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Advances in the biomedical application of polymer-functionalized carbon nanotubes

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Nowadays, carbon nanotubes (CNTs) have attracted the attention of scientists because of their unique electronic, magnetic, optical, mechanical, and chemical properties. However, their poor solubility in solvents, especially in water, limits their applications in several promising fields such as biomedicine, biomedical imaging, and cancer therapy. The attachment of hydrophilic segments to CNTs is a very efficient method for overcoming this problem. This review covers the latest advances in the synthesis of water-soluble CNTs with an emphasis on the molecular structure of various categories of hydrophilic molecules/macromolecules which have been grafted onto the surface of CNTs. Indeed, from the viewpoint of chemical synthesis, covalent bonding of several water-soluble molecules/macromolecules including small water-soluble organic molecules, linear, hyperbranched and dendritic polymers/biopolymers, glycoconjugate molecules/polymers as well as biomolecules onto the surface of CNTs has been deeply surveyed. Moreover, the most recent and interesting bio-applications of polymer-functionalized water-soluble CNTs have been properly reviewed.

1. Introduction

Dispersing or dissolving of CNTs in aqueous solutions has been a challenge for chemists, biochemists, and materials scientists in recent years. Functionalization of CNTs *via* attaching hydrophilic segments to their sidewall can improve their water solubility and will combine the unique properties of CNTs with other materials. Modification of CNTs by other materials might be utilized to tailor the interactions of CNTs with environmental constituents including solvents and cells. Water-soluble and biocompatible functionalized CNTs are able to cross the cell membrane shuttling a wide range of biologically active molecules including drugs, proteins, DNA, and RNA into the cells. Indeed, functionalization and surface modification develop hemocompatibility in CNTs. Since functional groups and coating of the surface of carbon nanotubes

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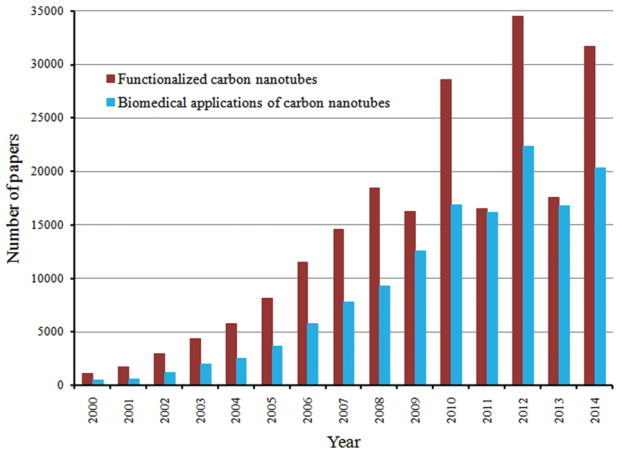

Fig. 1 Statistical diagram of published papers in the field of functionalized carbon nanotubes and their biomedical applications.

have been proven to dramatically change the CNT interactions with blood cells, polymers are promising candidates for developing this property for future biomedical applications.[1–6] In recent years, scientists have had a noticeable interest in functionalizing carbon nanotubes and their biomedical applications. Fig. 1 shows a statistical diagram based on the data obtained from the Google scholar search engine (keywords: functionalized carbon nanotubes and biomedical applications of carbon nanotubes) on January 24, 2015. It indicates that the number of published papers in this field still has a growing rate.

According to their chemistry and type of reaction, the covalent functionalization of CNTs is basically classified into oxidation, amidation, esterification, thiolation, halogenation, hydrogenation, and cycloaddition reactions as well as radical, carbene, and electrophilic additions. Also, many polymerization techniques including anionic polymerization,[7,8] radical polymerization,[9,10] condensation polymerization,[11–13] ring-opening polymerization (ROP),[14–17] plasma polymerization,[18,19] γ-irradiation polymerization[20,21] as well as reversible addition fragmentation chain transfer (RAFT) polymerization[22–27] and atom transfer radical polymerization (ATRP)[28–31] have been employed to functionalize CNTs.

In recent decades, functionalization and modification methods for solubilization of CNTs[32–43] in different solvents as well as their applications in biomedicine,[44] biomedical imaging, sensing and coating,[45–47] drug design and discovery,[48] cancer therapy,[49,50] cell therapy,[51] polymeric nanocomposites,[52–54] synthesis of inorganic hybrid nanomaterials,[55,56] switches, sensors and transistors,[57,58] catalysts,[59] photovoltaics,[60] and electrode material for rechargeable Li-ion batteries[61] have been summarized in many reviews and book chapters.

In this review, we intend to focus on the chemically grafted segments on CNTs including small water-soluble organic molecules, water-soluble linear, hyperbranched and dendritic polymers, water-soluble biopolymers, and glycoconjugate molecules, which are mainly responsible for solubility of CNTs in aqueous solutions, and as well as methods for their conjugation on CNTs. Bio-applications of polymer functionalized water-soluble CNTs will also be reviewed.

2. Toxicity of polymer-functionalized carbon nanotubes

In vitro studies have shown that the modification of CNTs alters their interactions with the lipid bilayer and enhances their uptake into the cells. Also, several studies have indicated that water-soluble functionalized carbon nanotubes exhibit less cytotoxicity and oxidative stress compared to the pure CNTs. In this section, thanks to the fact that the toxicity of CNTs and functionalized-CNTs has been numerously reviewed,[62–70] we have solely focused our attention on some of the remarkable points about the toxicity issues of poly(ethylene glycol) (PEG)-functionalized carbon nanotubes. Due to its biocompatibility and good solubility under various physiological conditions, PEG is widely employed for various purposes in CNT-based biomedical applications. It has been reported that when the molecular weight of PEG chains was less than 2000, the PEGylation did not prevent the cellular uptake of SWCNTs, whereas longer chains could reduce the nonspecific cellular uptake *in vivo*.[71] SWCNT functionalized with PEG grafted to poly(g-glutamic acid) and poly(maleic anhydride-*alt*-octadecene) has been exhibited to have a long blood circulation duration ($t_{1/2}$ = 22.1 hours).[72] Dai and his co-workers have reported that SWCNTs functionalized with phospholipid-PEG_{2000} are capable of gene silencing with no apparent cytotoxic effects on human T cells.[73] Schipper *et al.*[74] have also revealed no evidence of toxicity in mice over 4 months for SWCNTs modified with PEG (both covalently and non-covalently functionalized).

Mohsen Adeli

Mohsen Adeli received his undergraduate degree from Lorestan University (Iran) in 1996. He obtained his MS and PhD degrees from Tabriz University. After joining Lorestan University in 2005, he carried out postdoctoral research at the Institute for Nanoscience and Nanotechnology of Sharif University of Technology in 2007. He was promoted to the ranks of associate and full professor in 2010 and 2013 respectively. He joined the Free University of Berlin as a guest professor in 2014.

3. Oxidation of CNTs

Some of the most important chemical methods for preparing CNTs that are still dispersible in water are oxidation reactions. Several oxidizing reagents including HNO_3, H_2SO_4, H_2O_2, $KMnO_4$, OsO_4, $K_2S_2O_8$, $(NH_4)_2S_2O_8$, and O_3 gas have been used to oxidize CNTs. Among the procedures for the preparation of water-soluble CNTs *via* oxidation, acid treatment is a classic facile method which has been used and studied abundantly. In this method, the effect of oxidation on dispersibility, size, and structure of single-walled carbon nanotubes (SWCNTs) has been evaluated. Two oxidation protocols, sonication in HNO_3 (8 M) at 40 °C and reflux in HNO_3 (2.6 M), have been examined for SWCNTs. Raman spectroscopy has shown greater covalent functionalization through oxidation of SWCNTs by the reflux procedure than sonication.[75] Also, it has been proved that a HNO_3–H_2SO_4 mixture produces a higher density of surface functional groups than concentrated HNO_3 alone.[76] Moreover, the oxidation process of CNTs by HNO_3 has been kinetically controlled.[77] The outer walls of double-walled carbon nanotubes (DWCNTs) were selectively oxidized using a combination of oleum and nitric acid.[78]

In another study, multi-walled carbon nanotubes (MWCNTs) were covalently modified by two different oxidation methods using nitric acid and dielectric barrier discharge plasma under an oxygen-based atmosphere. Temperature-programmed desorption and GC (gas chromatography) results indicate that nitric acid treatment creates more acidic groups than plasma treatment.[79] A comparison between oxidized CNTs prepared by acid and O_3/UV methods in the case of defects produced on the sidewalls of CNTs has been carried out.[80]

