Carbon nanotubes assisted analytical detection – Sensing/delivery cues for environmental and biomedical monitoring

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Abstract

The architecture of carbon nanotubes (CNTs) demonstrate phenomenal electronic, mechanical, biological and thermal attributes for highly requisite real-time applications. For instance, electronic and biological features of CNTs are surprisingly striking to engineer robust sensing and/or delivery cues for environmental, analytical diagnostics, and biomedical settings. With CNTs enforcement, several types of pristine and hybrid nanomaterials have been fabricated, though using different support carriers and synthetic or biological materials and used as sensory items or exploited as drug delivery systems (DDSs). Regardless of intensive research and applied potentialities of CNTs, several concerns, such as biodegradability, biotoxicity, and biosafety remains challenging and should be dealt with care prior to design and fabrication. This is mainly because of the lacking standardized protocols and ramification of pristine CNTs or CNTs-based hybrid nano-constructs on the ecosystem and human body are not well-established. For the futuristic use of these remarkable materials in the environmental, analytical diagnostics, and biomedical settings, their biological attributes and multifunctional characteristics must be elucidated with state-of-the-art. Herein, we reviewed CNTs-assisted analytical

detection potentialities at large, and sensing/delivery potentialities of CNTs-based cues, in particular for environmental and biomedical monitoring. Several examples are given with particular emphasis to biosensors, DDSs, and implantations of CNTs-based cues to recognize viruses, cancerous cells, glucose, DNA, volatile organic compounds (VOCs) and various inorganic gases. The review is wrapped-up with concluding notes and brief outlook over the futuristic developments to further insight the CNTs-based robust cues and their perspectives for commercialization.

Key words: Carbon nanotubes; Nano-cues; Biosensors; Biomolecules; Drug release carriers; Analytical detection; Environmental and biomedical settings

Introduction

In the past few years, the fabrication of robust nano-structured material, so-called “smart biomaterials”, as sensing cues has gained great attention in various disciplines of science, as a booming field of contemporary research. For example, photoactive materials play important roles in the biosensing systems as transducer converting chemical information into detectable PEC signal. Photoactive material performs perform a leading role plays in biosensing of PEC signals through photoelectric conversion. High conversion efficiency and improved biocompatibility of photoactive materials contribute towards to high-performance PEC biosensors [1]. Vidya and Prabhat 2020, reported a fluorescence detection system for Adenosine tri-phosphate (ATP) based on the principle of dissociation of Thioflavin-T-sulphated-β-cyclodextrin assembly dissociation by Zn2+ followed by reassociation. Such smart biomaterials based sensors provide a reliable, sensitive, and highly selective approach for ATP [2]. Among nano-structured material, carbon nanotubes (CNTs) based sensing cues for analytical detection purposes are of supreme interest [3,4]. Owing to the unique structural, functional, electronic and optical attributes of CNTs, there has been a significant number of applications from the environmental and biomedical monitoring perspective, which this review aims to cover to advance the existing literature with recent trends in this particular field of interest.

CNTs, particularly single-walled carbon nanotube (SWCNTs) and/or multiwall carbon nanotubes (MWCNTs), grasp noticeable position for cutting-edge applications in the

environment, and biomedicine [5-7]. Nevertheless, prior to such advance applications, the engineered cues must be subjected to rigorous quality controls to avoid system failure. However, much sadly, there are no commonly accepted standard regulations to maintain the quality assurance amongst the commercial suppliers of CNTs. In this context, the CNTs and CNTs-based constructs, as an analytical target, are a subject of immeasurable interest [8-10]. Furthermore, tuning the CNTs-based nano-structured cues facilitate the bio-sensing applications is of crucial importance.

Herein, we comprehensively reviewed and discussed the applicability of numerous CNTs-based sensing/delivery cues with suitable examples. It is worth mentioning that CNTs are supreme candidates to engineer fascinating diagnostic/analytical devices/tools, for two reasons, i.e., (1) CNTs exhibit unique structural, functional, electronic and optical attributes that make them highly suitable to use for analytical detection, and (2) CNTs open-up innovative tactics to fully integrate and provide extraordinary potentials for further miniaturization. Following a brief introduction, we reviewed the recent advances in developing CNTs assisted biosensors, drug delivery systems (DDSs), and their suitable implantations to recognize viruses, cancerous cells, glucose, DNA, drug release carriers, volatile organic compounds and various inorganic gases.

CNT-based biological sensors

Detection of biological molecules and health monitoring are vital in the area of healthcare ranging from identification to immediate monitoring of the patient's condition. This claim the reduction of medical costs and mortality globally. For example, it provides early perceptions of a number of infections which in turn facilitate apposite preventative measures and treatment. Presently, expensive equipments and dedicated laboratories are required for a complete medical testing protocol. This necessitates the development of an efficient approach to deal with the problem. In a study a group of researchers devised a latest NaYF4:Yb,Tm@ ZnO-based biosensor for the detection of CEA linked with a 3D printed device, which was applied in an equipment used for the detection of cancer biomarker. NaYF4:Yb,Tm@ZnO-based PEC biosensor was used for highly selective sensing of CEA with the detection limit of 0.032 ng mL-1 [11]. Similarly,

Zhenzhong et al. (2018) introduced a digitalized paper electrode-based sensor associated with multiwalled carbon nanotube, for the detection of carcinoembryonic antigen (CEA). The efficiency of sensor toward targeted CEA was observed in the range of 0.5-60 ng/mL with 167 ng/mL as a limit of detection under optimal conditions [12]. A near-IR activated-based non-enzymatic PEC sensor was designed by Zhongbin et al. (2019) [13] for the detection of α-fetoprotein (AFP) within a dynamic linear range of 10 μg mL-1 to 50 μg with1.2 μg mL-1 as a limit of detection accompanied decreasing photocurrent with the rise in AFP concentration. Herein, the CNTs based sensors dealing with the biological molecules are presented for the benefit of researchers working in the field of biomolecular sensors [14,15].

CNTs and volatile organic compounds (VOCs)

Biological volatile organic compounds are not only product and sub product of the cell metabolism/stress triggered by reactive oxidative species (ROS) [16-18]. They are categorized on the basis of their functionalities: aliphatic and aromatic hydrocarbons, aldehydes, ketones, nitriles, alcohols and esters [18]. VOCs concentration varies in breath and in body excreted fluids with the change in diet, environmental contact, and diseased state of body [19]. Typically, VOCs started by the cellular activity in human body include aldehydes, hydrocarbons, and ketones [15]. VOCs higher concentration can find in normal breath samples; sensor arrays are constructed to differentiate among chemical species. Arrays of sensors can build “fingerprints” for a class or provided compound. Haick and coworkers demonstrated the first CNT-based detection of VOCs with an objective to differentiate between the humanly subjects of cancer of lungs and renal failure [20]. They designed semiconducting SWCNTs based sensing arrays having coating of organic materials then, examined their operation to differentiate between healthy breathing and breath of diseased subjects, Figure 1 [21]. The obtained signals’ PCA demonstrated the difference between healthy and cancerous breath, was merged due to the effect from humidity, for an effective discrimination was reduced on the relative humidity from 80% to below 10% [21]. Later in their study, chemiresistors were replaced with FET devices having minimal effects from humidity [20]. Recently, they further reported functionalized SWCNTs arrays together with modified gold NPs on molecular

