REVIEW PAPER

Review on Biomedical Applications of Carbon Nanotubes for Cancer treatment

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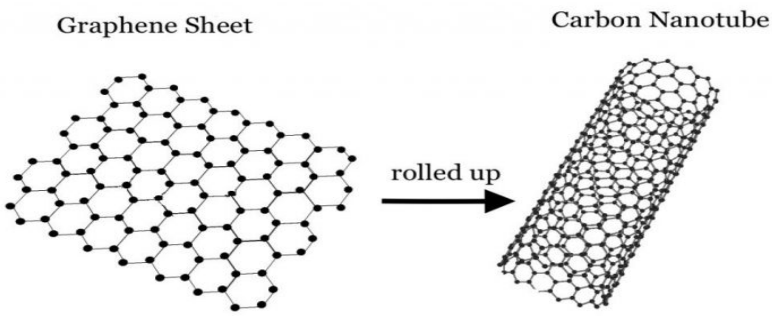
Introduction:
Cancer is a complex disease that claims millions of lives every year. Despite of having significant advances in cancer therapy, conventional treatments have some limitations and significant side effects also. Therefore, new methods for delivering anticancer molecules specifically to tumors to reduce side effects and improve therapeutic efficacy are greatly needed.
The goal of developing nanocarrier drug delivery systems is to enhance the therapeutic effect and reducing toxicity of therapeutically active materials. Carbon nanotubes (CNTs) are cylindrical molecules made of carbon atoms. CNTs are graphene sheets rolled into a cylinder that can be open ended or capped. CNTs have a high aspect ratio with diameters as small as 1nm and a length of several micrometers. Having high aspect ratio, surface area, and biocompatibility make them an effective medium for drug encapsulation and targeted delivery. Pristine CNTs are not soluble. Functionalization of CNTs enhances their solubility and ability to interact with cells, allowing for efficient drug loading and release. Due to their high surface area, they are capable of adsorbing or conjugating with various types of therapeutic molecules. As a result, CNTs can be surface engineered in order to enhance its dispersibility in the aqueous medium or to supply the suitable functional groups that can bind to the desired therapeutic material or the target tissue to show a therapeutic effect[1].
The potential of CNTs in cancer treatment is huge, with their ability to cross cell membranes and target specific cells making them an ideal drug delivery agent. Moreover, CNTs can be designed to target specific biomarkers, enhancing their selectivity and efficacy. The use of CNTs as a drug delivery agent could revolutionize cancer therapy, providing a more targeted and efficient approach to treat this devastating disease.
This dissertation aims to investigate the potential of CNTs as a drug delivery agent for cancer treatment, exploring their ability to encapsulate and deliver anticancer drugs, target cancer cells, and reduce substantial side effects . The results of this study tells about the development of CNT-based drug delivery systems, providing a new and innovative approach to cancer treatment.



Invention and Synthesis of Carbon nanotubes:
History:
In 1991**,** the single-wall Carbon Nanotube (SWCNT) was firstly discovered by Ijima and Ichihashi. They reported the formation of 1nm SWCNT by the carbon-arc synthesis. SWCNTs are one of the allotropes of carbon like fullerene and graphene. The true identity of the inventors of Carbon nanotubes is a subject of debate. The mainstream scientific groups believe that Ijima from Japanese electric co., LTD.(NEC) discovered the CNT in 1991. Although Ijima is credited for discovering CNTs, it turns out that the timeline of it dates back much before 1991.
In 1952, Radushkevich and Lukyanovich published a sharp image of 50 carbon nanotubes in the Soviet Union in the Journal of Physical Chemistry. This discovery was largely ignored because of the political situation tensions during cold war.

Synthesis of CNTs:
1. *Arc Discharge Method:* It requires a high temperature to vaporize the carbon atoms into plasma

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state. In inert gas atmosphere when the pressure is nearly 50 to 700 millibar, an electric arc can be generated between two closely spaced graphite electrodes. To produce the carbon plasma, the temperature needs to exceed 3000º Celsius. With arc plasma, the flexible CNTs with lesser defects can be produced.

2. *Laser Ablation Method:* The principle of Laser Ablation method is similar to Arc discharge method. Here Laser is used as energy source to heat the carbon target. But this process is difficult to scale up and expensive.

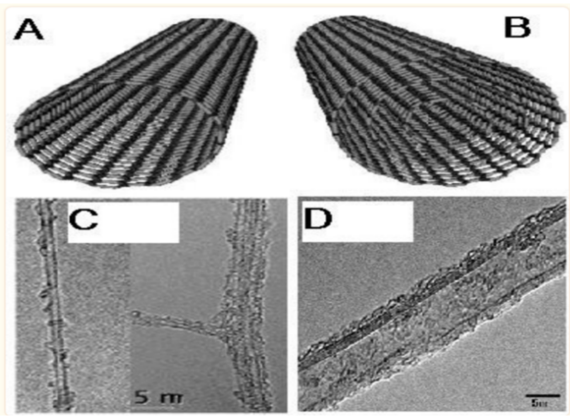
3. *Chemical Vapor Deposition Method (CVD):* To synthesis CNT using CVD transition metal catalyst (Co, Ni, Cu etc.) is needed for thermal dehydrogenation reaction. This method is a low-cost, high-yield, and easy-control method to produce CNT.

