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CARBON NANOTUBES: THE FUTURE OF CANCER TREATMENT

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ABSTRACT

Graphite is made up of layers of carbon atoms arranged in a hexagonal lattice, like chicken wire (see fi the term nanotube is normally used to refer to the carbon nanotube, which has received enormous attention from researchers over the last few years and promises, along with close relatives such as the nanohorn, a host of interesting applications. The theoretical minimum diameter of a carbon nanotube is around 0.4 nanometers, which is about as long as two silicon atoms side by side, and nanotubes this size have been made. Average diameters tend to be around the 1.2 nanometer mark, depending on the process used to create them. Carbon nanotubes are extremely thin (their diameter is about 10,000 times smaller than a human hair), hollow cylinders made of carbon atoms. Biological systems are known to be highly transparent to 700- to 1, 100-nm near-infrared (NIR) light. It is shown here that the strong optical absorbance of single-walled carbon nanotubes (SWNTs) in this special spectral window, an intrinsic property of SWNTs, can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters. For oligonucleotides transported inside living cells by nanotubes, the oligos can translocate into cell nucleus upon endosomal rupture triggered by NIR laser pulses. Continuous NIR radiation can cause cell death because of excessive local heating of SWNT *in vitro*. Selective cancer cell destruction can be achieved by functionalization of SWNT with a folate moiety, selective internalization of SWNTs inside cells labeled with folate receptor tumor markers, and NIR-triggered cell death, without harming receptor-free normal cells. Thus, the transporting capabilities of carbon nanotubes combined with suitable functionalization chemistry and their intrinsic optical properties can lead to new classes of novel nanomaterials for drug delivery and chemotherapy

INTRODUCTION:

What is so special about Carbon Nanotubes? Carbon nanotubes are one of the most commonly mentioned building blocks of nanotechnology [1]. With one hundred times the tensile strength of steel, thermal conductivity better than all but the purest diamond, and electrical conductivity similar to copper, but with the ability to carry much higher currents, they seem to be a wonder material. However, when we hear of some companies planning to produce hundreds of tons per year, while others seem to have extreme difficulty in producing grams, there is clearly more to this material than meets the eye.

In fact nanotubes come in a variety of flavors: long, short, single-walled, multi-walled, open, closed, with different types of spiral structure, etc [4]. Each type has specific production costs and applications. Some have been produced in large quantities for years while others are only now being produced commercially with decent purity and in quantities greater than a few grams. In this brief white paper we hope to resolve some of the confusion surrounding what may be one of the most significant new materials since plastics.

Carbon Nanotube Production Processes: Production processes for carbon nanotubes, crudely described, vary from blasting carbon with an electrical arc or a laser to growing them from a vapor, either en masse (usually in tangled bundles) or on nanoparticles [7], sometimes in predetermined positions. These processes vary considerably with respect to the type of nanotube produced, quality, purity and scalability. Carbon nanotubes are usually created with the aid of a metal catalyst and this ends up as a contaminant with respect to many potential applications, especially in electronics. IBM have very recently, however, grown nanotubes on silicon structures without a metal catalyst.

Arc discharge: Nanotubes were observed in 1991 in the carbon soot of graphite electrodes during an arc discharge, by using a current of 100 amps, that was intended to produce fullerenes. However the first macroscopic production of carbon nanotubes was made in 1992 by two researchers at NEC's Fundamental Research Laboratory. The method used was the same as in 1991. During this process, the carbon contained in the negative electrode sublimates because of the high discharge temperatures [10]. Because nanotubes were initially discovered using this technique, it has been the most widely-used method of nanotube synthesis. The yield for this method is up to 30 percent by weight and it produces both single- and multi-walled nanotubes with lengths of up to 50 micrometers with few structural defects.

Laser ablation : In the laser ablation process, a pulsed laser vaporizes a graphite target in a high-temperature reactor while an inert gas is bled into the chamber. Nanotubes develop on the cooler surfaces of the reactor as the vaporized carbon condenses. A water-cooled surface may be included in the system to collect the nanotubes.