basis to identify seventeen different disease conditions with 86 % accuracy from 1404 subjects [22]. Different groups worked on CNT-based sensing arrays to differentiate between different VOCs. They further fabricated PCA plots from chemiresistors signals containing SWCNTs and 8-metalloporphyrins to make difference among different types of VOCs, such as (a) hydrocarbons, (b) aromatic hydrocarbons, (c) ketones, (d) amines and (e) alcohols. They differentiated amines from other VOCs by using charge-transfer competence and considerable differentiation among the rest 4 types based their swelling effect and intermolecular interaction [23]. Shirsat et al. reported hybrids of SWCNTs and metalloporphyrins to distinguish methanol, ethanol, acetone, and methyl ethyl ketone [24]. The responses of sensory arrays are dependent on the surfactant-analyte interactions and assembly with MWCNTs [25]. Every sensor discriminates up to a limit; however, e, g PCA established separation between water, toluene, ethanol, methanol, acetone, and chloroform [25]. Selective sensing arrays are successfully produced by noncovalent functionalization; they are unable to produce significant sensing strength toward the severe conditions. Sarkar et al. covalently linked poly(tetraphenylporphyrin) on SWCNTs for the detection of acetone, and the sensing stability exceeds over 180 days period [26]. Wang and Swager used cross-sensitive recognition groups for the functionalization of MWCNTs following two steps synthesis procedure Figure 2 [27]. Each selector is used to amplify the targeted analyte interactions. Allyl- and Propargyl-MWCNTs are polar, hydrogen-bond acceptors and favorable to strongly interact with large dipoles vapors. Long alkyl chains (3 and 4) selectors with favorable dispersive interactions designed to sense aliphatic compounds. Calix(4)arenes [28] used to adsorb the vapors of chlorinated and aromatic hydrocarbons because of highly polarized pocket; however, crown ether [29] offered basicity due to H-bonding interactions with alcohols and acids. Therefore, the sensing arrays classified the tested VOCs into 5 different categories without having the humidity interference. Furthermore, the responses distinct patterns, when subjected to LDA precisely recognized all twenty VOCs. Furthermore, the chosen selectors differentiated chemical spaces in an adequate way. Therefore, the precise chemical designs, instead of randomly collected selectors, are ideal at precise characterization of VOCs complex. Sensory arrays are advantageous by covering multiple units is the “fingerprints” library what can be easily modernized for new class analyte detection. One

targeted biomarker is sufficient proof for the presence of a disease; hence the single analyte detection could be a strong diagnostic tool [30]. Therefore, sensory arrays will beneficial when applied in parallel with sensors for single analyte detection. Wang et al. designed CNTs with vertical alignment having conductive coating of polymer to observe n-pentane with 50 ppm of LOD and appreciable precision over chemicals like methanol and toluene [31]. Poly(3,4-ethylenedioxythiophene) (PEDOT) used as coating material for vertically aligned CNTs through chemical vapor oxidative deposition subsequently nonconducting polystyrene (PS) coating. Pentane adsorption on PEDOT surface interrupts the pathways' conductivity, and selectivity is observed by PS layer what eliminates VOCs with certain polarity [31]. Calix(4)arenes have an interacting potential with aromatic hydrocarbons. Figure 3 shows quartz crystal microbalance (QCM) analysis and NMR binding analysis, the authors confirmed the selectivity resulted from the advantageous p-xylene binding inside the cavity of calixarene over 2 other isomers [32]. Ding et al. designed chemFET sensors using SWCNTs/TiO_2 composites that showed response at 400 ppb to acetone vapor. The suggested sensory mechanism depends on the electron/hole pairs generation in TiO_2 layer through UV photoinduction and acetone adsorption that prevents significant conductance drop [33]. This sensor used for the detection of acetone up to 20 ppm in humidity and O_2 despite disturbances caused by water vapor and air. Yoon et al. have incorporated soft Lewis acid Pd^{2+} cations enfolded around SWCNTs. Wherein, selective sensor was produced by the coordination of PdCl2 with P4VP-wrapped SWCNTs toward thioethers vapors [34].

Harnessing the power of CNTs for glucose detection

The detection of glucose level in blood is a commonly used medical test. This concentration indicates how to manage diabetes, resulting an increase in the glucose sensors demand. Both chemFET and electrochemical sensors are being used with selector such as glucose oxidase (GOx). The reduction potential in H_2O_2 production and transfer of electron from GOx to CNT electrodes beneficial for electrochemical sensing by composites of GOx/CNT [35]. However, the enzymatic adsorption onto CNT electrodes reported several problems, such as denaturation and enzyme leaching (Balasubramanian et al. 2006). For this purpose, metal and metal oxide are used to solve this problem.

Suitable examples were mentioned for MWCNTs by Wang et al. (2009) [32] coated with ZnO NPs and by Chen et al. (2012) [36] coated with Pt−Pd bimetallic NPs. A polymeric layer was applied to remove commonly used interferents. Different groups reported adsorption of GOx on CNTs using electropolymerization of conductive polymers. Herein, GOx is combined with a monomer and then electropolymerization at CNT electrode. Gao et al. reported a large range of 2.5− 20 mM and resulted that the aligned Fe particles and MWCNTs were crucial to lower down H_2O_2 oxidation potential, in this way veroxidation of PPy can be prevented. Firstly, SWCNTs were attached to the gold electrodes surface with a mixed single layer of cystamine and thioethanol together with EDC. On the other hand, nonenzymatic CNT glucose sensors mainly dependent on the characteristics of metal-based NPs coated on CNTs to build glucose response electrochemically. Lin et al. applied copper and nickel NP-coated MWCNTs to show an activity toward the oxidation of glucose [37], while Gougis et al. deposited AU nanoparticles onto CNT electrodes [38]. Currently, Baghayeri et al. described the electrodeposition of silver nanoparticles onto MWCNTs functionalized with metformin, used as selective glucose electrochemical sensors, Figure 4 [39]. Those sensors showed a minimal detection limit at 0.3 nM without interference from biological entities found inside blood serum and urine samples. Lerner et al. detected glucose by means of complexes formed by boronic acid moieties, Figure 5 [40].

Harnessing the power of CNTs for DNA detection

DNA detection has prime importance toward analysis of genetic disorders, detection of pathogens, anticipation biowarfare agents, and drug discovery [35]. Sensors comprising optical, piezoelectric, and electrochemical transductions occur due to the selective base-pair interactions within the strands of DNA [41]. CNT-based DNA sensors were initially studied because of high selectively, precision, and reproducibility. In these sensors, a single-stranded DNA (ssDNA) was immobilized on the electrode and electrical current changes were activated due to complementary sequence hybridization [42]. Several researchers stated that chemFETs can be used to sense resistance change of CNT or groups of CNTs in DNA presence. To monitor FET transfer properties of pristine SWCNTs upon the addition of ssDNA oligonucleotides. Subsequently, DNA hybridization with