In this manner, the room temperature functionalization of CNTs using an O_3–water vapour mixture has been performed. It has been shown that more oxygenated functional groups could be grafted onto the CNT surfaces due to the addition of water vapour, compared to traditional approaches in which a high density of ozone is required. The existing hydroxyl radicals in the O_3–water vapour mixture are considered to be responsible for the increased CNT oxidizing degree.[81] A theoretical study has also opened new insights into the chemical oxidation of SWCNTs.[82] Moreover, a novel approach has been recently developed for synthesizing nitrogen-doped CNTs using liquid amines (such as isopropylamine, *n*-propylamine and *n*-butylamine) as fuels in flame. These amines not only create a high reaction temperature but also provide a source of nitrogen for functionalization of CNTs.[83]

4. Conjugation of various hydrophilic molecules/macromolecules onto the surface of CNTs

Since it has been proved that functionalization of carbon nanotubes by even short molecular chains disperses their bundles and is a promising way to avoid their asbestos-like pathogenicity, to obtain multifunctional hybrid nanomaterials useful for biomedical applications, one of the best plans is to covalently graft water-soluble molecules/macromolecules onto their surface.[2] In this approach, various hydrophilic molecules/macromolecules including small water-soluble organic molecules, water-soluble linear, hyperbranched and dendritic polymers, water-soluble biopolymers and glycoconjugate molecules have been successfully linked to the sidewall of CNTs *via* chemical bonds.

4.1. Small water-soluble organic molecules

Many hydrophilic organic molecules have been employed for functionalization and solubilization of CNTs in water, which include adenosine and adenosine monophosphate (**a**, **b**),[84,85] *N*-(ethylene glycol derivatives) of pyrrolidine (**c**, **d**, **e**),[86,87] diethylentriamine pentaacetic (DTPA) labelled by ^{111}In (**f**),[88] 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic (DOTA) labelled by ^{111}In linked by thiourea spacer (**g**),[89] several water-soluble benzene derivatives (**h**),[90,91] 4-(triethylenglycol) benzene (**i**),[92] phosphoryl choline (**j**),[93] isophthalic acid (**k**),[94] benzene sulfonic acid and sodium sulfonate (**l**, **m**),[95,96] direct blue 71 dye (**n**) and nonylamine (**o**),[97] triethylenetetramine (TETA) (**p**),[98] lysine (**q**),[99,100] ethylene glycol diethanolamine (**r**),[101] cobalt(II) tetracarboxyl-phthalocyanine linked by amine spacers (**s**),[102] three amino acids (**t**),[103] 2,4,6-triarylpyrylium water-soluble derivatives (**u**),[104] chemotherapeutic agents having NH, NH_2, and OH functional groups,[105] antibody of P-glycoprotein[106] and hydroxyapatite.[107] The molecular structures of some of these functionalities are shown in Fig. 2.

Some important reports which often contain the solubility values of modified CNTs in water have been described in detail.[108] For example, a small organic amino acid molecule, lysine, has been grafted onto the surface of MWCNTs and highly water-soluble nanotubes have been obtained. Their stable aqueous solution (10 mg mL^{-1}) which is nearly twice more in magnitude than oxidized MWCNTs has been prepared.[102] Also, it has been reported that SWCNTs modified by *N*-(ethylene glycol) derivatives of pyrrolidine (Fig. 2d) synthesized by 1,3-dipolar cycloaddition reaction[86] possessed a remarkably high solubility (20 mg mL^{-1}) in water for more than a month. The analogous MWCNTs modified by **d** compound (Fig. 2) were less soluble than the SWCNTs (12 mg mL^{-1}).[87] Furthermore, carboxylic acid-functionalized SWCNTs prepared *via* the reaction of amino acids, $NH_2(CH_2)_nCOOH$, with fluoronanotubes showed similar levels of sidewall functionalization; but the solubility in water was controlled by the length of the hydrocarbon side chain (n). It has been reported that a 6-aminohexanoic acid derivative was soluble in water (0.5 mg mL^{-1}) between pH 4 and 11, whereas the glycine and 11-aminoundecanoic acid derivatives were insoluble for all pH values.[103]

4.2. Water-soluble linear polymers

The functionalization of CNTs with polymers (polymer grafting) is particularly important for preparation of hybrid nano-

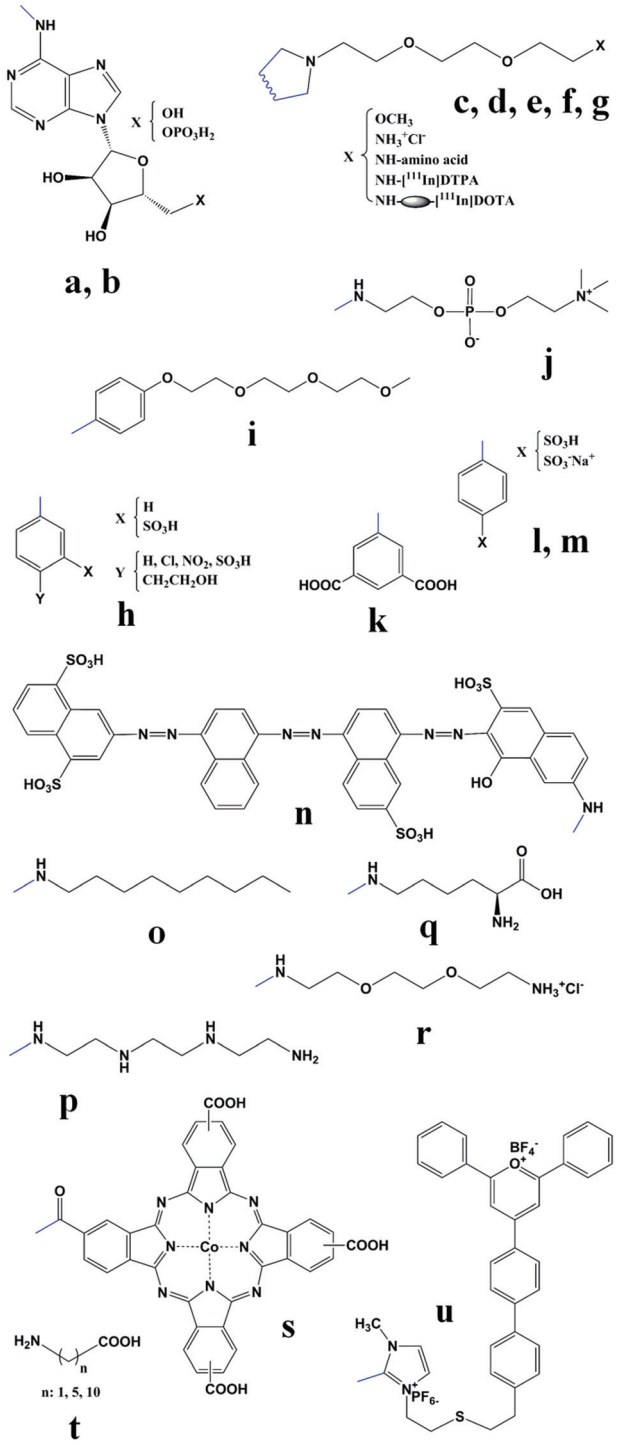

Fig. 2 Structures of some small water-soluble organic molecules which have been covalently employed for solubilization of CNTs in water.

materials that are useful in nanomedicine. Two main categories "grafting to" and "grafting from" approaches have been reported for the covalent grafting of polymers onto the sidewall of CNTs. The "grafting to" approach is based on the attachment of the as prepared or commercially available polymers on the CNT surface by chemical reactions, such as amidation, esterification, and radical coupling. In the "grafting from" approach, the polymer is linked to the CNT surface by *in situ* polymerization of monomers in the presence of reactive CNTs or CNT supported initiators.[49] Water-soluble polymer-grafted CNTs have been formed by covalently attaching nanotubes to highly water-soluble linear polymers, such as polyethylene glycol (PEG) (**a**, **b**),[109–122] poly(vinyl alcohol) (PVA) (**c**),[123–126] poly(vinyl acetate-*co*-vinyl alcohol) (PVA-VA) (**d**),[127] polyethylenimine (PEI) (**e**),[128,129] poly(propionylethylenimine-*co*-ethylenimine) (PPEI-EI) (**f**),[130–132] poly(acrylic acid) (PAA) (**g**),[133,134] poly(methacrylic acid) (PMAA) (**h**),[21] poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) (**i**),[135,136] poly(2-diethylaminoethyl methacrylate) (PDEAEMA) (**j**),[137] poly(glycerol mono-methacrylate) (PGMA) (**k**),[138] poly(*N*-(2-hydroxypropyl) methacrylamide) (PHPMA) (**n**),[26] poly(2-vinylpyridine) (**o**),[139] poly(sodium 4-styrene sulfonate) (**p**),[140,141] and poly(*m*-amino benzene sulfonic acid) (PABS) (**q**).[142] Moreover, in several reports, polyacrylamide (PAAm) (**l**)[143,144] and poly(*N*-isopropylacrylamide) (PNIPAM) (**m**)[25] have been covalently attached to CNTs *via* RAFT polymerization and ceric-induced redox radical polymerization. The macromolecular structures of these linear water-soluble polymers are indicated in Fig. 3.