This process was developed by Dr. Richard Smalley and co-workers at Rice University [10], who at the time of the discovery of carbon nanotubes, were blasting metals with a laser to produce various metal molecules. When they heard of the existence of nanotubes they replaced the metals with graphite to create multi-walled carbon nanotubes. Later that year the team used a composite of graphite and metal catalyst particles (the best yield was from a cobalt and nickel mixture) to synthesize single-walled carbon nanotubes. The laser ablation method yields around 70% and produces primarily single-walled carbon nanotubes with a controllable diameter determined by the reaction temperature. However, it is more expensive than either arc discharge or chemical vapor deposition.

Chemical vapor deposition (CVD): Nanotubes being grown by plasma enhanced chemical vapor deposition. During CVD, a substrate is prepared with a layer of metal catalyst particles, most commonly nickel, cobalt, iron, or combination. The metal nanoparticles can also be produced by other ways, including reduction of oxides or oxides solid solutions. The diameters of the nanotubes that are to be grown are related to the size of the metal particles.

This can be controlled by patterned (or masked) deposition of the metal, annealing, or by plasma etching of a metal layer. The substrate is heated to approximately 700°C. To initiate the growth of nanotubes, two gases are bled into the reactor: a process gas (such as ammonia, nitrogen or hydrogen) and a carbon-containing gas (such as acetylene, ethylene, ethanol or methane). Nanotubes grow at the sites of the metal catalyst; the carbon-containing gas is broken apart at the surface of the catalyst particle, and the carbon is transported to the edges of the particle, where it forms the nanotubes. This mechanism is still being studied. The catalyst particles can stay at the tips of the growing nanotube during the growth process, or remain at the nanotube base, depending on the adhesion between the catalyst particle and the substrate.

CVD is a common method for the commercial production of carbon nanotubes. For this purpose, the metal nanoparticles are mixed with a catalyst support such as MgO or Al_2O_3 to increase the surface area for higher yield of the catalytic reaction of the carbon feedstock with the metal particles [12]. One issue in this synthesis route is the removal of the catalyst support via an acid treatment, which sometimes could destroy the original structure of the carbon nanotubes. However, alternative catalyst supports that are soluble in water have proven effective for nanotube growth.

If a plasma is generated by the application of a strong electric field during the growth process (plasma enhanced chemical vapor deposition*), then the nanotube growth will follow the direction of the electric field. By adjusting the geometry of the reactor it is possible to synthesize vertically aligned carbon nanotubes (i.e., perpendicular to the substrate), a morphology that has been of interest to researchers interested in the electron emission from nanotubes. Without the plasma, the resulting nanotubes are often randomly oriented. Under certain reaction conditions, even in the absence of plasma, closely spaced nanotubes will maintain a vertical growth direction resulting in a dense array of tubes resembling a carpet or forest.

A small SWNT sample produced by super-growth: Super-growth CVD (water-assisted chemical vapor deposition) process was developed by Kenji Hata, Sumio Iijima and co-workers at AIST, Japan [1]. In this process, the activity and lifetime of the catalyst are enhanced by addition of water into the CVD reactor. Dense millimeter-tall nanotube "forests", aligned normal to the substrate, were produced. The forests growth rate could be expressed, as

$$H(t) = \beta\tau_o(1 - e^{-t/\tau_o}).$$

In this equation, β is the initial growth rate and τ_o is the characteristic catalyst lifetime. Their specific surface exceeds 1000 m^2/g (capped) or 2000 m^2/g (uncapped), surpassing the value of 520 m^2/g for HiPco samples. The synthesis efficiency is about 100 times higher than for the laser ablation method. The time required to make SWNT forests of the height of 2.5 mm by this method was 10 minutes in 2004 [1, 2]. Those SWNT forests can be easily separated from the catalyst, yielding clean SWNT material (purity>99.98%) without further purification. For comparison, the as-grown HiPco[2]

CNTs contain about 30% of metal impurities; it is therefore purified through dispersion and centrifugation that damages the nanotubes.

Nanocrystals could be route to carrier-free drug delivery: A novel method of delivering a hydrophobic (water-insoluble) drug, in which the compound effectively acts as its own carrier, has shown comparable efficacy both in vitro and in vivo to the same drug formulated in a conventional delivery vehicle.

