developed for a wide variety of applications such as smart stimulus-response drug-delivery systems by focusing on the application of acoustic energy to tissues or cells by mediating vibration, heating or cavitations. For example, the creation of a high intensity ultrasound device has facilitated the targeted release and delivery of therapeutics, a technique that may increase the efficacy and lower the required dosage of such pharmaceuticals. To do so, a high intensity therapeutic ultrasound transmission device is used. A recent patent by Hardy and co-workers describes a targeted therapeutic delivery system comprising novel SWCNT-based nanocarriers designed for the intracellular therapeutic delivery of pharmaceuticals *via* acoustic energy [38, 39]. In this patent, SWCNTs functionalized with targeting groups (antibody fragments and small nucleic acid oligomers) and therapeutics are actively delivered to the target cell(s). Once the nanocarriers populate the targeted region, controlled delivery of the attached drug is achieved by disassociating it from the SWCNTs using high-intensity ultrasound. Another drug delivery technology describes the development of a SWCNT-based thermo-sensitive delivery system [40]. This method exploits the near infrared absorption properties of SWCNT to modulate the release of the therapeutic compound *via* infrared irradiation. This novel technique facilitates the controlled delivery of the therapeutic entity by switching on or off the NIR radiation, thus achieving inducible drug release.

4. IMAGING

Current medical imaging modalities such as optical imaging, X-ray, magnetic resonance imaging (MRI), computed axial tomography (CAT) and positron emission tomography (PET) possess unique strengths and weaknesses. For each imaging modality substantial attention has been devoted to the development of contrast agents. Recent SWCNT patents describe various devices that overcome challenges associated with the instrumentation used for medical imaging, and development of high performance contrast agents.

X-ray systems are widely used in clinical imaging. However, the process of x-ray generation is inherently very inefficient, with approximately ninety nine percent of the energy emitted by the electron stream converted (upon impact with the anode) into thermal energy instead of x-rays. Thus, the focus spot temperature can be very high if the electron current is high or continuous exposure is required. In order to avoid damage to the anode, it is essential to remove this heat as rapidly as possible. Furthermore, the high temperature heating for thermionic emission of the electrons reduces the lifetime of the cathode filament, which is typically around a few hundred hours in medical applications and a thousand hours in analytical applications. A possible improvement in the generation of x-rays is the introduction of field emission cathode materials. Field emission is the emission of electrons under the influence of a strong electric field. To this end, a patent by Takahashi *et al.*, discusses the ability of SWCNTs to emit electrons by field emission at room temperature and claims that the unique thermal properties of SWCNTs enable cathode temperatures to be controlled, thus modulating the level of electron emissions from the cathode [41]. Furthermore, other recent patents reveal that SWCNTs may be used as a cold cathode electron emission source for x-ray diagnostics [42, 43]. These technologies facilitate high energy conversion efficiency and compact design by easily focusing the cold cathode-emitted electrons and dramatically reducing the heating at the anode.

Magnetic Resonance Imaging (MRI) utilizes a pulse of radiofrequency (RF) to excite nuclear magnetic resonance (NMR) active nuclei (mostly water protons) that have been aligned using a strong external magnetic field. When this RF pulse is turned off, the proton nuclei return to their initial equilibrium position (also known as relaxation). An electrical signal is generated by these alignment changes that can be detected by a scanner and specialized signal acquisition and processing techniques for image reconstruction. Different relaxation times of the protons have been established for various fluids organs and tissues in many different species, differences that generate the contrast in the images. Today, these MRI systems face smaller static magnetic field requirements and smaller hardware demands aiming to significantly reduce system size and the associated operating costs. SWCNTs emit low electrical noise levels that permit the construction of RF receiving electronics that yield maximum power reception, thereby providing high signal quality and narrow bandwidth for highly selective imaging. The narrow bandwidth can then be used for efficient imaging in the presence of a magnetic field where slice selectivity for imaging are enhanced accordingly [44]. Additionally, imaging coils comprised of SWCNTs can lead to substantial reductions in system size and cost due to their enhanced signal-to-noise ratio [45].

The strategies patented for development of SWCNT-based contrast agents for biomedical imaging include encapsulation of medically relevant metal ions within their carbon sheath, the functionalization of the carbon sheath with a variety of imaging agents and exploiting the intrinsic physical properties of the SWCNTs. Wilson *et al.* have patented SWCNT-based contrasts agents for CT and MRI [46]. Image enhancement is achieved by loading the interior hollow space of a SWCNT with metal atoms or ions that are paramagnetic (a requirement for MRI contrast agents) or have a large x-ray cross-section (a requirement for CT contrast agents). In this capacity, the SWCNT would act as a carrier for the imaging agent, sequestering the toxicity of the contrast agent within the interior of the SWCNT. Furthermore, they disclose that SWCNTs can be used as carriers for other diagnostic or therapeutic entities.