In some cases, the water-solubility value of CNT-linear polymer hybrid materials has been reported. Based on these reports, the solubility of CNT grafted by PEG[120] and PABS[120] in water is around 5 mg mL^{-1}. In another case, a high water solubility of a few tenths of g mL^{-1} has been achieved on the basis of the carboxyl-based coupling of hydrophilic polymers such as PEG.[122] Also, PEG-functionalized DWCNTs with water-solubility around 0.37 mg mL^{-1} have been synthesized by [2 + 1] cycloaddition reaction.[121]

Recently, Xia and his co-workers[145] have proved that the surface charge and type of functionalization dominate the cellular processing and toxicity of MWCNTs, dramatically (Fig. 4).

They found that compared to the as prepared MWCNTs, those with negative surface charges (COOH-MWCNTs and PEG-MWCNTs in the above figure) decreased the production of pro-fibrogenic cytokines and growth factors, while neutral

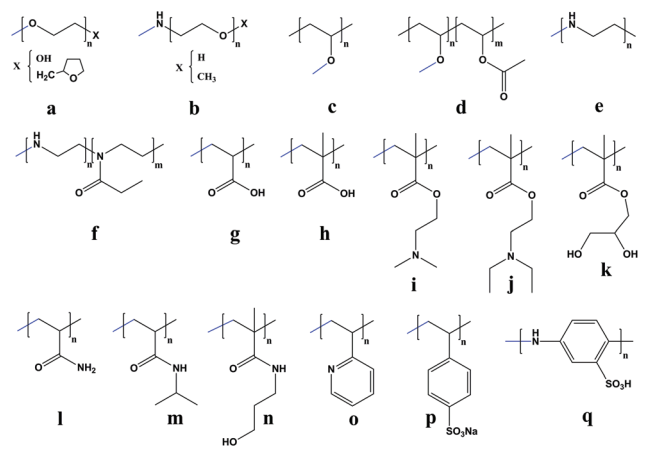

Fig. 3 Macromolecular structure of linear polymers utilized for solubilization of CNTs in water.

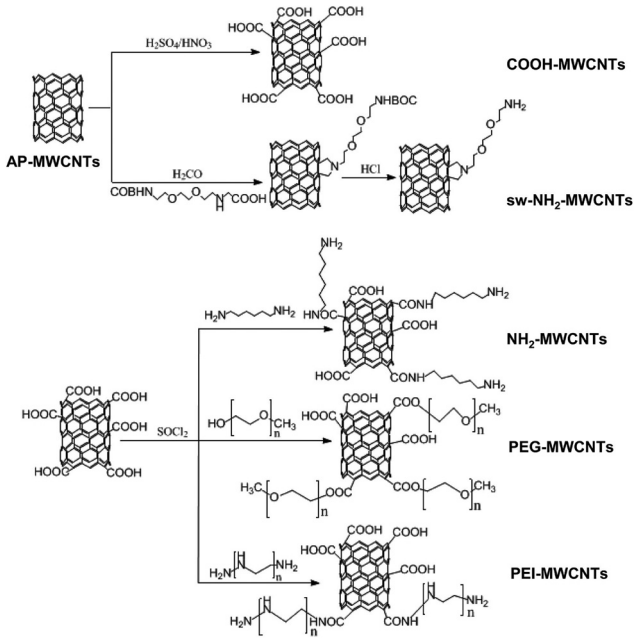

Fig. 4 Functionalization of MWCNTs to obtain surfaces with different charges: MWCNTs with negative surface charges have been prepared by the usual acid treatment while those with a positive surface charge have been synthesized by cycloaddition, or amidation reactions. MWCNTS with a neutral surface charge have been prepared by conjugation of PEG to their functional groups through ester bonds.[145]

and weak cationic functionalization (NH_2-MWCNTs and sw-NH_2-MWCNTs) showed intermediary effects. In contrast, the strongly cationic PEI-functionalized tubes (PEI-MWCNTs) induced robust biological effects. In addition to this research work, there are many other papers in which the relationship between the functionalization of carbon nanotubes and their interactions with the immune system and the risk or benefit of these interactions have been explained.[146,147] Moreover, it has been shown that modification of carbon nanotubes by PEG increases their half-life in the body and there is a direct relationship between the molecular weight of the PEG conjugated to carbon nanotubes and its blood clearance time.[148] Additionally, *in vitro* tests show that the type of post-functionalization has a big effect on the sub-cellular localization of SWCNTs. It has been proved that the conjugation of targeting ligands to SWCNTs modified by PL-PEG could cause their cellular uptake by the type of cells which contain receptors of these ligands.[149]

Partially fluorinated SWCNTs (containing defect sites) have been cut using an H_2O_2–H_2SO_4 solution (Fig. 5). It has been reported that a highly oxidizing medium is able to cut SWCNTs at the defect sites and that carboxylic acid groups are expected to reside at the ends of the tubes. Thus, "cut" tubes can be expected to yield water-soluble SWCNTs by PEGylation through the carboxyl functional groups that are introduced during the cutting process (Fig. 5). The PEGylated cut-SWCNTs showed no indication of flocculation (Fig. 5A–E) after several

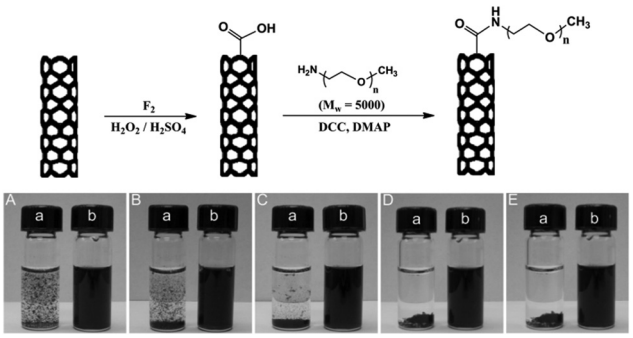

Fig. 5 (above) Schematic representation of synthesis of PEGylated cut-SWCNTs and (below) photographs of (a) pristine SWCNTs and (b) PEGylated cut-SWCNTs in water: (A) immediately after sonication, (B) after 10 min, (C) after 1 h, (D) after 24 h, and (E) after 10 days.[116]

weeks, whereas a solution of purified pristine SWCNTs tends to flocculate a few minutes after sonication.[116]

Using acid treatment, short SWCNTs with different lengths have been prepared and then star PEG copolymers have been conjugated to the carboxylic acid functional groups onto their surface by amidic bonds. *In vitro* studies show that the cellular uptake, intracellular localization, and excretion of SWCNTs and also their partitioning between the daughter cells after cell division strongly depend on their length. Different *in vitro* tests show that targeting ligands do not affect the uptake of functionalized SWCNTs with a 35 nm average length. However for those having an average size around 50 nm, active targeting affects their cellular uptake (Fig. 6).[150]

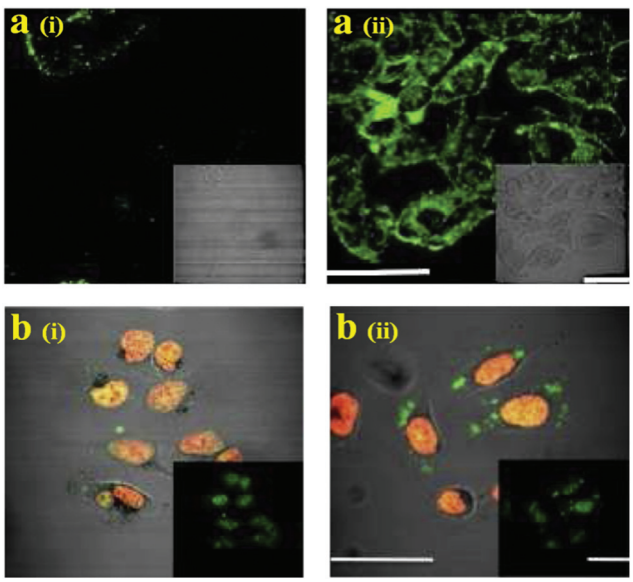

Fig. 6 Confocal fluorescence images of HELA cells after 4 h incubation with SWCNTs with (i) and without (ii) folic acid as the targeting ligand. The average lengths of SWCNTs are (a) 50 and (b) 30 nm respectively. Scale bar is 50 μm.[150]