Method	**Are Discharge**	**Laser Ablation**	**Chemical Vapor Deposition**
Description	Arc evaporation of graphite in the presence of inert gas; CNT formed; CNT formed on electrodes during quenching	Vaporization of graphite target by laser; CNT formed on receiver during quenching.	Decomposition of hydrocarbons over transition metal catalyst to form CNT.
Operating Temperature	>3000 °C	>3000 °C	<1200 °C
Operating Pressure	50-7600 Torr generally under vacuum	200-750 Torr generally under vacuum	760-7600 Torr
Advantages	Good quality	Good quality; single conformation SWNT formed;	Easy scale up; it is possible to synthesis on templates;
Disadvantages	Difficult to scale it up	Difficult to scale it up; expensive	Quality is not that good

Structure and properties of Carbon nanotubes:

Structure:

According to the number of graphic shells, CNTs are mainly categorized as single-walled (SWNTs) and multi-walled carbon nanotubes (MWNTs). SWNTs are formed by single graphene sheet into a cylindrical shape having a diameter of 0.4 to 2 nm and their length is in the micro meter range. In a bundle structure, SWNTs are organized hexagonally forming a crystal-like structure. Three different types of SWNTs are characterized. These are 'zigzag', 'armchair' and 'chiral.' These structural variations show differences in electrical conductivity and mechanical strength. MWNTs are made by few concentric cylinders with regular interlayer spacing. Depending on the number of layers, the inner diameter of MWCNTs diverges from 0.4 nm up to a few nm and outer diameter varies characteristically from 2 nm up to 20 nm. The interlayer spacing ranges between 0.34 to 0.39 nm. Multiwalled carbon nanotubes can be formed in two structural models: Russian Doll model and Parchment model. When a carbon nanotube contains another nanotube inside it and the outer nanotube has a greater diameter than thinner nanotube, it is called the Russian Doll model. On other hand, when a single graphene sheet is wrapped around itself manifold times, the same as a rolled up scroll of paper, it is called the Parchment model[2].



(A) Schematic structure of SWCNT and (B) MWCNT. The transmission electron microscope (TEM) images of a (C) SWCNT and (D) MWCNT

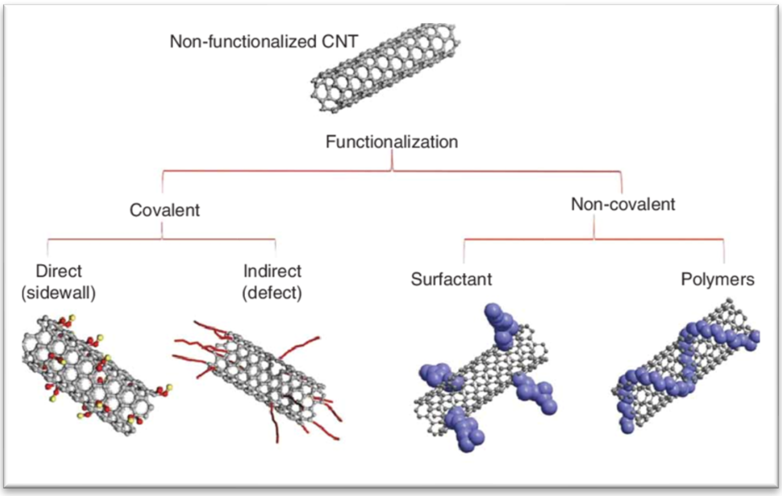
Properties:

- CNTs have the sp^2 bonds between each carbon atoms so they have a higher tensile strength than steel . The bond is even stronger than the sp^3 bond of diamond. Theoretically, SWCNTs may really have a tensile strength hundreds of times stronger than steel.
- Another property of CNTs is also elasticity. Under high force and pressure and also when exposed to axial tensions, it can bend, twist and will finally return to its original structure, without damaging the nanotube. Its Young's modulus is between 270 and 1700 GPa.
- Each carbon atom is arranged in a hexagonal lattice. The atoms are covalently bonded to three adjacent carbon atoms through sp2 molecular orbitals. As a result, the fourth valence electron remains free in each unit, and these free electrons delocalize on all atoms and resulting the electrical properties of the CNT.
- Carbon nanotubes also have attracting thermal properties. thermal conductivity of MWNTs was 3,000 W/K at room temperature, which is higher than that of graphite[3].

Functionalization of Carbon nanotubes for use in medicine and other biomedical applications:

Pure CNTs cannot be well dispersed in water and most solvents. Due its hydrophobic nature it has strong tendency to aggregate into bundles, which leads to toxicity also. For its use in biomedical applications, it needs to be surface engineered or functionalized so that it can disperse in aqueous solutions.