The new approach is based on a method known as reprecipitation, whereby a compound is dissolved in a mixable solvent such as DMSO and injected into water. The molecules then self-assemble as pure nanosized crystals and remain stably dispersed in water. They found the nanocrystal formulation was taken up by tumours in vitro and in vivo, showing similar efficacy to the same drug using conventional surfactant-based delivery (1% Tween-80/water).

CNTs as Biosensors:

Glucose detection biosensors: Carbon nanotube-plasma polymer-based amperometric biosensors for ultrasensitive glucose detection have been fabricated. DNA detection biosensors. An aligned carbon nanotube ultrasensitive biosensor for DNA detection was developed [4]. The design and fabrication of the biosensor was based on aligned single wall carbon nanotubes (SWCNTs) with integrated single-strand DNAs (ssDNA).

DNA-wrapped Carbon Nanotubes Serve As Sensors In Living Cells: Single-walled carbon nanotubes wrapped with DNA can be placed inside living cells and detect trace amounts of harmful contaminants using near infrared light, report researchers at the University of Illinois at Urbana-Champaign. Their discovery opens the door to new types of optical sensors and biomarkers that exploit the unique properties of nanoparticles in living systems. The DNA starts out wrapping around the nanotube with a certain shape that is defined by the negative charges along its backbone.

When the DNA is exposed to ions of certain atoms such as calcium, mercury and sodium the negative charges become neutralized and the DNA changes shape in a similar manner to its natural shape-shift from the B form to Z form. This reduces the surface area covered by the DNA, perturbing the electronic structure and shifting the nanotube's natural, near infrared fluorescence to a lower energy. "The nanotube surface acts as the sensor by detecting the shape change of the DNA as it responds to the presence of target ions

CNTs in Drug Delivery and Cancer Therapy: Drug delivery is a rapidly growing area that is now taking advantage of nanotube technology. Systems being used currently for drug delivery include dendrimers, polymers, and liposomes, but carbon nanotubes present the opportunity to work with effective structures that have high drug loading capacities and good cell penetration qualities. These nanotubes function with a larger inner volume to be used as the drug container, large aspect ratios for numerous functionalization attachments, and the ability to be readily taken up by the cell. The advantages of carbon nanotubes as nanovectors for drug delivery remain where cell uptake of these structures was demonstrated efficiently where the effects were prominent, showing the particular nanotubes can be less harmful as nenovehicles for drugs. Also, drug encapsulation has been shown to enhance water dispersibility, better bioavailability, and reduced toxicity.

Encapsulation of molecules also provides a material storage application as well as protection and controlled release of loaded molecules . All of these result in a good drug delivery basis where further research and understanding could improve

upon numerous other advancements, like increased water solubility, decreased toxicity, sustained half-life, increased cell penetration and uptake, all of which are currently novel but undeveloped ideas.

Selective cancer cell destruction: Carbon nanotubes can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction . Biological systems are known to be highly transparent to 700- to 1,100-nm near-infrared (NIR) light. Researchers showed that the strong optical absorbance of single-walled carbon nanotubes (SWNTs) in this special spectral window, an intrinsic property of SWNTs, can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters.

Practical Applications of Carbon Nanotubes in Medicine-CNTs in Drug Delivery: Drug delivery has been a major area of focus for researchers aiming to improve the efficacy of therapeutic molecules. Some obstacles these researchers are trying to overcome include poor drug distribution among cells, unwanted damage to healthy tissue, toxicity, and lack of the ability to select a particular cell type for treatment. Microorganisms play an essential role in the biogeochemical cycling of elements and in the formation of unique minerals.

Biogenic minerals are often formed in the nanometer scale through diverse microbiologically mediated physiological and metabolic activities and by passive surface reactions on cell walls or extracellular structures. They have unique chemical and physical properties [15, 16] as well as diverse morphologies [17, 18] that are not easily duplicated by means of strictly abiotic or Synthetic reactions [16]. Bacterial dissimulator metal reduction, for example, can result in the biogenesis of diverse minerals, such as magnetite (Fe3O4) [19, 20] and uraninite (UO2) [21, 22], with unique nanometer-size domains. Because of their small size and large specific surface area, biogenic nanoparticles have found wide use in various medical, biotechnological, chemical, and electronic applications. The small diameter of a carbon nanotube (CNT) also has an important effect on the mechanical properties, compared with traditional micron-size graphitic fibres[3]. Perhaps the most tricking effect is the opportunity to associate high flexibility and high strength with high stiffness, a property that is absenting graphite fibers. These properties of CNTs open the way for a new generation of high performance composites The mechanical properties are strongly dependent on the structure of the nanotubes. This is due to the high anisotropy of graphite.