4.3. Water-soluble hyperbranched and dendritic polymers

In the category of hyperbranched and dendritic polymers, polyglycerol (PG),[151–153] poly(citric acid) (PCA),[154–156] poly(citric acid-*co*-D-sorbitol) (PCAS),[157] poly(propyleneimine) dendrimer (PPI),[158] fourth generation poly(amidoamine) dendrimer (PAMAM, G4)[159,160] and dendron[161] have been attached to the surface of CNTs in order to solubilize them in aqueous solutions. The molecular structures of these hyperbranched and dendritic polymers are shown in Fig. 7. Recently, a review paper has summarized hyperbranched and dendritic polymers (organic-soluble or water-soluble) which are (covalently or non-covalently) attached to the surface of CNTs.[42]

In 2009, new biocompatible and water-soluble hybrid nanomaterials containing MWCNTs as the core and hyperbranched polyglycerol (PG) (Fig. 8) as the shell were successfully synthesized by our group. In this work, pristine MWCNTs were opened and functionalized through treatment with an acid and polyglycerol was covalently grafted onto their surface by the "grafting from" approach based on anionic ring opening polymerization of glycidol monomers. *In vitro* cytotoxicity tests and the hemolysis assay showed no adverse effects on HT1080 cells and red blood cells. Hence, the functionalization of CNTs with hyperbranched polyglycerol decreases their *in vitro* cytotoxicity and makes them promising nanomaterials in nanomedicine.[151]

Polycitric acid functionalized carbon nanotubes have been synthesized and their toxicity has been investigated. Incubation of the functionalized carbon nanotubes with cells even in high concentrations (mg mL^{-1} range) does not show any significant adverse effect on them.[162]

In an attractive study, PAMAM dendrimers (G4) were covalently attached on the surface of MWCNTs. The cytotoxicity to human osteosarcoma MG-63 cells and protein and the DNA immobilization ability of the hybrids were then evaluated in detail. The cytotoxicity results showed that MWCNT-PAMAM hybrids are highly biocompatible especially compared to MWCNT-COOH. Also, fluorescence microscopy images indicate that the functionalization of MWCNTs with PAMAM dendrimers improved the biomolecule-immobilization ability of the hybrids by about 70-fold and simultaneously decreased their cellular toxicity by about 30%. The cytotoxicity of MWCNT-PAMAM hybrids has been evaluated by both an MTT viability assay and morphological observation of MG-63 cells using bright-field optical microscopy. MTT assays showed that only 69% of cells were alive after incubation with 25 μg mL^{-1} of MWCNT-COOH for 24 h, whereas after incubation with 25 μg mL^{-1} of MWCNT-PAMAM hybrid, 89% of the cells were alive. Also, in both cases, a significant dose-dependent decrease in cellular viability was observed. Moreover, microscopic studies confirmed the results of MTT assays and, as shown in Fig. 9(a and b), the morphological studies of MG-63 cells incubated with MWCNT-PAMAM hybrids have shown that these cells lived better than those incubated with MWCNT-COOH. Furthermore the number of MG-63 cells did not obviously decrease until the concentration of MWCNT-PAMAM hybrid become larger than 50 μg mL^{-1}. In addition, at concentration <25 μg mL^{-1}, the MWCNT-PAMAM hybrids were almost nontoxic when they were exposed to MG-63 cells over 24 h, indicating that they could be used as biocompatible carriers for intracellular biomolecule transporting. Besides their good cellular biocompatibility, the ability of MWCNTs to immobilize biomolecules is also critical for intracellular delivery, biosensing, and targeting applications. The authors

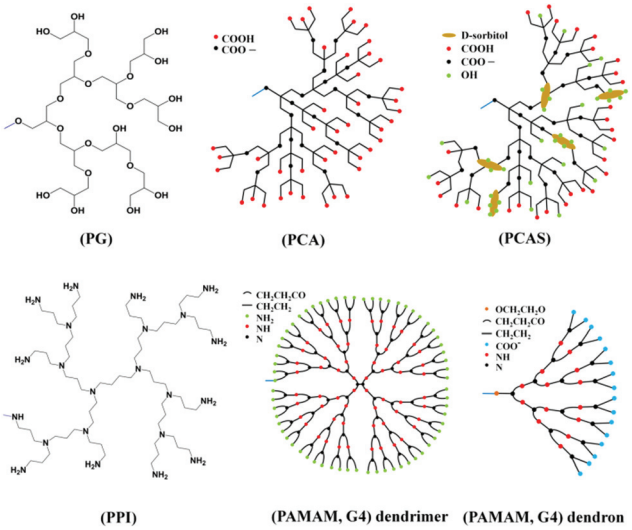

Fig. 7 Macromolecular structure of hyperbranched and dendritic polymers utilized for solubilization of CNTs in water.

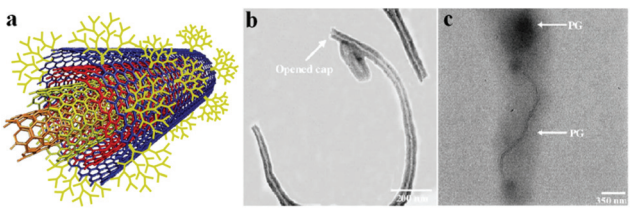

Fig. 8 (a) Schematic representation of MWCNT-g-PG and TEM images of (b) opened MWCNT and (c) MWCNT-g-PG.[151]

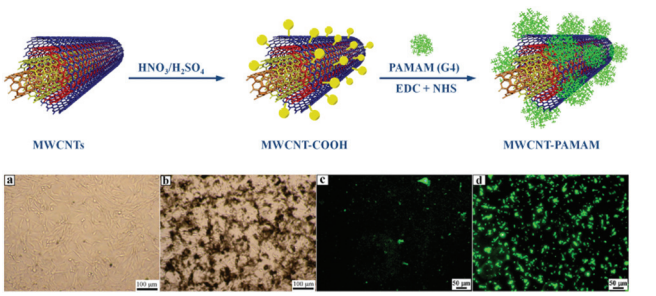

Fig. 9 (Above) Schematic representation of the synthesis of MWCNT-PAMAM hybrids and (below) morphologies of MG-63 cells after incubation for 24 h with 25 μg mL^{-1} of (a) MWCNT-COOH, (b) MWCNT-PAMAM hybrids and the fluorescence images of (c) MWCNT-COOH-BSA-FITC and (d) MWCNT-PAMAM-BSA-FITC.[159]

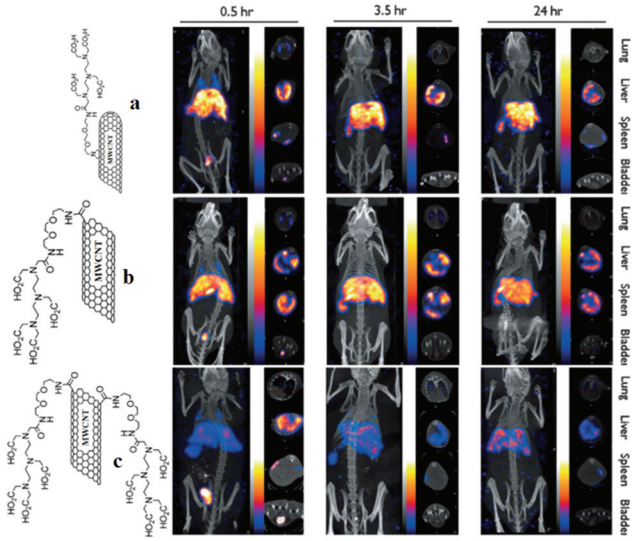

Fig. 10 Nano-SPECT/CT fused images of the whole body of a mouse. Images have been recorded 0.5, 3.5 and 24 h after injection of samples shown on the left side.[163]

probed this capability by using fluorescein isothiocyanate labelled bovine serum albumin (BSA-FITC) as the model. The immobilization of BSA-FITC on MWCNT-COOH and MWCNT-PAMAM hybrids was characterized by fluorescence microscopy. As shown in Fig. 9(c and d), significant fluorescence was observed for MWCNT-PAMAM-BSA-FITC whereas only a little fluorescence was observed for MWCNT-COOH-BSA-FITC.[159]