There are two types of process for CNT surface modification: *non-covalent* and *covalent methods*. Both covalent and noncovalent modification strategies could distinctively improve the dispersity of CNT in aqueous solutions[4].



The covalent and noncovalent modifications of CNT are discussed in more detail below:

Covalent surface modification of carbon nanotube:

The covalent modification of CNT has various strategies, the most used ones are: a) oxidation of CNT followed by conjugation of hydrophilic molecules by esterification; b) cycloaddition reactions to generate of functional groups on CNT sidewalls.

Oxidation of CNT is carried out by refluxing of pristine CNT in strong acidic media, e.g., HNO3/H2SO4. In this condition, the caps at both ends of nanotube are opened. Carboxylic groups are formed at the ends of CNTs and at some defect sites on nanotube sidewalls. The carboxylic groups are usually used for further derivation of the CNT through esterification or amidation reactions. The carboxyl groups can be activated by thionyl chloride and in next step it reacts with amine groups-containing molecules. In most cases, the length of nanotubes gets shortened, but the electronic properties of such functionalized CNT remain intact.

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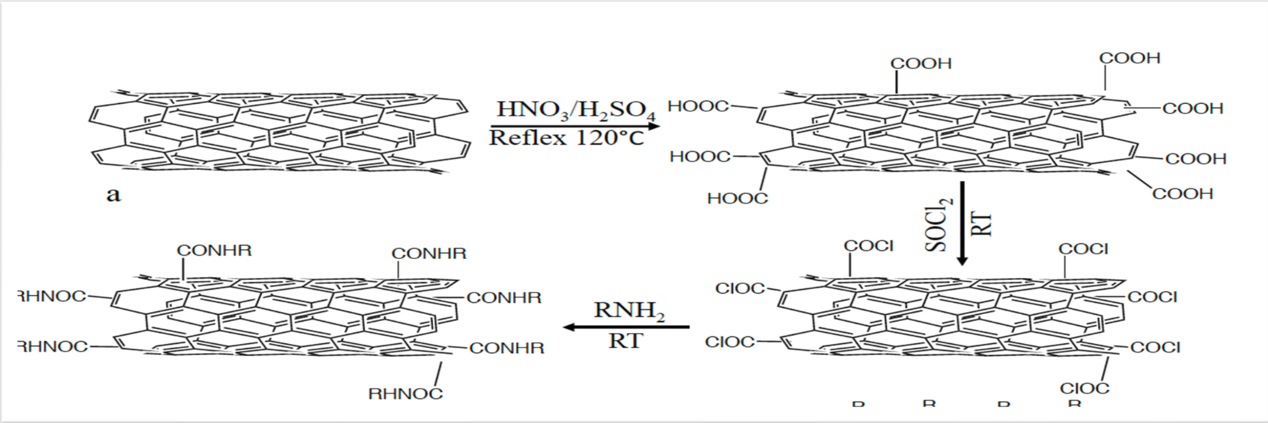
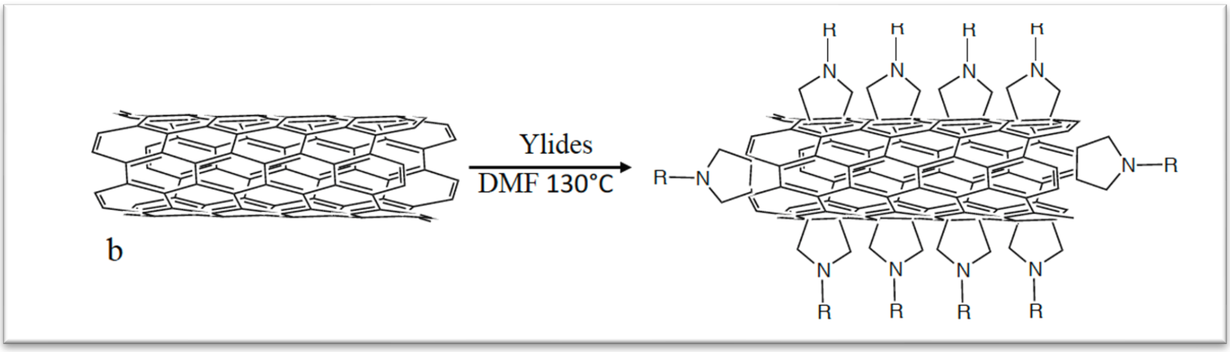


Oxidization of carbon nanotube followed by further attaching hydrophilic molecules via

Cycloaddition reaction is another very useful methodology for covalent modification of CNT. Cycloaddition of CNT forms pyrrolidine-fused rings on nanotube surfaces by reacting with ylides. In contrast to oxidation of CNT, cycloaddition produces a large number of pyrrolidine rings all-around of the nanotubes, including sidewalls and the ends of CNT.

Thus, the resulting surface active CNT can be well-dispersed in water. This method also greatly shortens the length of the CNT, which could improve its toxicological effects. In addition, the pyrrolidine rings generated from cycloaddition can be substituted with many functional groups, which allows further binding with therapeutic agents, including DNA, antibiotics and chemotherapy drugs through covalent conjugation. However, cycloaddition of CNT alters the sp2-conjugated structure of CNT, which affects its electronic properties[5].