Safety Concerns: Despite promising research, there are potential caveats associated with carbon nanotube-mediated drug delivery such as the nanotubes potential toxicity and possible negative effects on human organs. Nanotubes are very stable molecules and are therefore likely to persist in the body after initial treatment. Experiments in living cells and mice have shown that there is no apparent toxic effect in the short term.

However, whether there are longer-term effects and whether nanotubes can be used in humans are still unknown. High levels of carbon nanotubes in the mouse reticuloendothelial system (RES), which includes the liver and spleen, implying that the nanotubes may be accumulating in these areas. Their latest experiments suggest that nanotubes trapped in these organs would be slowly excreted from mice within a few months. However, even if the nanotubes themselves are safe, chemotherapy drugs carried into RES organs by nanotubes may still have toxic effects.

Small Tubes, Big Potential: In addition to toxicity studies, the Stanford researchers have also been working on getting nanotubes to carry small

interference RNAs (siRNAs), proteins and plasmids into living cells. Early experiments have shown that carbon nanotubes can achieve a higher success rate in penetrating living cells and lower toxicity as compared to traditional liposome-mediated methods. This success could lead to new alternatives in RNAi for biomedical research and possible solutions in gene therapy.

"You can attach a combination of drugs or peptides on the nanotube surface," Liu further stressed, "which could create a higher order of specificity and effects in cancer therapy. also target nanotubes to specific organs or tissues if there exists signal ligands for specific targeting." This would open other avenues for nanotube-mediated drug delivery. Due to their ability to non-covalently interact with a wide range of important molecules, carbon nanotubes are unique and exciting among nanomaterials. By loading cancer drugs onto carbon nanotubes and delivering them to tumors, the work done by Dai and other researchers at Stanford opens up a new door to in vivo cancer therapy. While we may have to wait a little longer for carbon nanotubes to enter clinical applications, nanotube biotechnology will undoubtedly aid our understandings of the life sciences and provide new approaches in chemistry, biology and medicine.

Nano Technology may in fact hold the keys to fighting many different types of cancer in the human bio-system. The technologies are so promising we may see survival rates skyrocket, thus everyone can live strong in the upcoming decade. Nano Tubes use in fighting cancer is indeed, a unique process [19]; it works by inserting tiny microscopic carbon synthetic rods into the body to deliver the cancer treatment to the exact spot needed. By directly aiming the rods into the cancer cells, the healthy tissue is saved. Chemotherapy seems to becoming a thing of the past. That is the theory that nuking the body and seeing which dies first; the cancer or the person. Even when the human survives it is left with huge amounts of destroyed tissue, which was not cancerous. When you see a person who is using chemotherapy to treat the cancer you see their hair fallout, but that is only one of many dire and serious side effects.

These nanotubes are so small they are the width of a DNA strand. The nano tubes will be heated up using near infrared light in a laser beam, which takes about two-minutes. The cancerous cells are quickly destroyed. This research is only in the preliminary stages but should be solved within the coming decade.

The nano tubes will be coated with a vitamin called folate, which is found in cancerous cells, but does not normally bind with healthy cells. Once these tubes touch the cancerous area they quickly bind and then are electrified with near infrared laser light, killing the cells. Nano Tube technologies are quickly coming of age and once they are available this process should be relatively easy to use. One cancer already targeted is Lymphoma and tests of the process are being done on mice with good results. There are other cancers it might work on well to and have been suggested. For instance Ovarian Cancers, Cervical Cancer and others; Nano Technology and biomedical processes are coming of age as we speak.

Nanotubes Destroy Kidney Tumors: By injecting multi-walled carbon nanotubes (MWCNTs) [21] into tumors and heating them with a quick, 30-second zap of a laser. A development in a new type of therapy that effectively kills kidney tumors in nearly 80% of treated mice. "When dealing with cancer, survival is the endpoint that you are searching for, it's great if you can get the tumor to shrink, but the gold standard is to make the tumor shrink or disappear and not come back. It appears that we've found a way to do that." Nanotubes are

long, thin, nanoscale tubes made of carbon. For the study, researchers used MWCNTs, which contain several nanotubes nested within each other. The tubes, when noninvasively exposed to laser-generated, near-infrared radiation, respond by vibrating, thus creating heat. If enough heat is conducted, tumor cells near the tubes begin to shrink and die.