selected DNA caused the reduced conductance at the voltage of gate. Such scheme successfully differentiated between mutant and HFE gene alleles (wild-type), resulted in the hereditary hemochromatosis. In this way, the sensitivity can be improved of FET-based devices for the detection of DNA complementary strands [43]. Upon the addition of intercalator, the hybridized sensors having DNA presented noticeably reduced conductivity than those of the samples with incompatible DNA. Dong et al. introduced the usage of Au NPs, functionalized with DNA, to improve FET sensors having the LOF of 100 fM, Figure 6 [44]. Herein, every targeted DNA bind to the Au NPs functionalized with DNA wherein SWCNT with immobilized DNA. Remarkably, the authors have described that Ta electrodes-based devices possessed larger enhancement than those of the AU electrode-based devices. The selectivity promoted through the DNA−CNT composites-based sensors is emphasized through the base-pair mismatches detection ability. The charge transfer can transpire through the aromatic DNA base-pairs over significant distances, it has a prime level of sensitivity toward the base pairing integrity. The authors reported an original conductivity measurements of single DNA duplex supported through covalent bonds between a single SWCNT, Figure 7a [45]. They cut individual SWCNTs through an electron beam to fabricate the devices and then ensured the carboxylic acid functional groups presence on the gap both sides through oxygen plasma. The gaps were connected by ssDNA anchored through amide linkages at both ends. This device clearly observed the conductivity difference between duplexes. Figure 7b displays that a single mismatch (both CA and GT) causes current reduction through the strand of DNA. Weizmann et al. demonstrated the ssDNA-bridged CNTs networks for complementary DNA chemiresistive detection, Figure 8 [46]. The ssDNA gaps furnished the insulation of materials. Double-stranded DNA assemblies were formed through the selective binding of ssDNA analyte; however, extended sequence of DNA transport cannot provide enough sensing conductivity.

Detection of substance in humane body

Numerous studies have applied biosensors of different types to detect various substances such as drugs (acetaminophen), H_2O_2, neurotransmitters (dopamine), urea and glucose, among others. The material constituent's modification for every biosensor and

functionalized CNTs are observed to enhance the response and device properties. Bioanalytical studies are mainly based on the conductive polymers, to their charge carry ability, sensitivity, and biocompatibility up to negligible perturbations. The CNTs fabrication in electrodes prepared through conductive polymers constructs p-p hydrophobic and electronic interactions with the aromatic compounds. Microorganisms having multiple enzymes are involved in biosensing of conductive polymers. Enzymes may be simply applied in numerous substrates under particular conditions of culture. However, a minimal distance between microbial cells and transducer is recommended for efficient biochemical signals what may be attained through immobilization of surface cells of transducer [47]. Paracetamol is widely used for the pain relief, an analgesic and antipyretic drug., it is essential to know about its mechanistic toxicity. The paracetamol can be sensed using different techniques: liquid chromatography; electrospectrophotometry. The electrochemical methods have the following characteristics including fast response, low cost, high sensitivity, simple instrumentation, and low required power. The electrochemical methods have been applied to analyze the electroactive compounds [47]. Bayram and Akyilmaz (2016) [47] designed *Bacillus* species based microbial biosensor to determine the sensitivity of paracetamol. This biosensor comprised of MWCNTs modified gold electrode, glutaraldehyde crosslinking agent and polyaniline (PANI). They introduced a microbial system used for the quantitative detection of paracetamol. Additionally, the connections between PANI and MWCNTs offer improved stability and biosensor responses' conductivity. Dopamine as neurotransmitter is accountable for transmitting motor, cognitive, and behavioral functions. Parkinson's disease is sensed by the neurotransmitter disorder. The dopamine detection is a big challenge because of its lower concentration than those of uric and ascorbic acids.56 The biosensors selectivity can be improved to modify the electrode materials through platinum, glassy carbon or gold with CNTs. Palomäki et al. (2018) [48] applied films of tetrahedral amorphous carbon (ta-C) to detect dopamine with uric and ascorbic acids at physiological concentrations. Comparing electroanalytical performance and biocompatibility, MWCNTs were grown by CVD on top of ta-Cy. Such direct growth of MWCNTs on ta-C surface ensures reproducibility and appropriate mechanical strength. They determined that the detection limits did not improve by the modification of ta-C films

with MWCNTs but provided the selectivity for dopamine detection and dopamine interferents, ascorbic and auric acids, simultaneously, at physiologically concentrations. Considering the electroanalytical behavior, ta-C and ta-C+ MWCNTs have great tendency to use for the in vivo sensing. The CNTs proportion of length/diameter offers high proportion of surface/volume and promote their rapid electron transfer ability. Chen et al. applied BCNTs to produce an amperometric enzymatic sensor. A poly(o-aminophenol) film (POAP), was used for the electrode protection from contaminating in H_2O_2, AU, glucose biosensors, was used to immobilize GOD. Thus, the glucose biosensor performance dependent on the glassy carbon electrode, examined in detail, high precision, short response time, low LOD, and good stability were found. Thus, BCNTs have potential applications in amperometric biosensors [49]. Enzymes specific catalytic activity for certain analytes together with their viable accessibility proves them desirable for the biosensors' fabrication. However, the leading challenge is the enzymes stability on transducers' surface as the enzyme's contamination directed toward the poor analytical performance. The enzymatic biosensors production may involve different treatments for immobilization [50]. H_2O_2 is widely applicable for pathogen elimination, cell signaling, disinfection, bleaching and control of odors. H_2O_2 concentration monitoring is practiced observing the enzymatic reactions progress. The biomolecules and transition metal complexes such as myoglobin, hemoglobin (HB), and Prussian blue are used to develop the H_2O_2 sensors. HB is an economical and stable protein molecule what can interact with oxygen, H_2O_2, and carbon dioxide in the biocatalyst. PANI/polysaccharide composites are the potential applicants for numerous applications, and natural polysaccharide (starch) are abundantly available, used for manufacturing of biocompatible materials. The urea evaluation can be made using techniques such as chromatographic, spectrophotometric, calorimetric, electrochemical and fluorimetry techniques. However, electrochemical technique, have advantages of lower cost, high selectivity and sensitivity of analyte detection and less operating time. The urease application coupled with MWCNTs-PAMAM was utilized to determine the urea level in human body. The optimized pH, operating potential, temperature, and storage characteristics decide the analytical performance of the G5 electrode. It is resulted the G5 of MWCNTs-PAMAM demonstrated a considerably improved performance of

biosensor compared to PAMAM of other generations, associated with the enzyme immobilization efficiency. Additionally, the urea biosensor showed high sensitivity, shorter response time, low detection limit, high sensitivity, stability, and reproducibility. This biosensor can be used to quantify human blood urea different samples [51].