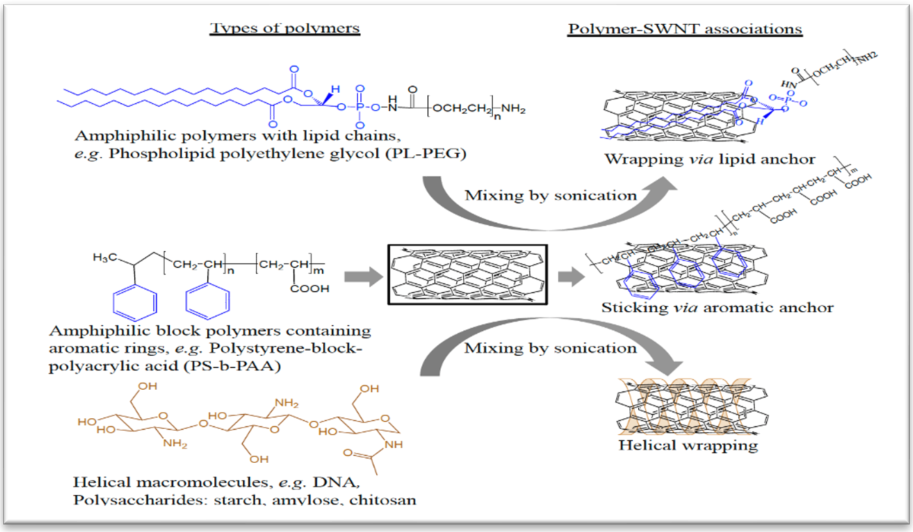


b) 1,3-dipolar cycloaddition reaction

Noncovalent surface modification of carbon nanotube:

Noncovalent modification of CNT is carried out by attaching coating materials via van der Waals force, π-stacking or hydrophobic interactions. Like covalent modification, noncovalent modification does not disrupt the sp2 hybridization, as a result the optical or electronic properties of CNT are preserved, which are important for biomedical applications of CNT in imaging and detection. Surfactants are very potent for noncovalent modifications of CNT. Although, high concentration of surfactant is required, which is very toxic for the cells, decreasing its usefulness in biological applications. Amphiphilic polymers are also used in this process. There are three types of polymers that have been shown effective in CNT dispersion:

1) aliphatic chain-containing polymers e.g., phospholipid conjugated polyethylene glycol (PL-PEG); 2) polyaromatic rings-containing amphiphilic block polymers, e.g., polystyrene-polyacrylic acid; 3) macromolecules that display helical structure, such as DNA and some Polysaccharides (starch, amylose etc.) in which the aliphatic chain wraps CNT through Van de Waal force and other hydrophobic interactions and stick tightly to CNT through π-stacking[6].



Schematic presentation of non-covalent functionalization of carbon nanotube with different types of polymers.

A New Targeted Delivery Approach by Gelatin-Functionalized Carbon Nanotubes Loaded with Cisplatin:

Carbon nanotube has hydrophobicity and self-aggregation phenomenon that can impact its bio application as nano drug delivery agent. Researchers have developed a polydopamine (PDA) coating on pristine CNT, comprising reactive groups that permit Michael's addition reactions with gelatin (Gel) molecules. Dopamine has a strong drug adsorption capability, which can enhance the drug-loading capacity. Gelatin can make carbon nanotubes more soluble and less harmful to biological systems.

Chemotherapy drugs like Doxorubicin, cisplatin, paclitaxel, and camptothecin are now used in nano-delivery systems. These can be filled into carbon nanotubes by using gelatin-surface-modified carbon nanotubes (CNTs/Gel) as the drug delivery vehicle[7].