SWCNTs have also been proposed as contrast agents for hyperpolarized ^{13}C MRI in a patent by Hurd *et al.* [47]. ^{13}C MRI detects naturally abundant ^{13}C (present in approximately 1.1% of total carbon). The concentrations of ^{13}C in living tissues is very low, which compares very unfavorably to high concentrations of tissue water protons (^{1}H) that are utilized for ^{1}H MRI. Further, ^{13}C has a lower gyromagnetic ratio compared to ^{1}H leading to reduced sensitivity. Thus, ^{13}C nuclei are needed to be present in at least 10X higher concentrations to have equivalent signal to ^{1}H in a given magnetic field. Hyperpolarized techniques change the nuclear spin state to overcome the low sensitivity of ^{13}C MRI. Hurd *et al.*, in their patent, propose that SWCNTs exposed to hyperpolarization techniques excite nuclear spin transitions in the ^{13}C nuclei of the SWCNTs. They claim that their technology enhances the ability to detect ^{13}C magnetic resonance signals and generate a clear image, as well as collect dynamic flow data diffusion data and perfusion data from the signals.

SWCNTs have spectral properties that are highly sensitive to their surrounding environment. For example, semiconducting SWCNTs have been shown to exhibit photo-luminescence in the near-infrared portion of the electro-magnetic spectrum and chemical entities linked their surface can further affect their spectral properties. The dynamic spectral capabilities of SWCNTs make them suitable for a wide variety of sensing and monitoring applications. Smalley and co-workers describe a technique that utilizes SWCNTs to detect malignant cells [29, 30]. In this method, individually-suspended nanotubes are reacted with a biological targeting moiety, such as a monoclonal antibody or other moiety that will target the tumor cells. The subject is injected with the SWCNT constructs, subjected to an NIR source and scanned for near-IR fluorescence emission to map the SWCNTs, leading to the identification and location of the malignancy.

5. TISSUE REGENERATION

A major focus of research in the field of regenerative medicine is the development of new materials to direct, monitor and evaluate tissue growth. SWCNTs have been widely investigated to aid tissue regeneration and create engineered tissues [5, 48]. Synthesis of SWCNT based scaffolds and composite materials for tissue engineering must retain the three dimensional structural integrity of SWCNT's carbon network. The double bonded sp^2 structure present in SWCNTs, when compared to those in graphite and fullerenes are much stronger, making them ideal for tissue engineering [49]. A number of recent patents filings document these scientific breakthroughs.

Electrical stimulation has been explored as a treatment for damaged bone tissues. A recent patent claims that electrically conducting SWCNTs can improve cytocompatibility and improve specific cell functionality and proliferation [50]. Supronowicz *et al.*, describe a method for enhancing osteoblast proliferation by utilizing electrically conducting SWCNT-based orthopaedic/dental implants. In this method, the SWCNT-based implant is in contact with osteoblasts. An electric current is passed through the implant; stimulating the osteoblasts to promote bone growth. Another SWCNT-based technique patented by Carroll *et al.*, claims that electrically stimulated cells cultured on SWCNTs proliferate more rapidly than on control surfaces [51].

Natural bone is a complex composite tissue with multiple levels of hierarchical organization. Stupp *et al.*, describes a nanostructure system used to mimic and recreate the structural and functional interaction between collagen and hydroxyapatite crystals in bone or the extracellular matrix [52]. Here, the inventors describe a SWCNT-based composition that provides a molecular structure that functionally mimics endogenous collagen fibrils, as well as a SWCNT structured fibrous system that can be utilized as a template or scaffolds for bone and tissue development. The inventors claim that these techniques provide a nano-system capable of targeted cellular or mineral growth.

SWCNTs have also been incorporated into polymer-based porous scaffolds for tissue engineering. A recent patent by Mikos *et al.* describes a method that utilizes SWCNTs as reinforcing agents in synthetic biodegradable and biocompatible polymers that enhance the mechanical properties of the scaffolds. The main purpose of incorporating SWCNTs to form nanoscaffolds is to leverage their beneficial mechanical properties such as, their high compressive modulus to improve the nanocomposite's mechanical properties for *in vivo* bone regeneration applications [53].