It has been also found that MWCNT-PAMAM could efficiently deliver the GFP gene into cultured HeLa cells. The surface modification of MWCNTs with PAMAM decreased the cytotoxicity of the hybrid system by about 38%, compared to acid-treated MWCNTs and pure PAMAM dendrimers. The MWCNT-PAMAM hybrid can be considered to be a new carrier for delivering biomolecules into mammalian cells.[160]

The effect of the density of functionalization of carbon nanotubes (0.058, 0.115 and 0.320 mmol of amino groups per gram of nanotube material for compounds **a**, **b** and **c** in Fig. 10, respectively) on their biodistribution has been investigated by conjugation of small dendritic molecules onto their surface. Initiated from a cycloaddition reaction for functionalization of pristine carbon nanotubes and by post-functionalization, different functional groups with different densities are consequently introduced on their surfaces (Fig. 10). A higher density of functionalization leads to reduced RES accumulation and the higher is the urinary excretion (Fig. 10).[163]

4.4. Water-soluble biopolymers

Several bioactive macromolecules have been mostly chemically attached to CNTs *via* classical carbodiimide-activated amidation. Proteins such as bovine serum albumin (BSA),[164,165] immunoglobulin and horse radish peroxidase,[166] human caspase 4 and soybean peroxidase (SBP),[167] GroEL[168] and horse spleen ferritin[164,165] have been linked to CNTs using diimide activation. Also, nucleic acids and amino-terminated DNA strands,[169–172] peptide nucleic acid (PNA, an uncharged DNA analogue)[173] and peptidomimetic molecules[174] have been chemically attached to CNTs.

4.5. Glycoconjugate molecules

In a covalent approach, some sugar derivatives such as glucosamine (**a**),[175] three amino β-D-pyranosyl sugars (**b**, **c**, **d**),[176] a series of dendritic β-D-galactopyranosides and α-D-mannopyranoside (**e**, **f**, **j**, **k**, **l**, **m**),[177,178] poly(lactobionamidoethyl methacrylates) glycopolymers (**g**),[179] poly(3-*O*-methacryloyl-α,β-D-glucopyranose) (**h**), and their hyperbranched glycopolymers synthesized *via* ATRP[180] and biantennary D-GlcNAc-Na^{125}I appended glycoconjugates (**i**)[181] have also been grafted onto the surfaces of CNTs. Structural information for these sugar derivatives can be found in Fig. 11. In the case of polysaccharides, only starch[182] and chitosan[183] have been covalently utilized for water-solubilization of CNTs. Recently, the current research highlights of glycoconjugate-functionalized CNTs for biomedical applications have been comprehensively reviewed.[47]

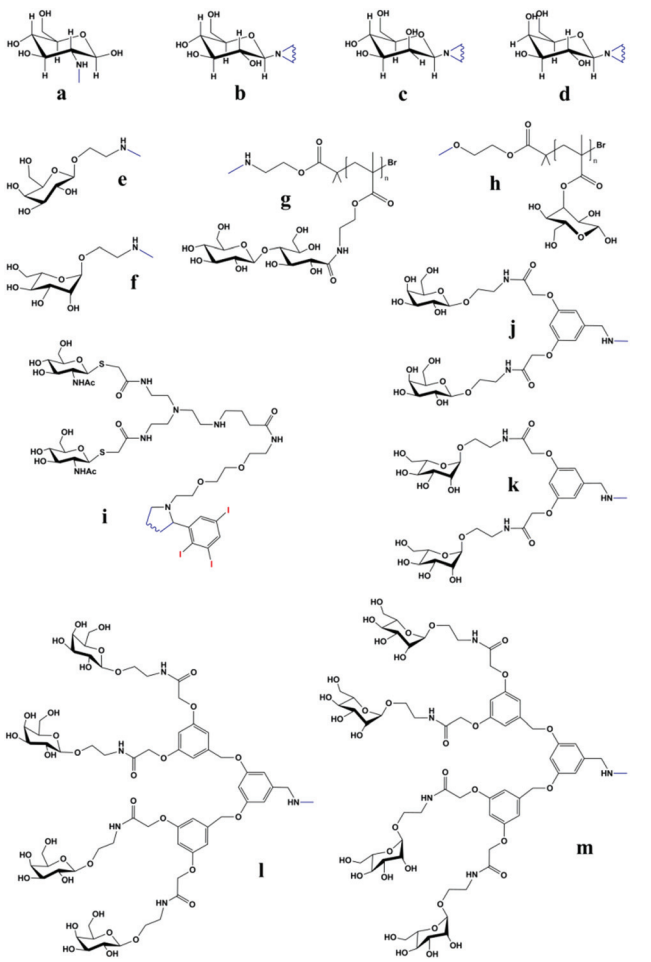

Fig. 11 Structure of sugar derivatives which are attached to the surface of CNTs for water-solubilization.

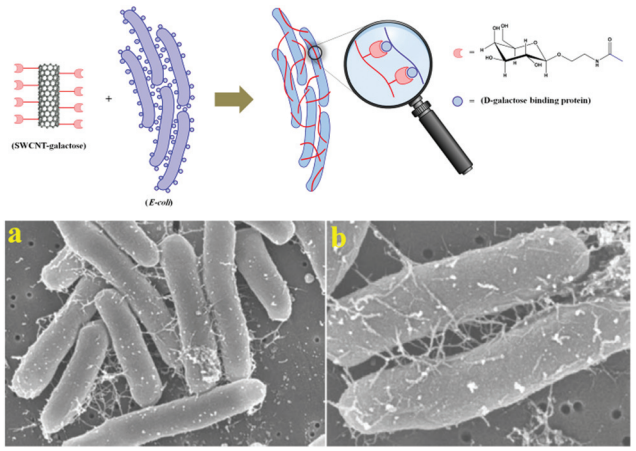

Fig. 12 (above) Schematic depiction of the interaction of glycoconjugate-functionalized SWCNTs with pathogenic *E. coli* receptors and (below) (a, b) SEM images show the binding of glycoconjugate-functionalized SWCNTs to *E. coli* bacteria.[180]

The water-solubility value of CNT-glycoconjugate molecules has been reported. The grafting of glucosamine onto the surface of nanotubes was attained by changing their carboxylic functional groups to acyl chloride and then reaction with this sugar. Subsequently, amide bonds were formed between the glucosamine and the SWCNT. This grafting process results in the solubility of SWCNT in water, ranging from 0.1 to 0.3 mg mL^{-1}, depending on temperature.[177] Also, three amino β-D-pyranosyl sugars have been linked to CNTs through sugar azide functionalization. Water-solubility was found to be highest for galactopyranosyl (1.3 mg mL^{-1}) and lowest for glucopyranosyl and mannopyranosyl (0.6 mg mL^{-1}) derivatives.[178] Towards the goal of developing CNT-based pathogen sensors, Gu *et al.* functionalized the surface of SWCNTs with multivalent carbohydrate ligands to efficiently capture pathogenic *E. coli* cells. The galactose functionalities of the nanotube surfaces not only increased the solubility of the CNTs, but also enhanced the interaction with the receptors on pathogenic bacteria cells (Fig. 12). The results have clearly showed that functionalized CNTs can help identify, immobilize, and concentrate bacterial cells in a solution.[180]

5. Functionalization of carbon nanotubes by biomolecules

Carbon nanotubes have been used as probes to investigate movement mechanisms inside the cells. A single walled carbon nanotube functionalized by DNA strands having counterparts of the C-terminal Halo-tag of kinesin has been conjugated to this motor. Highly stable near-infrared luminescence of single-walled carbon nanotubes allows the investigation of the movement of this molecular motor along the MT embedded in an actin–myosin network.[184] In this study a regime of active random "stirring" that constitutes an intermediate mode of transport has been observed. It has been found that the high-frequency motion is thermally driven and at times greater than 100 milliseconds, with non-equilibrium dynamics dominating. Tracking the molecular motor by fluorescence of the functionalized single-walled carbon nanotube shows that in addition to direct transport along microtubules, there are also strong random dynamics driven by myosins that cause an enhanced nonspecific transport.