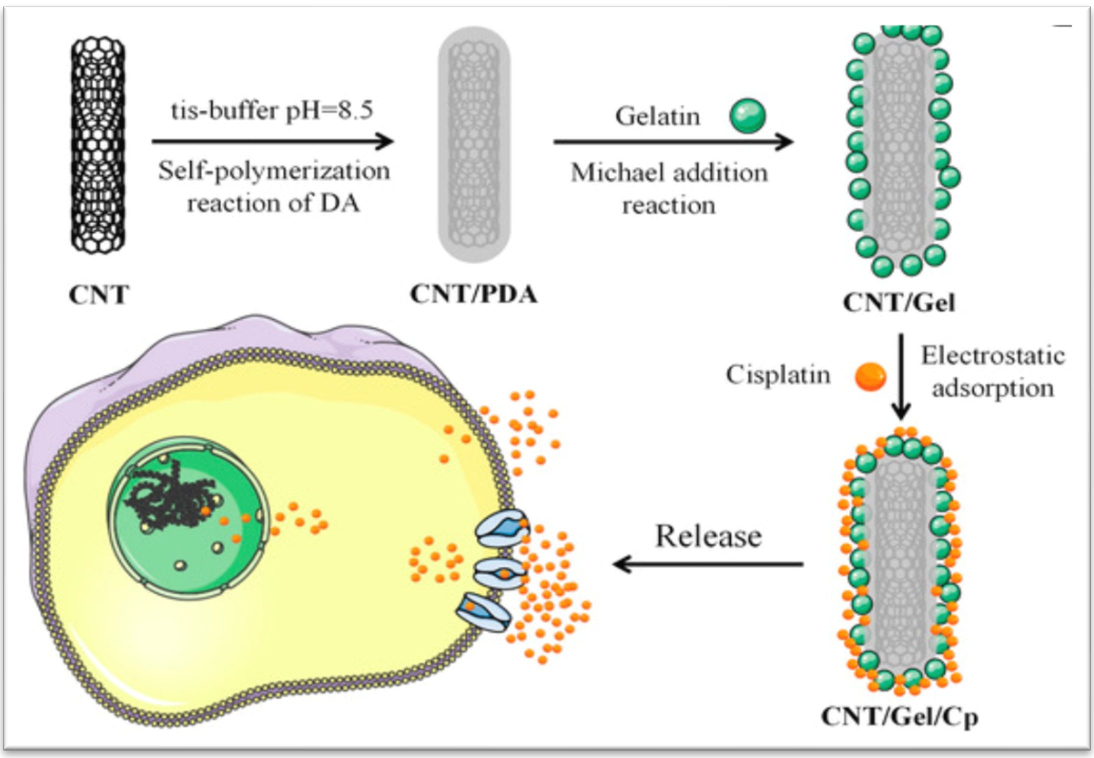
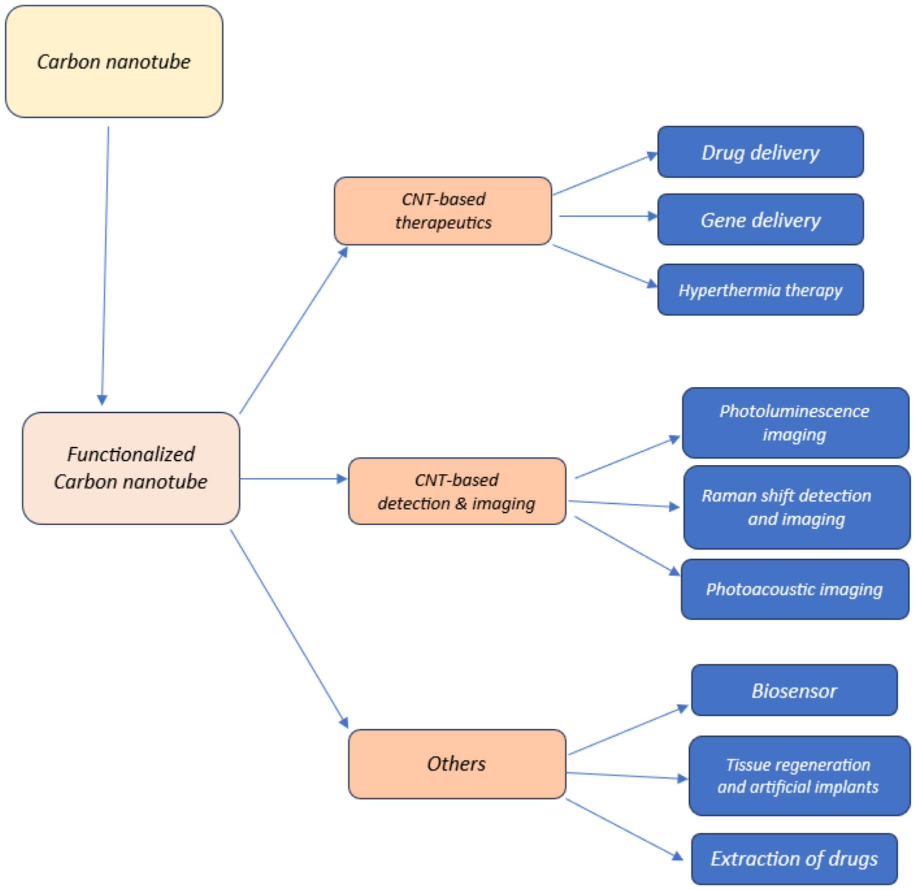


Illustration of the process for the preparation of CNT/Gel/Cp and its mechanism of action for antitumor effects.

Application of Carbon nanotubes for Cancer treatment:

From decade, Carbon nanotubes have been highly explored for many biomedical applications, particularly in the field of cancer treatments. Studies have shown that CNT coated with PEG generally obtain a prolonged blood circulation, which favors tumor specific targeting. The tumour targeting efficiency of CNT can be further enhanced by conjugation of tumour targeting molecules. Also, the optical properties of CNT, such as NIR absorption, photoluminescence, and Raman shift etc., can be used for biological detection and imaging.

In the upcoming sections, applications of CNTs for cancer related therapies are briefly discussed, including gene delivery, hyperthermia cancer therapy, tumour detection & imaging, and chemotherapy drug delivery.