Harnessing the power of CNTs for virus's detection

Viruses are non-cellular infectious agents. Viruses promote different diseases in human body and in animals. Thus, virus's detection efficiency has an extreme importance and alternatives are searched in this regard. For this purpose, CNTs are being increasingly employed, because of electrical properties and high surface area [14]. Earlier, several detection studies were applied, for example, in the detection of dengue [52-55]. Dengue is a viral disease which is primarily spread by mosquitoes, Wasik et al. (2017) [52] have reported heparin functionalized SWCNTs functionalized to design electronic chemiresistive biosensor. The authors introduced functionalization of SWCNTs with 1-pyrenemethylamine through non-covalent modification. Three different constituents of ethyl-3-dimethyl aminopropyl carbodiimide, heparin and N-hydroxy succinimide and were used to prepare the biosensor. It was observed that an increase in the electrical resistance occurs during functionalization and dengue virus interaction to heparin receptor. Tran et al. (2017) [53] reported CNT field effect transistor (CNTFET) in which functionalization of CNTs based on nitric acid and then, influenza virus DNA was immobilized on the CNTs network through physisorption. This was done through dipping of DNA sensor in a targeted DNA solution, dissolved in PBS. Some factors such as the concentration of the probe, thermal impact, immobilization time, reproducibility, range of detection and response time, are assessed. The results showed DNA sensor exhibited a short time to response together with high duplicability Fu et al. (2017) [54] reported a fast and highly efficient influenza virus (AIV) detection subtype H5N1 DNA sequences. SWCNTs (sc-SWCNTs) and nitrogen-doped MWCNTs (N-MWCNTs) were used in the biosensor as sensing elements. SWCNTs have no horizontal alignment. So, 5 to 20 mm length of sc-SWCNTs were achieve through short fragments CVD epitaxial elongation on the substrates made of quartz. After CNTs preparation, they founded target substrate arrays. Then, a standard microfabrication procedure was used to fabricate chemiresistor-

type sensors. Generally, CNT-based DNA sensors showed remarkable characteristics, such as flexibility, small size, easy to use, and overly sensitive, what make them favorable in portable applications and clinical diagnostics [54].

Harnessing the power of CNTs for cancer detection

Cancer disrupts the immune system and defense mechanism of the host [56]. This disease has become caused of countless death around the globe therefore several efforts were put to reduce the effect of this disease in the recent times. In this connection CNTs have been reported for the development of fast and effective detection as well as treatment tool of several cancer diseases [57-60]. Zanganeh et al. (2016), [57] developed an electrical biosensor for detection of cancer cells. The CNTs were conjugated to folic acid (FA-VACNTs) molecules. The direct-current plasma enhanced CVD was applied to produce CNTs for biosensor. The CNTs were then functionalized to form NH_2-VACNTs by double barrier discharge plasma system. Human lung cells QUDB and MRC-5 were isolated, which are carcinoma and normal tumors, respectively. The biosensors were tested by taking cells of same concentrations from culture flask and applying on VACNT and FA-VACNT using microfluidic pump. The FA-VACNT electrodes showed better electrical response of the sensors. This device could be applied to detect and monitor cancer [57]. The nanohybrid microelectrode has shown good detection performance for H_2O_2 with efficient structural mechanics integrated with electrochemical properties. Therefore, this biosensor has demonstrated high sensitivity and selectivity over a wide linear range with excellent mechanical stability and better biocompatibility and could be useful in chemotherapy or radiotherapy treatments [58]. CNTs based biosensors were also helpful in cancer treatment by detection of the concentration of substances. In this regard, H. Zhou et al. (2018) [61] produced an analytical device which could detect anticancer drug in the whole blood, using as a model system to detect methotrexate (MTX). MTX is used to cure several cancers; though, disproportionate use of it can cause intoxication. Controlling the MTX concentration in blood by optimized dosage is important to reduce its side effects. Uniformly distributed tungsten phosphide and nitrogen-doped CNTs produced synergistic effect to transmit electronic channel which ensured excellent

performance of the proposed sensor with a reproducibility for detection of MTX, satisfactory selectivity, short response time, wide and detection range in whole blood.

Harnessing the power of CNTs as drug release carriers

Controlled drug release has become the furthermost challenging as it requires to overcome both biological as well as physicochemical barriers [62]. SWCNTs and MWCNTs have been potentially used in vaccines, immunopotentiation and gene transfer fields of medicinal chemistry [63,64]. Since 2004, CNTs were reported for drug delivery, [65] and after that several methods have been manifested to enhance the use of nano-materials for DDSs. In this field the recent CNTs approaches are functionalization, coating with polymers, encapsulation, liposomes, and fabrication of structures for example, buckypapers, hydrogels, irregular meshes, and membranes, as shown in Fig. 5. The purpose of these modifications was to improve CNTs' dispersion in biological fluids, water solubility and simultaneously decrease their cytotoxicity [66]. More than 60% CNTs as drug delivery are applied for cancer treatment which is now considered a fatal disease worldwide [67]. Death rate in the recent years has increased due to various cancer diseases as per Annual Report [68], where, pancreas, brain and liver are among other types of cancers. Due to this reason the scientists have given much attention to this area. As reported by Wang and coworkers (2015) [69], that compared to nonfunctionalized CNTs, functionalized ones are less toxic which can be excreted from the human system. Added modifications such as, encapsulation or functionalization, can also be carried out on CNTs after loading a model drug. To overcome the challenges for triggered drug delivery, efforts are being carried out by using several alternative options. Some of them will be presented here. A dual drug delivery system which is pH responsive have been developed by Yang et al. (2017) [70]. This system can be used for cancer chemotherapy. The group utilizes the bigger inner-diameter MWCNTs. Doxorubicin (Dox) and Cisplatin (CDDP) anti-tumorous drugs were taken as non-covalent functionalization agents. The inner-side of MWCNTs were encapsulated by CDDP, and folic acid (FA). Different pH conditions were employed to manifest a biphasic release profile of FA bonded DDDS and DOX was noticed with the pH-sensitive release pattern. DOX and CDDP share a collegial antitumor activity by hindering cell growth and ultimately leading the cell to its death. In

2016, a bio-based scheme for Michael addition reaction and surface PEGylation of CNTs together with mussel-based chemistry was introduced by Xu et al. The later was a new strategy motivated by the efficiency of mussel to adhere to various material surfaces. The mussel proteins have amino acid 3,4- dihydroxyphenyl-L-alanine as the vital constituent which is responsible for its strong adhesive ability [71]. For the intracellular delivery of Dox, Xu et al. (2016) [71] demonstrated that PEGylated CNTs had biological potential. These PEGylated CNTs with enhanced biocompatibility toward cancer cells and are well dispersed in organic solutions and water, are fairly proved by results. PEGylated CNTs was efficiently used as substrate to load Dox and introduced into cancer cells. Because of the design-ability of polymerization and effectively strong adhesion of PDA, this technique could also be implied for surface modification to subsume other polymer materials. Based on photothermal effects, a thermos-sensitive hydrogel to control drug release was proposed by Dong et al. in 2017 [72]. Chitosan (CH) and MWCNTs combined with DDS had built on a thermosensitive hydrogel concept. Firstly, Dox was loaded on MWCNTs with non-covalent bonds and followed by addition of CH, the stirring mixture was resulted in CH-MWCNTs. Free Dox and Dox-loaded CH-MWCNTs having anti-tumor cell proliferation effect demonstrated that at any concentration, CH-MWCNTs loaded with Dox had decreased toxicity in comparison to free Dox, and ultimately the Dox is brought properly by CH-MWCNTs to the tumor cells and release it in the cytoplasm. So, decreased toxicity avocats the prolonged therapeutic effects. The encapsulation of hydrophilic drugs is proficient with MWCNTs/hydrogel as a drug carrier for in vitro drug release, it accelerates the drug release rate after initiation of photothermal conversion which is stimulated with an 808 nm laser irradiation. Sciortino et al. (2017) [73] used Dox as an anticancer drug and mentioned the efficiency of using MWCNTs by evaluating length and incubation time. Long (500 222 nm) and short (130 85 nm) MWCNTs were loaded with Dox and embellished with biotin. The non-internalized long MWCNTs release Dox impromptu which lessen the differences as indicated by the afterwards testing [73]. Dox is being extensively studied as an anti-tumor drug just like CNTs, and it could be seen from previously mentioned examples that many endeavors have been done for introducing numerous alternatives to overcome its leftover cytotoxicity. SWCNTs were modified by applying a simple non-covalent method with an asparagine–glycine–arginine