The localized delivery of heat or cold as a mode of tissue repair has long been practiced in medicine, as the generation of heat affects the joining of the tissue. However, recent improvements to methods developed for the targeted delivery of heat have been proposed using SWCNT-based techniques. A methodology described by Rice University inventors involves localized induction of hyperthermia in tissue by delivering SWCNTs to tissue and exposing the nanotubes to an energy source facilitating the emission of thermal energy from the SWCNTs [54]. Here, the nanotubes absorb energy and convert it to heat in order to raise the temperature of the surrounding tissue. SWCNT-based techniques that effectively induce precise localized heating permit the targeted destruction of certain cell types, such as cancer, in a therapeutic manner while minimizing the collateral damage to nearby cells and tissue.

Medical devices or implants are routinely coated with biomaterials to improve functionality, longevity and integration into the body**.** Conventional methods of coating stents or other implantable medical devices with a pharmaceutical-polymer layer require require a solution to physically wet the surface of the stent; a process that often cause uneven and unpredictable application and distribution of the pharmaceutical. A technology described by Hoerr *et al.*, may improve the quality of a coating and the performance of a drug coated device, such as a stent, by utilizing SWCNTs in the coating [55]. This methodology includes: preparing a solution of SWCNTs conjugated to a pharmaceutical and coating the medical device with a SWCNT based solution.

6. CURRENT & FUTURE DEVELOPMENTS

The aforementioned advancements in SWCNT production have led to commercial ventures that facilitate large scale production of SWCNTs. Bayer MaterialScience, of Hamburg, Germany, one of the world's largest developers of CNTs, estimates that the industry will grow at an annual rate of 25%, and eventually annual CNT sales will reach over $2 billion, up from $6 million in 2004. Bayer is currently building the largest nanotube production facility in the world to mass produce both SWCNTs and MWCNTs. Furthermore, companies such as First Nano Inc., Southwest Nanotechnologies Inc., CarboLex Inc., NanoLab, NanoIngtegris Inc., and Nanothinx have started producing high quality, low cost CNTs for research applications. The availability of bulk quantities of SWCNTs has facilitated research and the development of a number of SWCNT-driven technologies. SWCNTs have demonstrated suitability as enabling components for various electronic, biochemical, and mechanical devices. Among these devices are chemical force sensors, gas detectors, field emission displays, molecular wires, diodes, transistors and contrast agents. For biomedical applications, products that utilize SWCNTs *ex vivo* are already commercially available. For example, Applied Nanotech, Inc. of Austin, Texas has developed a miniaturized sensor system that utilizes coated SWCNT's to detect a wide variety of molecules evaluate from patients *ex vivo* and the surrounding environment. Applied Nanotech, Incorporated's proprietary technology utilizes the stability and unique structure of SWCNTs to detect metabolic enzymes from small amounts of blood, urine or saliva; as well as harmful gases such as carbon monoxide. Similarly, Nanōmix, Inc. of Northridge, California utilizes its SWCNT-based *Sensation*™ detection platform to produce several point-of-care medical products, including Asthma monitoring devices for the detection of nitric oxide in a patient's breath and Capnography devices that detect carbon dioxide in a patient's breath, a technology useful for sleep apnea screening, breathing quality assessment, and anesthetic administration.

However, progress has been slow in developing SWCNT-based products for *in vivo* biomedical applications.

The toxicity and biodistribution of SWCNTs *in vivo* still needs to be thoroughly understood before their translation into clinic. Additionally, high costs and time constraints associated with SWCNT production and processing (purification and sorting) are barriers for some applications. However, these costs are highly dependent on the specific application of SWCNTs. Nevertheless, the development of SWCNT-based biomedical technologies represents a challenging, but potentially rewarding opportunity to develop the next generation biomedical products.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

[1] Kroto HW, Heath JR, O'Brien SC, Curl RF, Smalley RE. C60: Buckminsterfullerene. Nature 1985; 318(6042): 162-3.

[2] O'Connell M. Carbon Nanotubes Properties and Applications. Boca Raton: Taylor & Francis 2006.

[3] Dresselhaus M. Introduction to Carbon Materials Research. Carbon Nanotubes Synthesis, Structure, Properties and Applications. New York: Springer 2001.

[4] Ajayan PM. Single-walled carbon nanotube-polymer composites: Strength and weakness. Adv Mater 2000; 12(10): 750-3.

[5] Harrison BS, Atala A. Carbon nanotube application for tissue engineering. Biomaterials 2007; 28(2): 344-53.

[6] Prato M, Kostarelos K, Bianco A. Functionalized carbon nanotubes in drug design and discovery. Acc Chem Res 2008; 41(1): 9.