Using a mouse model, the researchers injected kidney tumors with different quantities of MWCNTs and exposed the area to a 3-watt laser for 30 seconds. They found that the mice that received no treatment for their tumors died about 30 days into the study. Mice that received the nanotubes alone or laser treatment alone survived for a similar length of time. However, in the mice that received the MWCNTs followed by a 30-second laser treatment, the higher the quantity of nanotubes injected, the longer the mice lived and the less tumor re-growth was seen.

SWCNT-Breast Cancer: Chemically functionalized single-walled carbon nanotubes (SWNTs) have shown promise in tumor targeted accumulation in mice and exhibit biocompatibility, excretion and little toxicity. Here, we demonstrate in-vivo SWNT drug delivery for tumor suppression in mice. We conjugate paclitaxel (PTX), a widely used cancer chemotherapy drug to branched polyethylene-glycol (PEG) chains on SWNTs via a cleavable ester bond to obtain a water soluble SWNT-paclitaxel conjugate (SWNT-PTX).

SWNT-PTX affords higher efficacy in suppressing tumor growth than clinical Taxol® in a murine 4T1 breast-cancer model, owing to prolonged blood circulation and 10-fold higher tumor PTX uptake by SWNT delivery likely through enhanced permeability and retention (EPR). Drug molecules carried into the reticulo-endothelial system are released from SWNTs and excreted via biliary pathway without causing obvious toxic effects to normal organs. Thus, nanotube drug delivery is promising for high treatment efficacy and minimum side effects for future cancer therapy with low drug doses.

Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction: Biological systems are known to be highly transparent to 700- to 1, 100-nm near-infrared (NIR) light. It is shown here that the strong optical absorbance of single-walled carbon nanotubes (SWNTs) in this special spectral window, an intrinsic property of SWNTs, can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters. For oligonucleotides transported inside living cells by nanotubes, the oligos can translocate into cell nucleus upon endosomal rupture triggered by NIR laser pulses. Continuous NIR radiation can cause cell death because of excessive local heating of SWNT *in vitro*. Selective cancer cell destruction can be achieved by functionalization of SWNT with a folate moiety, selective internalization of SWNTs inside cells labeled with folate receptor tumor markers, and NIR-triggered cell death, without harming receptor-free normal cells. Thus, the transporting capabilities of carbon nanotubes combined with suitable functionalization chemistry and their intrinsic optical properties can lead to new classes of novel nanomaterials for drug delivery and cancer therapy.

DISCUSSION: A novel single-walled carbon nanotube (SWNT)-based tumor-targeted drug delivery system (DDS) has been developed, which consists of a functionalized SWNT linked to tumor-targeting modules as well as prodrug modules. There are three key features of this nanoscale DDS: (a) use of functionalized SWNTs as a biocompatible platform for the delivery of therapeutic drugs or diagnostics, (b) conjugation of prodrug modules of an anticancer agent (taxoid with a cleavable linker)

that is activated to its cytotoxic form inside the tumor cells upon internalization and *in situ* drug release, and (c) attachment of tumor-recognition modules (biotin and a spacer) to the nanotube surface.

To prove the efficacy of this DDS, three fluorescent and fluorogenic molecular probes were designed, synthesized, characterized, and subjected to the analysis of the receptor-mediated endocytosis and drug release inside the cancer cells (L1210FR leukemia cell line) by means of confocal fluorescence microscopy. The specificity and cytotoxicity of the conjugate have also been assessed and compared with L1210 and human noncancerous cell lines. Then, it has unambiguously been proven that this tumor-targeting DDS works exactly as designed and shows high potency toward specific cancer cell lines, thereby forming a solid foundation for further development.

CONCLUSION: Carbon nanotubes are one of the most commonly mentioned building blocks of nanotechnology. The treatment of cancer by nanotubes will be the most efficient and with fewer side effects compared to the other possible ways for cancer therapy.

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