(NGR) peptide. In addition, they were loaded with Gd–DTPA by n–p interactions and Dox by π–π stacking interactions. This system facilitates the diagnosis of the tumor and chemotherapy in a unique system by accumulating in and entering tumor cells. The developed material is capable of increasing drug intracellular accumulation by efficiently promoting cellular uptake, and they are appropriate carriers for DDS because having no cytotoxicity against MCF-7 cells. Moreover, scientists also used subcutaneous injection to prepare tumor-bearing mice model after the tumor and performed intracellular studies which spread to a volume of 100 mm^3. The tail vein intravenous injection was implied for treating tumor-bearing mice in order to evaluate targeting efficiency and bio-distribution of DOX/NGR-SWCNTs/Gd–DTPA. Tumor-bearing mice were also used as model to examine the antitumor potency, and coronal and axial MR images of mice were achieved. Excellent tumor targeting properties were manifested by the results. The developed system is noticed to be out of harm's way for tumor therapy at the treatment dosage and is indicated by systemic toxicity. DOX/NGR-SWCNTs/Gd–DTPA injection was used for the treatment of group resulted with increased signal intensity, furnishing outstanding image contrast in *in-vivo* MRI. The toxicity of SWCNTs is reduced by modification with hydroxypropyl-b-cyclodextrin (HP-b-CD) and the delivery of formononetin (FMN), which is an anticancer drug, were beautifully demonstrated by Liu et al. in (2018) [74]. SWCNTs were detected with relatively high entrapment efficiency on account of covalently functionalized and formerly carboxylated with cyclodextrin (CD-SWCNTs) and, FMN was loaded posteriorly which in-turn could be positiined on HP-b-CD (CD ''side'') of SWCNTs. Their results exhibited that FMN-loaded SWCNTs could be appropriate carriers of the anticancer drug for in vivo delivery, and the antitumor activity FMN is greatly enhanced as CD-SWCNTs-FMN. The previously cited SWCNTs were also used by Razzazan et al. (2016) [75] as a drug carrier for cancer treatment; instead gemcitabine (GEM) covalently bonded to the surface of the tubes was chosen as an anticancer agent. After a wide application of SWCNTs in successive acylation, carboxylation, PEGylation and amination reactions, SWCNTs and SWCNTs-PEG was covalently bonded to GEM. The drug entrapment efficiency of both SWCNTs–GEM and SWCNTs– PEG–GEM was observed to be alike, fairly enough to endorse intracellular cytotoxic and concentration effects. SWCNTs provide a pH-responsive release profile because they release GEM quickly at

lower pH values following cleavage of ester bonds. The cytotoxicity of SWCNTs PEG–GEM was reduced by PEGylation, MTT assay was used for evaluating in vitro cytotoxicity against MIA PaCa-2 and A549 cells. Instead of pure GEM, cell uptake of SWCNTs was improved when conjugated with GEM and PEG. Evaluation of the in vivo tumor volume in mice and perceived the enhanced antitumor activity of GEM owing to its delayed degradation while attached to SWCNTs. It was noticed that SWCNTs–PEG–GEM decreased the tumor growth, compared to SWCNTs–GEM, after 23 days. Consequently, the tumor efficacy of GEM increases when conjugated with PEGylated SWCNTs, advocating this novel platform to be a proficient for delivering hydrophilic anticancer drugs efficiently. This report is regarded as the solely introduction of the anti-cancer drug which is covalently attached to the surface of the CNTs. Currently, Schwengber and coworkers (2017) [76] have studied buckypapers of CNTs which are regarded as electromodulated transdermal DDS. Nylon membranes involving SWCNTs–COOH were used to produce buckypapers, and other model drugs were used like clonidine hydrochloride (CHC), ketorolac tromethamine (KT), flurbiprofen (FB) and selegiline hydrochloride (SHC). SWCNTs–COOH individually adsorbed the drugs into it, and an elevated level of drug loading (89 4%) was attained. The lowest value for FB was spotted for 8 h of release, followed by SHC, CHC and KT. Grounding on the drug usage, the bucky papers demonstrated the important attributes for passive drug release developed for controlled drug release.

Conclusion notes and future outlook

In conclusion, though the incorporating CNTs into analytical detection tools, i.e., biosensors have resulted a great deal of study in the past few years. However, the full potential of CNTs or CNTs-assisted multifunctional materials is yet to be realized. So far, the most widely employed applications of CNTs have been the engineering of numerous detection tools and/or as a sorption material for various polluting agents. In addition to the above-mentioned applications of CNTs and considering the extensive attention in CNTs, it is not astonishing that one can spotlight different analytical potentialities of CNTs.

The ongoing current pace in the development and deployment of these applications designates prompt application of CNTs in fabricating contemporary analytical

instrumentation and in developing new analytical tools. From the future applications perspective, the studies should be designed by imagining broader application of CNTs in nano-electronic tools for multi-industrial sectors. In addition, the strategy of individually addressed matrices of nano-electrodes may lead to the construction of robust multi-component biosensors. Moreover, considering the surface, chemical, or biological functionalization of CNTs or CNTs-assisted nanostructured cues can be exploited in developing new micro-separation techniques. In the near future, all above-mentioned analytical features of the growing environmental and biomedical monitoring field of nanotechnology should lead to momentous progress in analytics and related areas.

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Declaration of interests

The listed author(s) declare no conflict of interest.

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753 *Engineering: C*, *76*, 431-438.
754

Figure captions

Figure 1 SWCNTs based sensing arrays having coating of organic materials as lung cancer biomarkers. a) patterns of responses of chemiresistive networks of SWCNTs; b) PCA score plots of the 10 sensing arrays. [21].

Figure 2 MWCNTs for discrimination of 20 representative VOCs. a) Chemical structures, b) Patterns of changes, c) Principal component score plots. [27].

Figure 3 a) Chemical structures of xylene isomers and poly(3-hexylthiophene) (P3HT), b) SWCNTs, c) SWCNT and P3HT to p-xylene, o-xylene, and m-xylene at 400 ppm. [32].

Figure 4 Nonenzymatic glucose sensor based on Ag nanoparticles (NPs) on functionalized CNTs. [39].

Figure 5 Boronic acid-functionalized CNT-based FET sensor for the detection of glucose. [40].

Figure 6 Detection of femtomolar DNA using Au NPs to enhance SWCNT-based FET sensors. [44].

Figure 7 Conductivity of a single DNA duplex bridged between SWCNT. [45].

Figure 8 CNT-network-based DNA detection scheme. [46].