Since non-specific interactions between proteins and carbon based nanomaterials are well-known factors which dominate their biological behavior, the competition between proteins in blood to stack onto the single-walled carbon nanotubes has been fully investigated and it has been found that the π–π stacking interactions between the surface of this nanomaterial and the aromatic residues (Trp, Phe, Tyr) of proteins have a critical role in determining their adsorption capacity. A result of this competitive binding of blood proteins onto the surface of SWCNTs is a change in their cellular interaction pathways and diminished cytotoxicity (Fig. 13).[185,186]

Structure-based computational molecular modelling is a powerful tool to understand and to predict the interactions between nanomaterials and nano-biosystems. A comprehensive review with an overview on the reported research studies on this case has been published recently. In this review some

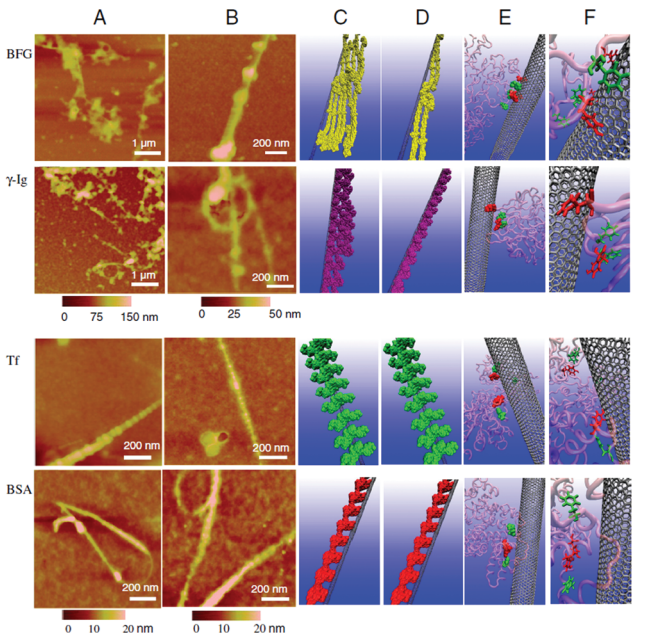

Fig. 13 AFM images of the functionalized SWCNTs by BFG, Ig, Tf, BSA proteins after incubation for 10 min (A) and 5 h (B); molecular modelling of the interactions between the same proteins shown in AFM images and SWCNTs after incubation for 10 min (C) and 5 h (D). The most effective region in the protein structures to interact with the surface of SWCNTs. Residues highlighted in the van der Waals representation corresponding to tyrosine coloured in red and phenylalanine coloured in green and the other parts of proteins are shown by pink colour (E). It has been show that tyrosine (red) and phenylalanine (green) residues interact with the six-membered rings of SWCNTs (silver) shown in silver (F).[185,186]

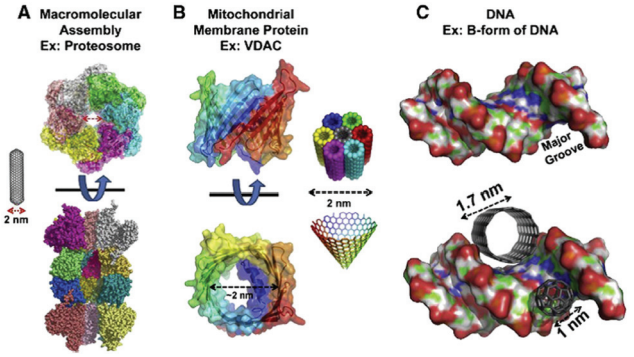

Fig. 14 Simulation studies show that the fitting of carbon based nanomaterials in some regions of biological systems is one of the most important factors affecting their interactions. Cartoon representation of the top view and side sectional views of (A) macromolecular assemblies of proteosomes, (B) mitochondrial outer membrane voltage-dependent anionic channel (VDAC), and (C) DNA show how a similarity in size between loops or channels of biomacromolecules or biosystems and carbon based nanomaterials can cause strong interactions between them.[187]

interesting aspects which are somehow difficult to understand by experimental works are shown and highlighted (Fig. 14).[187]

Recently interactions between two water-soluble proteins, bovine serum albumin (BSA) and egg white lysozyme (LYS) with MWCNTs having carboxyl functional groups on their sidewall, have been investigated. Since hydrophobic blocks and the surface charge of each protein depend on its structure and the main driving forces that stack proteins onto the surface of MWCNTs are hydrophobic and electrostatic interactions, in this case, carboxylate groups play different roles for different proteins. For example they suppressed the adsorption of BSA onto the surface of carboxylated MWCNTs, whereas the adsorption of LYS was enhanced.[188] Moreover, carbon nanotubes functionalized by peptides and biomolecules can also be used as vaccine scaffolds. Reported research work in this case has been reviewed by Scheinberg and co-workers, recently.[189] Also, one of the promising biomedical applications of the functionalized and non-functionalized carbon nanotubes is gene delivery and has also been reviewed.[190]

Usually DNA and RNA are able to stack onto the surface of pristine carbon nanotubes; however, it has been found that functionalization of CNTs with cationic polymers such as PEI or dendrimers causes the attachment of siRNA onto their surface. Moreover it has been proved that CNT–polymer conjugates exhibit a lower cytotoxicity than polymers alone.[191–193]

SWCNTs functionalized by poly(allylamine hydrochloride) with a positive surface charge are able to deliver siRNA and internalize into the pancreatic cancer cells and then release the transferred siRNAs successfully.[194] SWCNTs noncovalently-functionalized by succinated polyethyleimine have been used to deliver siRNA to the target cells *in vitro* and *in vivo*. It has been found that a significant uptake of Cy3-labeled siRNA specific to Braf (siBraf) and gene silencing in the tumour tissue occurred upon the administration of the siRNA attached to the functionalized SWCNTs.[195] Plasma polymerization of suitable monomers onto the surface of carbon nanotubes is a method which has been used to produce carbon nanotubes with reactive functional groups or positive surface charge for a greater modification and delivery of DNA.[196]

6. Bio-applications of the functionalized water-soluble CNTs

As mentioned earlier in the Introduction, there are many papers which have extensively reviewed the applications of CNTs and their derivatives.[47–61,197] In this part, some interesting applications of water-soluble functionalized CNTs in biomedicine, biomedical imaging, drug design and discovery, and cancer therapy will be briefly explained.

Due to their nano-needle structure, CNTs are supposed to cross the plasma membrane and directly enter into the cytoplasm most likely through an endocytosis-independent mechanism and without inducing cell death. CNTs cationically functionalized by PEI have been studied for siRNA delivery. The functionalized CNTs formed a complex with siRNA and showed a 10–30% silencing activity and a cytotoxicity of 10–60%.[128] In another cytotoxicity evaluation study of water-soluble SWCNTs, it has been found that by increasing the degree of sidewall functionalization using isophthalic acid, benzene sulfonic acid, and sodium sulfonate, the samples become less cytotoxic. Furthermore, the sidewall functionalized SWCNT samples were substantially less cytotoxic than the surfactant stabilized SWCNTs. Even though cell death did not exceed 50% for cells dosed with sidewall functionalized SWCNTs, optical and atomic force microscopes have shown a direct contact between cellular membranes and water-dispersible SWCNTs. For example, the SWCNTs in an aqueous suspension precipitate out and selectively deposit on the membrane.[94]

In another study, Davis and co-workers demonstrated that CNTs can be used to deliver a radio probe to specific organs in mice. In this research, first, they filled and sealed CNTs with $Na^{125}I$ and then, attached D-GlcNAc to the surface of CNTs as targeting agents for lung tissue. Next, single photon emission computed tomography (SPECT) was employed for *in vivo* tests of the obtained $Na^{125}I$-filled glycoconjugate-functionalized SWCNTs (D-GlcNAc-$Na^{125}I$@SWCNTs) in mice. It is expected that beyond this particular proof for a principle application of these hybrid nanomaterials, organ specific therapeutics and diagnostics can be developed by functionalizing CNT nanocapsules with the relevant glycoconjugates. As it is obvious from Fig. 15, successful lung targeting (Fig. 15b) *via* the linkage of D-GlcNAc groups onto the surface of CNTs has prevented the leakage of radionuclides to high-affinity organs such as the thyroid and stomach (Fig. 15c). Indeed, nanoencapsulation of ^{125}I within SWCNTs has interestingly created a promising way for changing the biodistribution of ^{125}I from the thyroid to the lungs.[181]

The biodistribution of ^{125}I-labeled MWCNTs which have been functionalized by PEG reveals a short circulation half-life