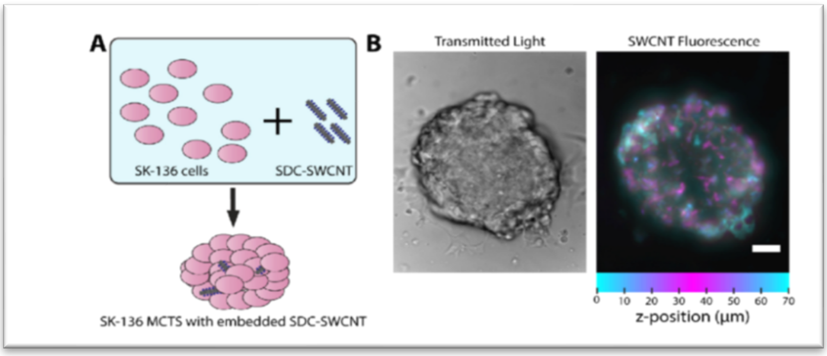


Carbon nanotube for imaging and detection of tumours:

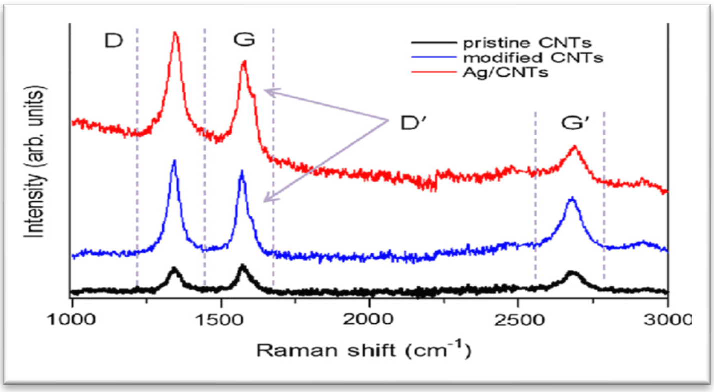
The molecular structure of CNT has multiple remarkable optical properties including strong NIR absorption, Raman shift and photoluminescence. These properties can be used for detection and imaging of tumours.

Semiconducting SWNT emits **NIR photoluminescence** upon photoexcitation. One advantage of the photoluminescence of SWNT over organic fluorescence dyes is that SWNT has no apparent photo bleaching, which is important for tracking the changes in living systems. NIR photoluminescence has been successfully applied for tracking endocytosis and exocytosis of functionalized SWNT in NIH-3T3 cells in real time. In vivo, antibodies conjugated SWNT was successfully applied for deep tissue penetration and high-resolution microscopy imaging of tumour vessels beneath thick skin is successfully accomplished.

SWNT also exhibits specific resonance **Raman scattering**. Having high sensitivity, the Raman spectrum of CNT requires only small quantity of samples. Since Raman spectrum of CNT is distinguishable from autofluorescence of the tissue samples, Raman micro spectroscopy of SWNT has been developed for imaging of tissue samples, living cells and small animal models[8].



Imaging of carbon nanotube photoluminescence



Raman spectra of pristine CNTs, modified CNTs, and Ag/ CNT hybrid nanocomposites

Carbon nanotube for thermal destruction of tumours:

Heat-based cancer treatment is a progressive research area. Tissues are known to be highly transparent to 700- to 1,100-nm NIR light, whereas, CNT strongly absorbs in this range, generating significant amount of heat. Antibodies conjugated SWNT effectively kill the cancer cells, but not the neighboring healthy cells by hyperthermia. Moreover, the thermal ablation effect of CNT can be enhanced by combination with chemotherapy drugs delivery by CNTs.

Carbon nanotube for gene delivery:

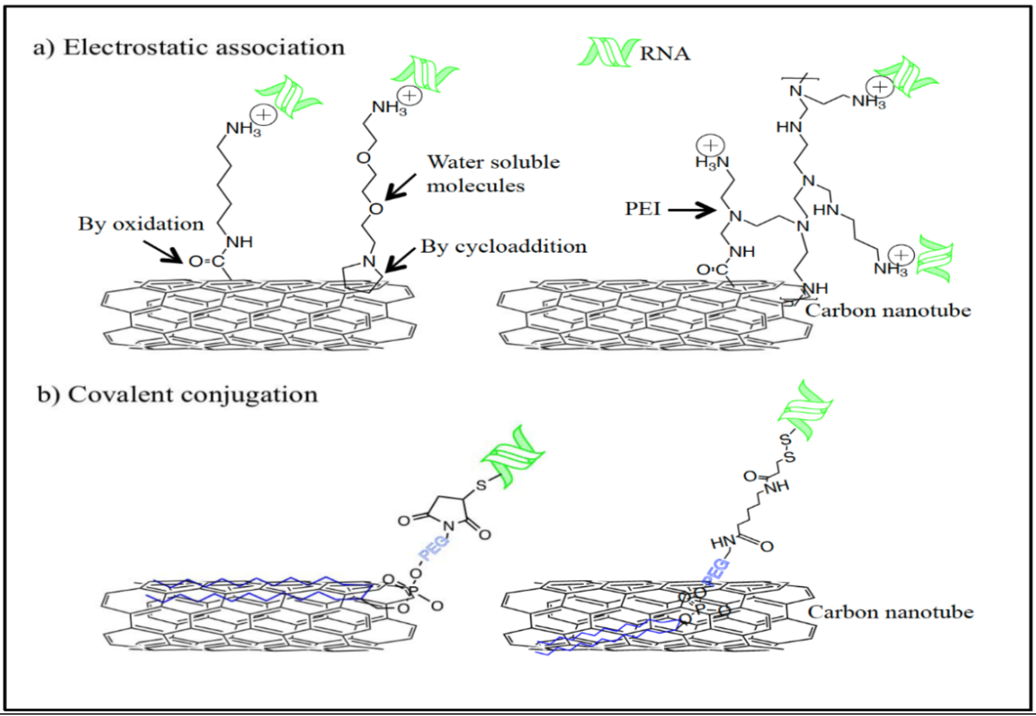
Gene therapy is a vital treatment method for cancer and other genetic diseases. DNA and siRNA are macromolecules that cannot penetrate through cell membrane. So, carriers are required to take them inside of cells to take effects. CNT is an excellent carrier for gene delivery.