List of Figures

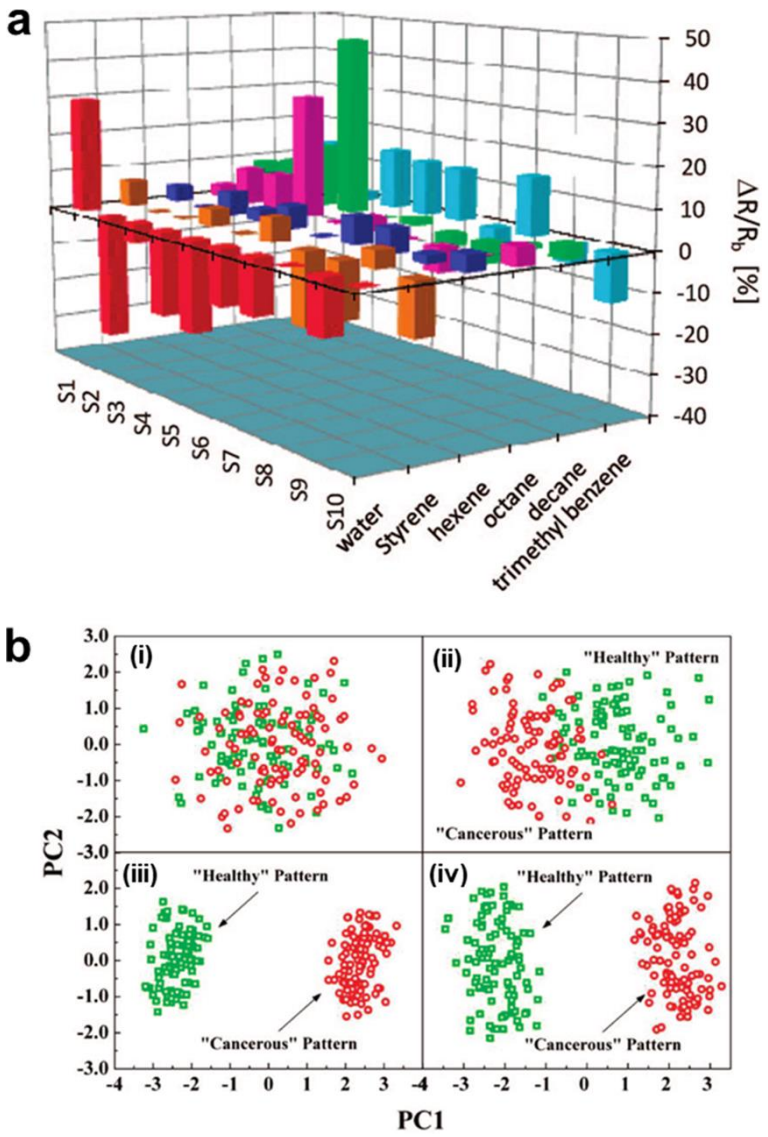
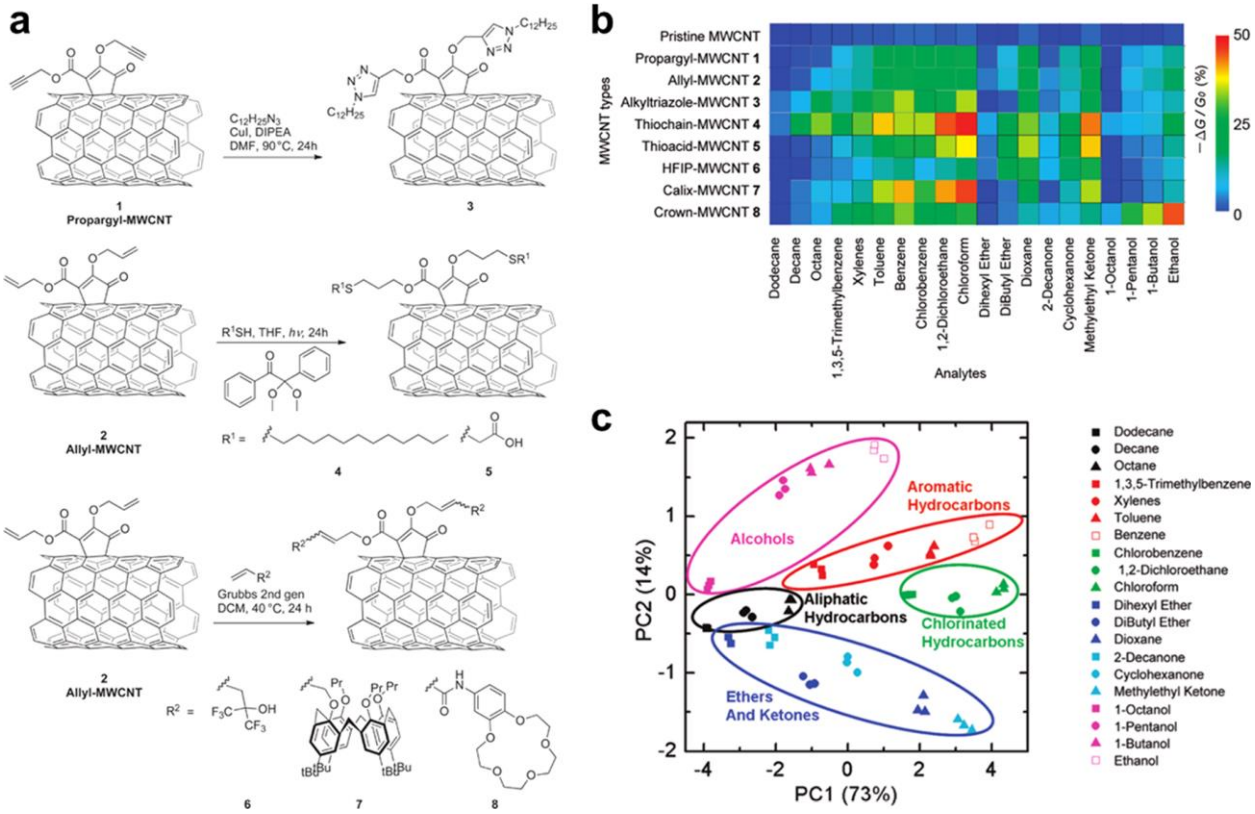


Figure 1


a
1
Propargyl-MWCNT
C12H25N3
CuI, DIPEA
DMF, 90 °C, 24h
3
2
Allyl-MWCNT
R1SH, THF, hν, 24h
R1 =
4
5
2
Allyl-MWCNT
Grubbs 2nd gen
DCM, 40 °C, 24 h
R2 =
6
7
8
b
Pristine MWCNT
Propargyl-MWCNT 1
Allyl-MWCNT 2
Alkyltriazole-MWCNT 3
Thiochain-MWCNT 4
Thioacid-MWCNT 5
HFIP-MWCNT 6
Calix-MWCNT 7
Crown-MWCNT 8
MWCNT types
Dodecane
Decane
Octane
1,3,5-Trimethylbenzene
Xylenes
Toluene
Benzene
Chlorobenzene
1,2-Dichloroethane
Chloroform
Dihexyl Ether
DiButyl Ether
Dioxane
2-Decanone
Cyclohexanone
Methylethyl Ketone
1-Octanol
1-Pentanol
1-Butanol
Ethanol
Analytes
−ΔG / Gs (%)
50
25
0
c
Alcohols
Aromatic Hydrocarbons
Aliphatic Hydrocarbons
Chlorinated Hydrocarbons
Ethers And Ketones
PC1 (73%)
PC2 (14%)
Dodecane
Decane
Octane
1,3,5-Trimethylbenzene
Xylenes
Toluene
Benzene
Chlorobenzene
1,2-Dichloroethane
Chloroform
Dihexyl Ether
DiButyl Ether
Dioxane
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Cyclohexanone
Methylethyl Ketone
1-Octanol
1-Pentanol
1-Butanol
Ethanol