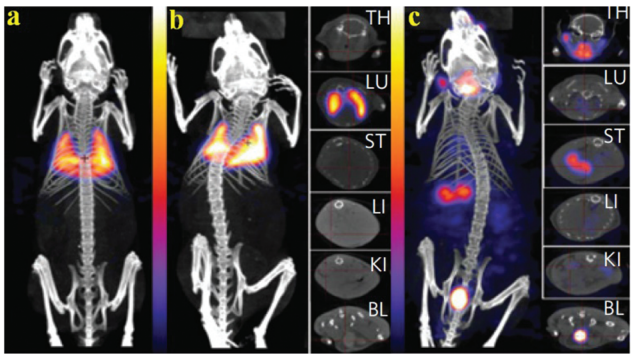

Fig. 15 Whole-animal SPECT/CT imaging, tissue biodistribution, blood circulation, and histology following intravenous administration of filled, functionalized SWCNTs. Whole-body SPECT/CT imaging was carried out immediately after tail-vein injection of (a) 50 μg (0.2 MBq) and (b) 250 μg (1.0 MBq) of the D-GlcNAcNa^{125}I@SWCNTs and (c) Na^{125}I (1.8 MBq) with a scanning time of 40–60 min. Cross-sections of the thyroid (TH), lung (LU), stomach (ST), liver (LI), kidney (KI) and bladder (BL) at equivalent time points are shown.[181]

for CNT-PEG-OH and a fast distribution in most of the organs of the body except the brain. They are sequestrated by the liver after intravenous injection mainly and hepatic accumulation decreases with the passing of time. In this work, the effect of the chain length of PEG on the biodistribution of functionalized MWCNTs has been investigated and a similar result except in the case of hepatic accumulation has been observed.[198]

Dai *et al*. have shown that SWCNTs are useful objects for fluorescence imaging of the brain of living mice in a new near-infrared window. They conjugated an IRDye800 which emits in the 800–900 nm NIR-I window compared to SWCNTs which emit in the 1000–1700 nm NIR-II window. This modification allows the comparison of the efficiency of dyes and SWCNTs under the same conditions and in the same time by using optical filters. It is found that in a depth sample immersion (1 cm), scattering of photons develops in both windows so that fluorescence imaging is not possible. Interestingly in a narrow part of the 1000–1700 nm window even at a 1 cm depth (1300–1400 nm NIR-IIa windows) imaging was successful, due to a lower scattering probably.[199] In another work the same research group has functionalized SWCNTs by phospholipid-PEG functionalization. A half-life blood circulation as long as 30 h is observed for the functionalized SWCNTs. The relationship between blood circulation and cellular uptake on functionalization has been investigated. Also the optimized molecular weight for amphiphilic PEG for which a strong graphitic "G" band can be observed has been reported.[200]

SWCNTs have been functionalized with diethylentriaminepentaacetic (DTPA) as a chelating molecule to obtain a water soluble system which is able to deliver radioisotope indium (^{111}In) for imaging purposes.[88] The synthesized hybrid nanomaterial was injected to the mice intravenously and tracked by using the radioactivity of the system upon gamma scintigraphy. It was found that f-SWCNTs are not retained in any of the reticuloendothelial system organs (liver or spleen) and are

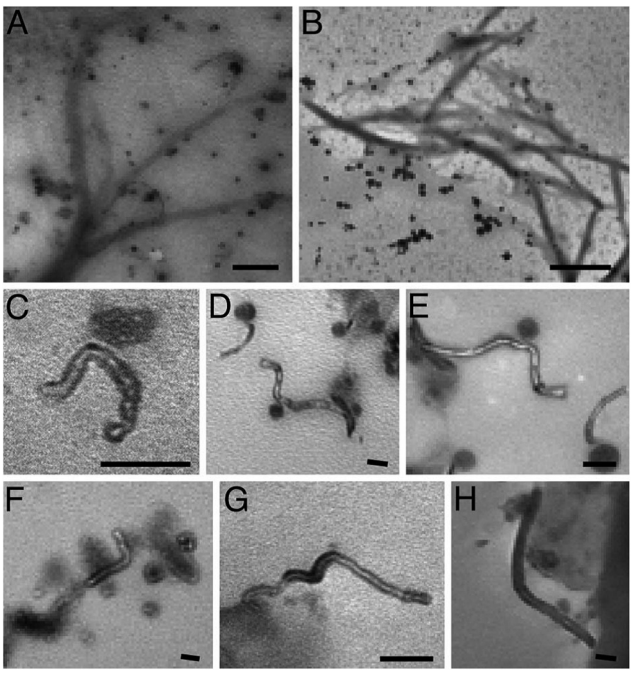

Fig. 16 TEM images of the single- and multi-walled carbon nanotubes exerted and as they exist in the urine of mice. The urine samples were collected and centrifuged and then both the supernatant and precipitations were evaluated and analyzed by TEM. Images (A) and (B) show that DTPA-SWCNTs exist in the supernatant (scale bars, 500 nm). C–E images are TEM images of DTPA-MWCNT in the supernatant and F–H pictures are DTPA-MWCNT in the precipitate (scale bars for C–H, 100 nm).[88]

rapidly cleared from systemic blood circulation through the renal excretion route. It was found that both functionalized SWCNTs and MWCNTs were excreted from the body without any change in their structure (Fig. 16).

Although Pantarotto *et al*. have reported the internalization of fluorescently-labelled nanotubes into cells with no apparently observed cytotoxicity effects without identifying the uptake mechanism,[201] Hussey *et al*. have presented their findings on the uptake of SWCNTs and SWCNT-streptavidin (SA, a protein with clinical applications in anticancer therapies)[202] conjugates into human promyelocytic leukaemia (HL60) cells and human T cells (Jurkat) *via* the endocytosis pathway. For detection of CNT interactions with HL60 cells, confocal microscopy was properly employed. Fig. 17a shows appreciable fluorescence on the surface and, more importantly, in the cell interior due to the interactions of fluorescently labelled nanotubes #2 (0.05 mg mL^{-1} SWCNT) with cells. After discovering that #2 is able to enter cells, Dai *et al*. decided to shuttle proteins into cells. For this purpose, they treated oxidized CNTs (#1) with EDC and biotin-LC-PEO-amine to obtain biotin-functionalized SWCNTs #3. Then, the ability of nanotubes to carry large cargos into cells, in this case SA ($M_w \approx 60$ kD), was evaluated (Fig. 17b).[203]

Moreover, a facile approach for modifying CNTs with multifunctional PAMAM dendrimers (G5) has been reported for cancer cell targeting and imaging. In this approach,

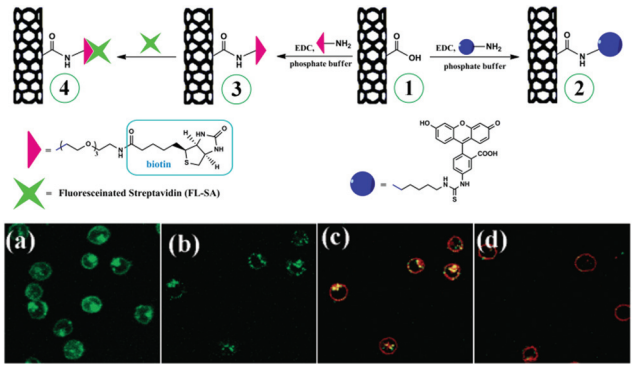

Fig. 17 (Above) Synthesis and scheme of various SWCNT conjugates, and (below) confocal images of cells after incubation with solutions of SWCNT conjugates: (a) after incubation with 2, (b) after incubation with a mixture of 4 (green due to SA) and the red endocytosis marker FM 4-64 at 37 °C (image shows fluorescence in the green region only), (c) same as (b) with additional red fluorescence shown due to FM 4-64 stained endosomes, (d) same as (b) after incubation at 4 °C.[203]

fluorescein isothiocyanate (FITC) and folic acid (FA) modified amine-terminated PAMAM dendrimers (G5, NH_2-FITC-FA) were linked to acid-treated MWCNTs, followed by acetylation of the remaining primary amine groups of the dendrimers. The resulting MWCNT/G5·NHAc-FITC-FA hybrid nanomaterials were water-dispersible, stable, and biocompatible. *In vitro* flow cytometry and confocal microscopy data have shown that the formed MWCNT/G5·NHAc-FITC-FA hybrid nanomaterials can specifically target cancer cells over-expressing high-affinity folic acid receptors. The results of this study suggest that, through modification with multifunctional dendrimers, complex CNT-based materials can be fabricated, thereby providing many possibilities for various applications in biomedical sensing, diagnosis, and therapeutics. The conjugation of the FITC-modified G5 dendrimers onto MWCNTs also enables confocal microscopic imaging of the cellular uptake of the functionalized MWCNTs. Fig. 18 shows that only KB-HFAR cells treated with MWCNT/G5·NHAc-FITC-FA display prominent fluorescence signals, which is associated with a specific uptake of MWCNT/G5·NHAc-FITC-FA into the cytoplasm and also onto the membrane of the cells (Fig. 18c and f). In contrast, the same KB cells treated with MWCNT/G5·NHAc-FITC do not show any salient fluorescence signals (Fig. 18b and e), which is similar to KB cells treated with PBS buffer (Fig. 18a and d). The weak fluorescence signals in both Fig. 18(a and b) originate from the intrinsic green fluorescence of the cells. These results suggest that binding and intracellular uptake do not occur significantly in the cells treated with non-FA modified MWCNTs.[204]