DNA or siRNA can be used as CNT surface coating molecules to disperse CNT in aqueous solution. Studies has shown that the siRNA functionalized SWNT readily enters cells and shows its biological activity in cultured cells.

Alternative process to the direct wrapping method, negatively charged DNA or siRNA can also be formulated with cationic polymer-coated CNT.

Cationic polymers, e.g., polyethylene imine (PEI), could protect encapsulated DNA or siRNA from degradation.

In addition to the above-mentioned gene formulating methods, genes can also be covalently conjugated to CNT via cleavable chemical bonds. Thiol-modified siRNA has been covalently conjugated to polymer PL-PEG functionalized SWNT by disulfide bond. The breaking of disulfide bonds by cellular thiol digesting enzymes allows the release of the siRNA for its actions upon cellular systems.



a) Binding of genes to cationic CNT by electrostatic association b) Covalent conjugation of genes

Carbon nanotube for chemotherapy drug delivery:
Since CNT is a nanosized hollow tube, both the interior and the surface of the nanotubes can be utilized for loading of small molecule drugs. Till date, many CNT-based drug delivery systems (DDS) have been designed for in vitro and in vivo delivery of chemotherapy drugs. By the linking of tumour-targeting molecules to the CNT-based DDS, the targeted SWNT-DOX have shown more effective suppression of the of cancer cells in vitro and in vivo. Anticancer agents, like cisplatin, are conjugated to oxidized SWNT via covalent bonding for delivery.

SWNT-cisplatin has exhibited its activity to specifically target and kill squamous cancer cells.

Alternatively, drug molecules can be covalently linked to polymer end of functionalized SWNT for delivery. For example, drug PTX was conjugated to PL-PEG functionalized SWNT for active treatment in murine breast cancer model, and the result has showed higher tumour growth inhibition and reduced side effects.

Researchers have shown that MWCNTs have high efficient drug loading capacity also. They could be used as proper drug nanocarriers and promising nanoplatforms for cancer therapy. Besides, to improve their compatibility and conjugation capability and also to reduce their toxicity, they are functionalized with chemical groups such as hydroxyl or carboxyl groups[9-15].

The examples of CNT-based targeted delivery systems are listed below:

Therapeutics	Targeting Moieties	Drug-loading Methods
Carboplatin	*N/A*	Filling
Cisplatin	EGF	Covalent conj.
Daunorubicin	Sgc8c aptamer	Adsorption
Docetaxel	NGR	Adsorption
Doxorubicin	Folate/Magnetic	Adsorption
Doxorubicin	RGD	Adsorption
Doxorubicin	Folate	Adsorption
Doxorubicin /hyperthermia	NGR	Adsorption
Gemcitabine	Magnetic	Adsorption
Methotrexate	*N/A*	Covalent conj.
Paclitaxel	*N/A*	Absoption
Paclitaxel	*N/A*	Covalent conj.
Platinum (IV)	Folate	Covalent conj.

Examples of carbon nanotube based drug delivery systems

CNT based chemotherapy drug delivery systems:
Several methods have been designed for CNT-based chemotherapy drug delivery using passive and active targeting strategies.
These methods can be categorized into five types of common schemes: I) filling drugs to the interior of CNT; II) adsorption of drugs to CNT sidewall; III) covalent conjugation of drugs to the CNT backbone modified by oxidation reaction; IV) covalent conjugation of drugs to the CNT backbone modified by cycloaddition reaction; V) covalent conjugation of drugs to CNT-dispersing polymers [16-22].