Figure 2

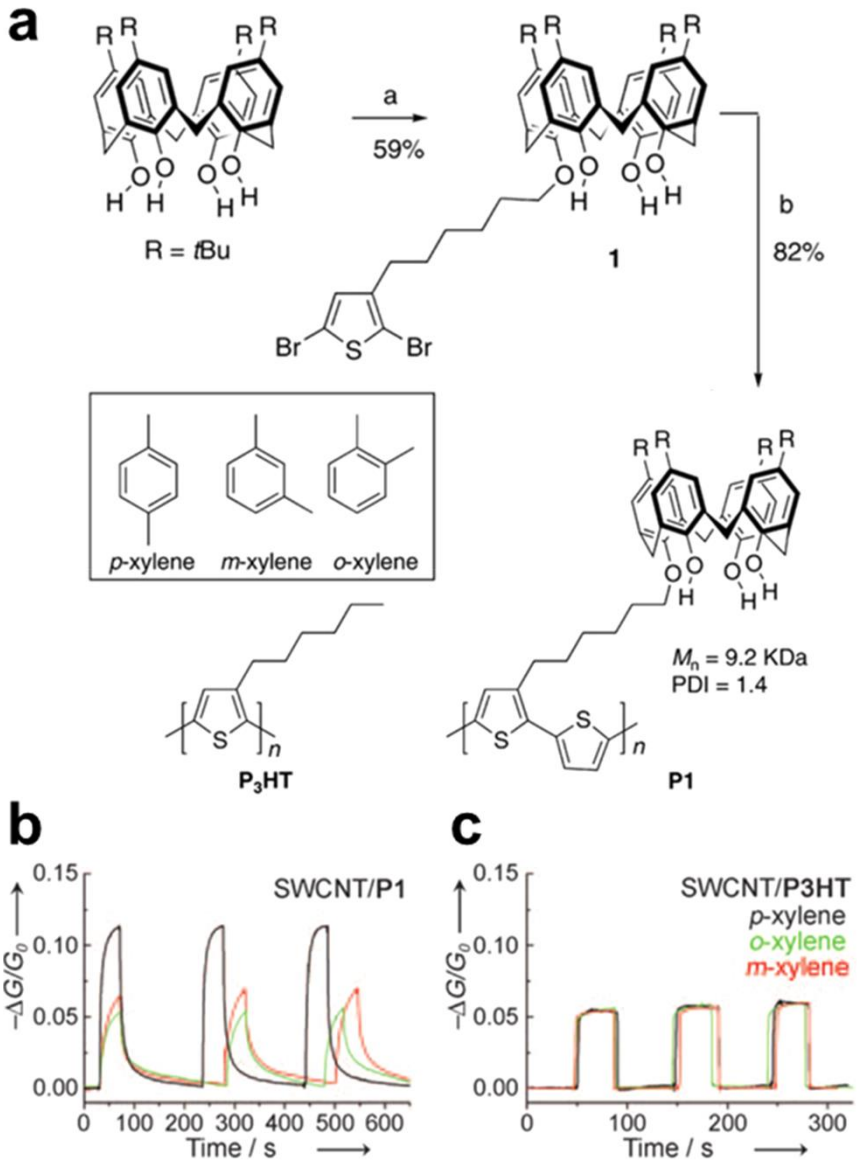
a
R = tBu
a
59%
1
b
82%
Br
S
Br
p-xylene
m-xylene
o-xylene
P3HT
Mn = 9.2 KDa
PDI = 1.4
P1
b
SWCNT/P1
−ΔG/G0
0.15
0.10
0.05
0.00
0 100 200 300 400 500 600
Time / s
c
SWCNT/P3HT
p-xylene
o-xylene
m-xylene
−ΔG/G0
0.15
0.10
0.05
0.00
0 100 200 300
Time / s

Figure 3

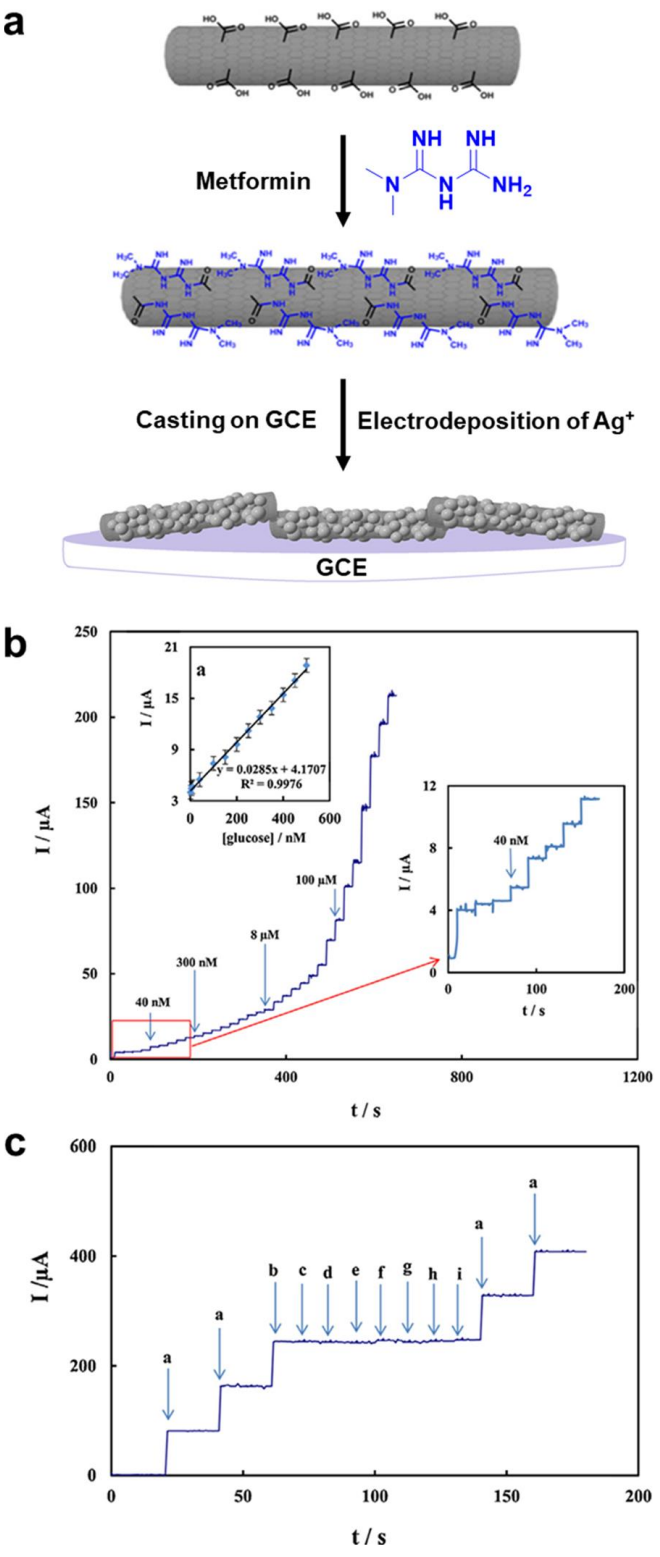
a
Metformin
NH
NH
N
N
H
NH2
Casting on GCE
Electrodeposition of Ag+
GCE
b
I / μA
t / s
40 nM
300 nM
8 μM
100 μM
y = 0.0285x + 4.1707
R² = 0.9976
[glucose] / nM
c
I /μA
t / s