[7] Tasis D. Chemistry of carbon nanotubes. Chem Rev 2006; 106(3): 1105-36.

[8] Yang W, Thordarson P, Gooding JJ, Ringer SP, Braet F. Carbon nanotubes for biological and biomedical applications. Nanotechnology 2007; 18(41): 412001-13.

[9] Liu Z, Tabakman S, Welsher K, Dai H. Carbon nanotubes in biology and medicine: *In vitro in vivo* detection, imaging and drug delivery. Nano Res 2009; 2: 85-120.

[10] Journet C, Maser WK, Bernier P, Loiseau A, de la Chapelle ML, Lefrant S, *et al*. Large-scale production of single-walled carbon nanotubes by the electric-arc technique. Nature 1997; 388(6644): 756-8.

[11] Guo T. Catalytic growth of single-walled nanotubes by laser vaporization. Chem Phys Lett 1995; 243.

[12] Cassell AM, Raymakers JF, Kong J, Dai H. Large scale CVD Synthesis of single-walled carbon nanotubes. J Phys Chem B 1999; 103(31): 6484-92.

[13] Cheng, H., Liu, C., Cong, H., Liu, M., Fan, Y., Su, G. Production of single-walled carbon nanotubes by a hydrogen arc discharge method. US6517800 **(2003)**.

[14] Simard, B., Barnett, M., Dénommée, S., Ruth, D. Process and apparatus for synthesis of nanotubes. US7374730 **(2008)**.

[15] Avouris, P., Derycke, V., Martel, R., Radosavljevic, M. Catalyst-free growth of single-wall carbon nanotubes. US6843850 **(2005)**.

[16] Gimzewski, J., Schlittler, R., Seo, J.W. Crystals comprising single-walled carbon nanotubes. US6800369 **(2004)**.

[17] Maruyama S, Kojima R, Miyauchi Y, Chiashi S, Kohno M. Low-temperature synthesis of high-purity single-walled carbon nanotubes from alcohol. Chem Phys Lett 2002; 360(3-4): 229-34.

[18] Popov VN. Carbon nanotubes: properties and application. Mater Sci Eng R Rep 2004; 3(43): 61-102.

[19] Zhang, X., Ma, J., Tennent, H., Hoc, R. Method for preparing single walled carbon nanotubes. US20080175786 **(2008)**.

[20] Tennent, H., Zhang, H.-F., Ma, J. Method for preparing single walled carbon nanotubes from a metal layer. WO2006110346 **(2006)**.

[21] Harutyunyan, A., Tokune, T., Fernandez, E.M. Catalyst for synthesis of carbon single-walled nanotubes. US7485600 **(2009)**.

[22] Resasco, D.E., Boonyarach K., Harwell, J.H., Alvarez, W., Balzano, L. Process and apparatus for producing single-walled carbon nanotubes. US6919064 **(2005)**.

[23] Resasco, D.E., Boonyarach, K., Harwell, J.H., Alvarez, W. Method of producing single-walled carbon nanotubes. US7094386 **(2006)**.

[24] Tulevski, G.S., Afzali-ardakani, A., Sanders, D.P. Method for the purification of semiconducting single walled carbon nanotubes. US7514063 **(2009)**.

[25] McGown L., Nalamasu, O., Yu, Y. Reversible biogel for manipulation and separation of single-walled carbon nanotubes. US20090111897 **(2009)**.

[26] Sitharaman B, Wilson LJ. Gadofullerenes and gadonanotubes: A new paradigm for high-performance magnetic resonance imaging contrast agent probes. J Biomed Nanotechnol 2007; 3: 342-52.

[27] Sitharaman B, Wilson LJ. Gadonanotubes as new high-performance MRI contrast agents. Int J Nanomed 2006; 1(3): 291-5.

[28] Liu Z, Davis C, Cai W, He L, Chen X, Dai H. Circulation and long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by Raman spectroscopy. Proc Natl Acad Sci USA 2008; 105(5): 1410-5.

[29] Smalley, R.E., Hauge, R.H., Kittrell, W.C., Sivarajan, R., Strano, M.D., Bachilo, S.M., R.B. Weisman, R.B. Single-wall carbon nanotubes of precisely defined type and use thereof. US20040038251 **(2004)**.

[30] Smalley, R.E., Hauge, R.H., Kittrell, W.C., Sivarajan, R., Strano, M.D., Bachilo, S.M., Weisman, R.B. Single-wall carbon nanotube compositions. US20060231399 **(2006)**.

[31] Hirsch, A.H., Sagman, U., Wilson, S.R. Use of buckysome or carbon nanotube for drug delivery. US7070810 **(2006)**.