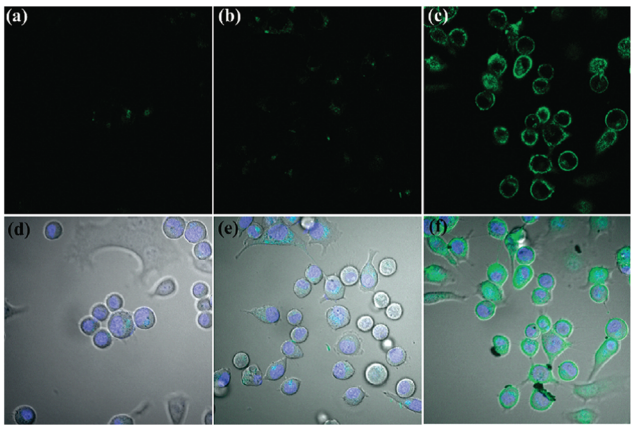

Fig. 18 Confocal microscopic images of KB-HFAR cells treated with (a, d) PBS buffer, (b, e) MWCNT/G5·NHAc-FITC (10 μg mL^{-1}) and (c, f) MWCNT/G5·NHAc-FITC-FA (10 μg mL^{-1}) for 2 h. Images were collected under similar instrumental conditions.[204]

Multidrug resistance (MDR), which could be correlated with cancer chemotherapy, tumour stem cells, and tumour metastasis, is a huge obstacle for effective cancer therapy. One of the underlying mechanisms of MDR is the increased efflux of anticancer drugs by over-expressed P-glycoprotein (P-gp) of multidrug resistant cells. In a recent work, antibodies of P-gp functionalized water-soluble SWCNTs (Ap-SWCNTs) have been synthesized *via* the biocompatible diimide-activated amidation reaction between the antibodies and the water-soluble oxidized SWCNTs, later loaded with doxorubicin (DOX) to challenge the MDR of K562 human leukaemia cells. The resulting Ap-SWCNTs could not only specifically recognize the multidrug resistant human leukaemia cells (K562R), but could also demonstrate an effective loading and controllable release performance for DOX toward the target K562R cells by exposure to near-infrared radiation. The binding affinity of Ap-SWCNTs toward drug-resistant K562R cells was 23-fold higher than toward drug-sensitive K562S cells. In addition, confocal laser scanning microscopy indicated that Ap-SWCNTs could specifically localize on the cell membrane of K562R cells and the fluorescence of DOX in K562R cells could be significantly enhanced after the employment of Ap-SWCNTs as carriers. Moreover, the composite of DOX and Ap-SWCNTs (DOX/Ap-SWCNTs) expressed 2.4-fold higher cytotoxicity and showed a significant cell proliferation suppression toward K562R leukaemia cells ($p < 0.05$) as compared with free DOX which is popularly employed in clinic trials. These results suggest that Ap-SWCNTs are promising drug delivery vehicles for overcoming the MDR induced by the over-expression of P-gp on the cell membrane. Ap-SWCNTs loaded with drug molecules can be used to suppress the proliferation of multidrug resistant cells, destroy tumour stem cells, and inhibit the metastasis of tumours.[106]

Recently, we increased the cytotoxicity of paclitaxel against SKOV3 ovary cancer cells and A549 lung cancer cells using a novel functionalized CNT-g-PCA hybrid nanomaterial. In this study, MWCNT-g-PCA was synthesized and utilized as a carrier for the anticancer drug paclitaxel. Interestingly, during the functionalization of MWCNTs with PCA, the conformation of the nanotubes changed from linear to a circular type. The release of paclitaxel from the MWCNT-g-PCA-PTX conjugates at an acidic pH was higher than at a neutral pH, which was suitable for the release of the drug in tumour tissues and tumour cells. The results of cytotoxicity assays demonstrated

that MWCNT-g-PCA-PTX shows a higher cytotoxic effect compared with unconjugated paclitaxel, which can be attributed to increased cell penetration.[156]

Water-soluble chemically-functionalized CNTs are also able to interact with mammalian cells and lead to their cytoplasmic translocation. Kostarelos *et al*. have synthesized seven types of covalently-functionalized water-soluble CNTs that exhibit a capacity to be taken up by a wide range of cells and can intracellularly traffic through different cellular barriers. In this study, the intracellular trafficking of individual or small bundles of functionalized CNTs (f-CNTs) occurred, and the transportation of nanotubes towards the perinuclear region was observed a few hours following the initial contact with the cells, even under endocytosis-inhibiting conditions. Other mechanisms (such as phagocytosis), depending on cell type, size of nanotube, extent of bundling, may also contribute to or be triggered by the ability of f-CNTs to penetrate the plasma membrane, and therefore can be directly involved in the intracellular trafficking of f-CNTs. Overall, it can be concluded that f-CNTs possess a capacity to be taken up by mammalian and prokaryotic cells and to intracellularly traffic through different cellular barriers by energy-independent mechanisms. The cylindrical shape and high aspect ratio of f-CNTs can allow their penetration through the plasma membrane, similar to a nanosyringe, as has been experimentally reported and theoretically simulated.[205]

In an another application of the functionalized water-soluble CNTs, common gram (*Cicer arietinum*) plants were treated with up to 6 mg L^{-1} of water-soluble CNTs produced by HNO_3 oxidation. The results show that the plant had an enhanced growth rate in every part including the roots, shoots and also in branching. It also indicates that unlike CNTs, water-soluble CNTs (wsCNT) are non-toxic to plant cells that conserve water transport in plants. For comparing the growth in the different parts of the plants, shoot length, branching, number of roots and their length, water uptake *etc*. were measured with or without wsCNT, using three different sets of 10 vials each (Fig. 19). In the first set, seeds were grown without wsCNT, *i.e.* only grown in double distilled water (5 mL of water); in the second set 100 mL wsCNT from the stock solution was used and double distilled water was added to make it 5 mL; in the third set 200 mL of wsCNT from the stock solution was reduced to 5 mL using double distilled water. For comparison the root length, shoot length, number of roots and water uptake by gram plants were monitored for 10 days (Fig. 19a and b). The presence of intracellular wsCNT inside the plants was verified *via* an examination of TS (transverse section) and LS (lateral section) of plants treated with and without wsCNT through optical microscopy. An effect was observed; wsCNTs, which were initially in the form of cluster aggregates like spaghetti, became aligned in the vascular bundle due to an endo-osmotic root pressure caused by xylem. These vascular bundles run all through the plant and consist of xylem and phloem. The presence of wsCNT in the plant root (especially in the xylem) can be detected by optical microscopy (Fig. 19b and d).[206]

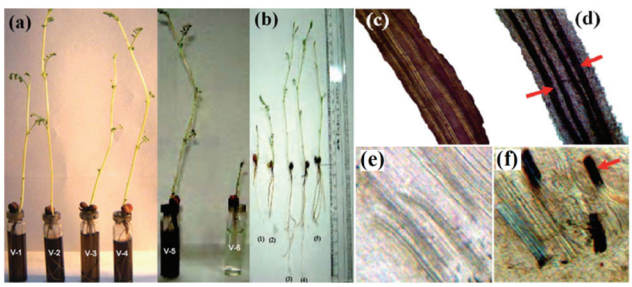

Fig. 19 Phenotypes of gram plants after 10 days, (a) gram plants grown (v-1 to v-5) with wsCNT, in comparison with blank (without wsCNT, v-6) (b) phenotypes of gram plants after 10 days marked with (b-1, b-2) grown without wsCNT and (b-3, b-4) under 200 mL and (b-5) under 100 mL of wsCNT. (c, e) Optical images of LS and TS of blank root; (d, f) LS and TS with wsCNT (red arrows mark wsCNT).[206]

7. Conclusion

Since the solubility of CNTs has been greatly improved through functionalization by water-soluble molecules/macromolecules *via* both covalent and noncovalent approaches, more research interest has recently been focused on the synthesis of novel water-soluble CNT nano-conjugates. As a developing and very promising category of hybrid nanomaterials, polymer-functionalized water-soluble CNTs have become one of the families of CNT-based materials with extraordinary properties by combining the advantages of water-soluble molecules/macromolecules and CNTs. In this review we have summarized the most significant and recent advances in the synthesis of polymer-grafted water-soluble CNTs and their interesting bio-applications in biomedicine, biomedical imaging, drug design and discovery, and cancer therapy. It is expected that this review will comprehensively explain the development in this area and facilitate its further progress.

Acknowledgements

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