I) Filling drugs to the interior of CNT:
Because of unique nano size hollow structure, CNT can be used as a nano-sized container to fill small molecule drugs. Drug filling to the inside portion of CNT is feasible because of capillary driving force. For the filling of drugs inside CNT, multi-walled carbon nanotubes are usually used, as they have larger inner diameter than SWNT, which allows a higher filling capacity. To fill drugs, the cap ends of the CNT need to be opened with treatment using nitric acid.

II) Adsorption of drugs to CNT sidewall:
Studies have also shown that pre-functionalized CNT exists a large surface area that can be used for direct binding of macro molecule drugs. Because the carbon atoms in CNT surface make a highly ordered benzene ring structure, the aromatic ring-containing drugs can be efficiently loaded on CNT via strong π-stacking force.
Using this method, a large amount of DOX (~ 400%w/w) have been loaded onto the pre-functionalized SWNT for delivery. Binding and the releasing of the drug molecules from the nanotube could be controlled by changing the pH.

III) Covalent conjugation of drugs to that CNT backbone modified by oxidation Reaction:
Oxidized CNT contains carboxyl groups, at the end and at some defect sites, that can be used for drug conjugation. Usually, the drugs become inactive when linking to CNT, and become active drugs when released to exert its effects, so the bonding between the drugs and CNT have to be cleavable. The common linkers used for drug delivery include ester, peptide, and disulfide bonds. These linkers could be cleaved by the enzymes present in the route of delivery e.g., cisplatin has been conjugated to the oxidized SWNT via a peptide linker.

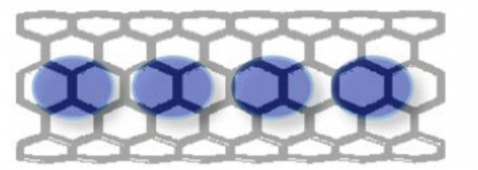
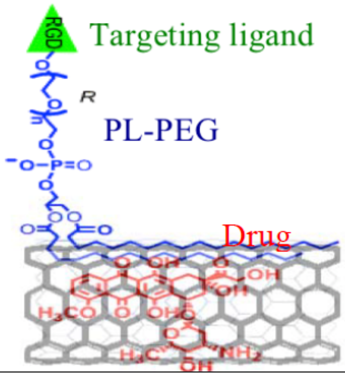
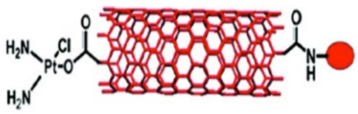
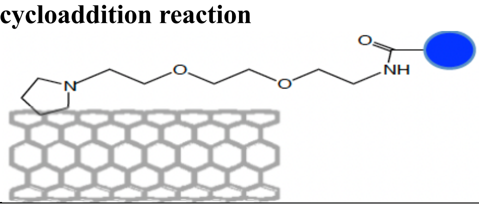
IV) Covalent conjugation of drugs to the CNT backbone modified by cycloaddition Reaction:

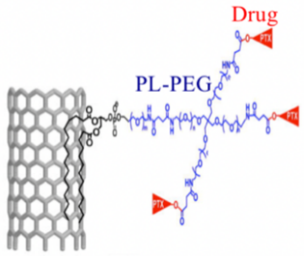
Cycloaddition reaction is a powerful process that generates substantial amounts of functional groups on sidewall and ends of CNT, which produces much higher level of drug loading than oxidized CNT. For example, drug methotrexate, due to limited cellular permeability, was linked to CNT via cycloaddition for intracellular drug delivery.

V) Covalent conjugation of drugs to CNT-dispersing polymers:

Alternative to direct drug-CNT conjugation, the drug molecules can also be linked to CNT-dispersing polymers for delivery. For example, PTX was conjugated to PL-PEG functionalized SWNT via reversible ester bond. By this drug-loading method, the amounts of drugs loaded on CNT depend on the amounts of polymers that can be attached to CNT.

Drug loading Methods

Filling 	• convenient formulation • preserved intrinsic electrical and optical Properties of CNT
Adsorption 	• convenient formulation • high loading capacity • preserved intrinsic CNT electrical and optical properties • both CNT surface and its dispersing polymer can be used for different functionalities, e.g., drugs, targeting molecules, etc.
Covalent conjugation to CNT modified by oxidization reactions 	• suitable for all types of drugs that contain reactive functional groups
Covalent conjugation to CNT modified by cycloaddition reaction 	• suitable for all type of drugs that contain reactive functional groups • high drug-loading capacity due to high level of functional groups generated on CNT

Covalent conjugation to CNT dispersing Polymers 	• suitable for all type of drugs that contain reactive functional groups • preserved intrinsic CNT electrical and optical properties

Conclusions:

CNTs can be functionalized so that some particular molecules are attached to their surfaces via covalent or noncovalent bonding. The needle-like shape of the CNTs enables them to penetrate the cellular membranes and transport the carried therapeutic molecules to the cells.
CNTs have some exclusive properties that would make them appropriate in the medical field due to their such ability to adsorb pathogenic microorganisms and conduct heat. CNTs have been introduced to drug delivery research for a limited number of years, so huge numbers of researches are expected to be accomplished in the forthcoming years in order to explore its potential.

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