[32] Hoch, R., Fischer, A., Tennent, H. Functionalized single walled carbon nanotubes. WO2006130150 **(2006)**.

[33] Dennis, D.M., Martin, C.R., Rogers, R.J., Stewart, J.D. Nanoparticle delivery system. US7195780 **(2007)**.

[34] Wong, S., Banerjee, S. Sidewall-functionalized carbon nanotubes, and methods for making the same. US7122165 **(2003)**.

[35] Fitzpatrick-McElligott, S.G., Lavin, J.G., Rivard, G.F., Subramoney, S. Method for introducing a biological substance into a target. US5466587 **(1995)**.

[36] Chauhan, A., Gulsen, D. Ophthalmic drug delivery system. EP1534202 **(2009)**.

[37] Shur, M., Dordick, J.S., Ajayan, P.M. Fluid delivery to cells and sensing properties of cells using nanotubes. US20040186459 **(2004).**

[38] Hardy, C. T., Kranz, H.K., Wood, T.E., Kaisaki, D.A., Gagliardi, J. J., Clark, J. C., Savu, P. M., Clark, P.G. Peptosomes for use in acoustically mediated intracellular drug delivery *in vivo*. US20080312581 **(2008)**.

[39] Hardy, C.T., Kranz, H.K., Wood, T.E., Kaisaki, D.A., Gagliardi, J.J., Clark, J.C., Savu, P.M., Clark, P.G. Materials, methods, and systems for cavitation-mediated ultrasonic drug delivery *in vivo*. US20080319375 **(2008)**.

[40] Vertommen, M.A.M.E., Asseldonk, V.D.T.A., Kemmere, M.F., Keurentjes, J.T.F. Drug delivery device comprising a pharmaceutically or biologically active component and an infrared absorbing compound. WO2008016297 **(2008)**.

[41] Takahashi, S., Kuribayashi, M., Osaka, N. X-ray generator. US6456691 **(2002)**.

[42] Keesmann, T., Grosse-Wilde, H. Field emission cathode having an electrically conducting material shaped of a narrow rod or knife edge. US5773921 **(1998)**.

[43] Zhou, O. Z., Lu, J. X-ray generating mechanism using electron field emission cathode. US6553096 **(2003)**.

[44] Viswanathan, R. R. Signal acquisition and processing method and apparatus for magnetic resonance imaging. US7560923 **(2009)**.

[45] Viswanathan, R. R. Method and apparatus for high-gain magnetic resonance imaging. US20080169811 **(2008)**.

[46] Wilson, L., K.R. Kissell, Hartman, K.B. Carbon nanotube based imaging agents. WO2007137256 **(2007)**.

[47] Hurd, R.E. Magnetic resonance imaging (MRI) agents: Water soluble carbon-13 enriched fullerene and carbon nanotubes for use with dynamic nuclear polarization. US20070025918 **(2007)**.

[48] Sitharaman B, Shi X, Walboomers XF, Liao H, Cuijpers V, Wilson LJ, *et al*. *In vivo* biocompatibility of ultra-short single-walled carbon nanotube/biodegradable polymer nanocomposites for bone tissue engineering. Bone 2008; 43(2): 362-70.

[49] Sedman V, Adler-Abramovich L, Allen S, Gazit E, Tendler SJB. Direct observation of the release of phenylalanine from diphenylalanine nanotubes. J Am Chem Soc 2006; 128(21): 6903-8.

[50] Supronowicz, P., Bizios, R., Ajayan, P., Siegel, R. Electrically conducting nanocomposite materials for biomedical applications. US20030153965 **(2003)**.

[51] Carroll, D., Wagner, W., Levi, N., Argenta, L., Morykwas, M. Methods and compositions for printing biologically compatible nanotube composites of autologous tissue. US20090117087 **(2009)**.

[52] Stupp, S.I., Hartgerink, J.D., Beniash, E. Self-assembly of peptide-amphiphile nanofibers under physiological conditions. US7371719 **(2008)**.

[53] Sitharaman, B., Shi, X., Mikos, A. G., Wilson, L. J. Carbon nanotube based nanocomposites. US200811972886 **(2008).**

[54] West, J.L., Drezek, R., Sershen, S., Halas, N.J. Optically-absorbing nanoparticles for enhanced tissue repair. US6685730 **(2004)**.

[55] Ranade, S.V. Method of incorporating carbon nanotubes in a medical appliance, a carbon nanotube medical appliance, and a medical appliance coated using carbon nanotube technology. WO2006052538 **(2006)**.