Figure 4

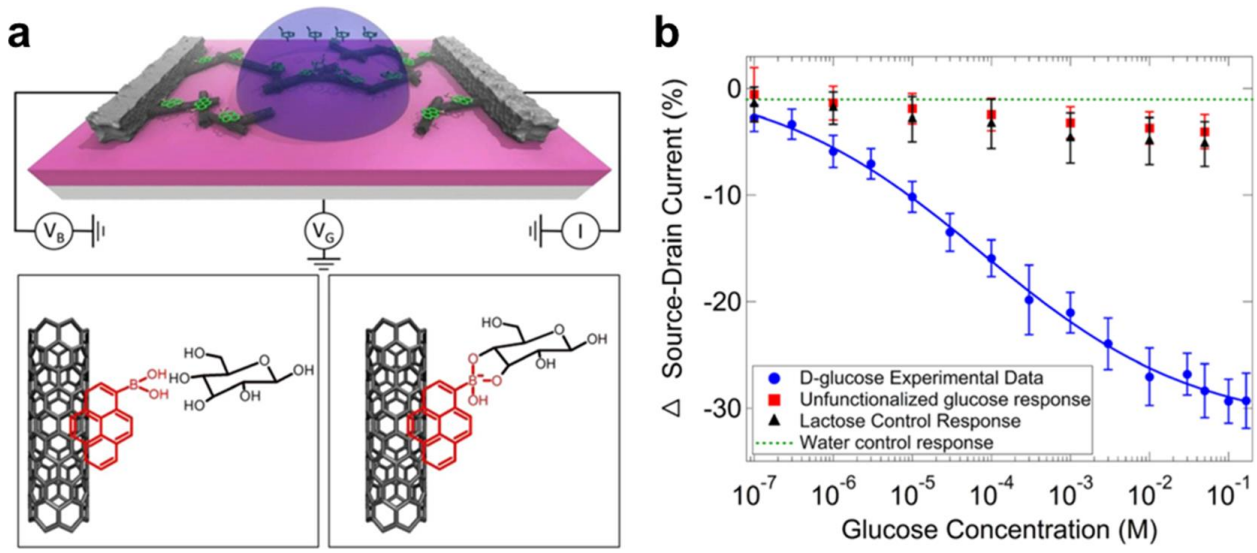
a
b
V_B
V_G
I
HO
OH
O
B
Δ Source-Drain Current (%)
0
-10
-20
-30
D-glucose Experimental Data
Unfunctionalized glucose response
Lactose Control Response
Water control response
10^-7
10^-6
10^-5
10^-4
10^-3
10^-2
10^-1
Glucose Concentration (M)

Figure 5

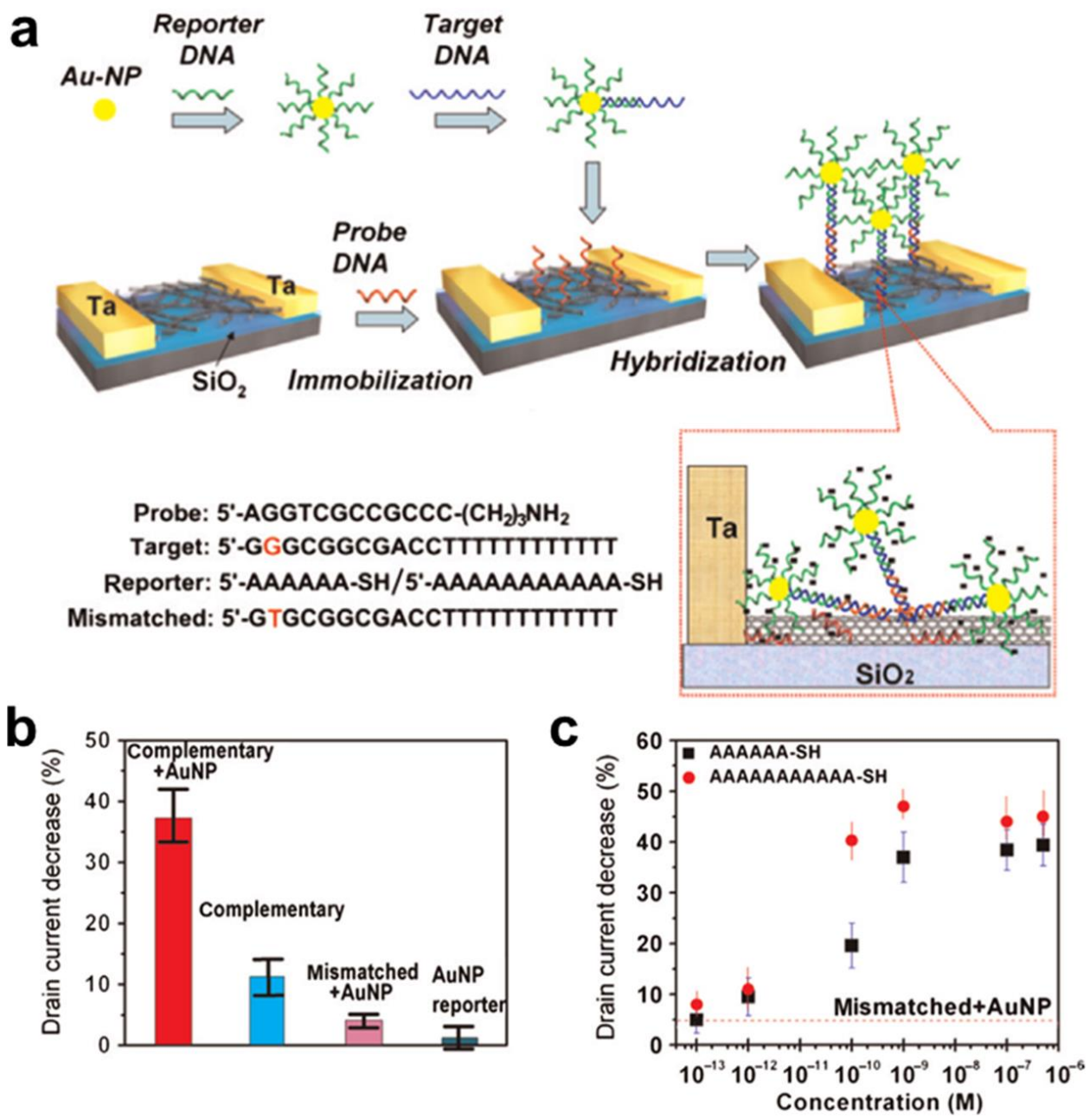
a
Au-NP
Reporter DNA
Target DNA
Probe DNA
Ta
Ta
SiO2
Immobilization
Hybridization
Probe: 5'-AGGTCGCCGCCC-(CH2)3NH2
Target: 5'-GGGCGGCGACCTTTTTTTTTTTT
Reporter: 5'-AAAAAA-SH/5'-AAAAAAAAAAA-SH
Mismatched: 5'-GTGCGGCGACCTTTTTTTTTTT
Ta
SiO2
b
Drain current decrease (%)
Complementary +AuNP
Complementary
Mismatched +AuNP
AuNP reporter
c
Drain current decrease (%)
AAAAAA-SH
AAAAAAAAAAA-SH
Mismatched+AuNP
Concentration (M)

Figure 6

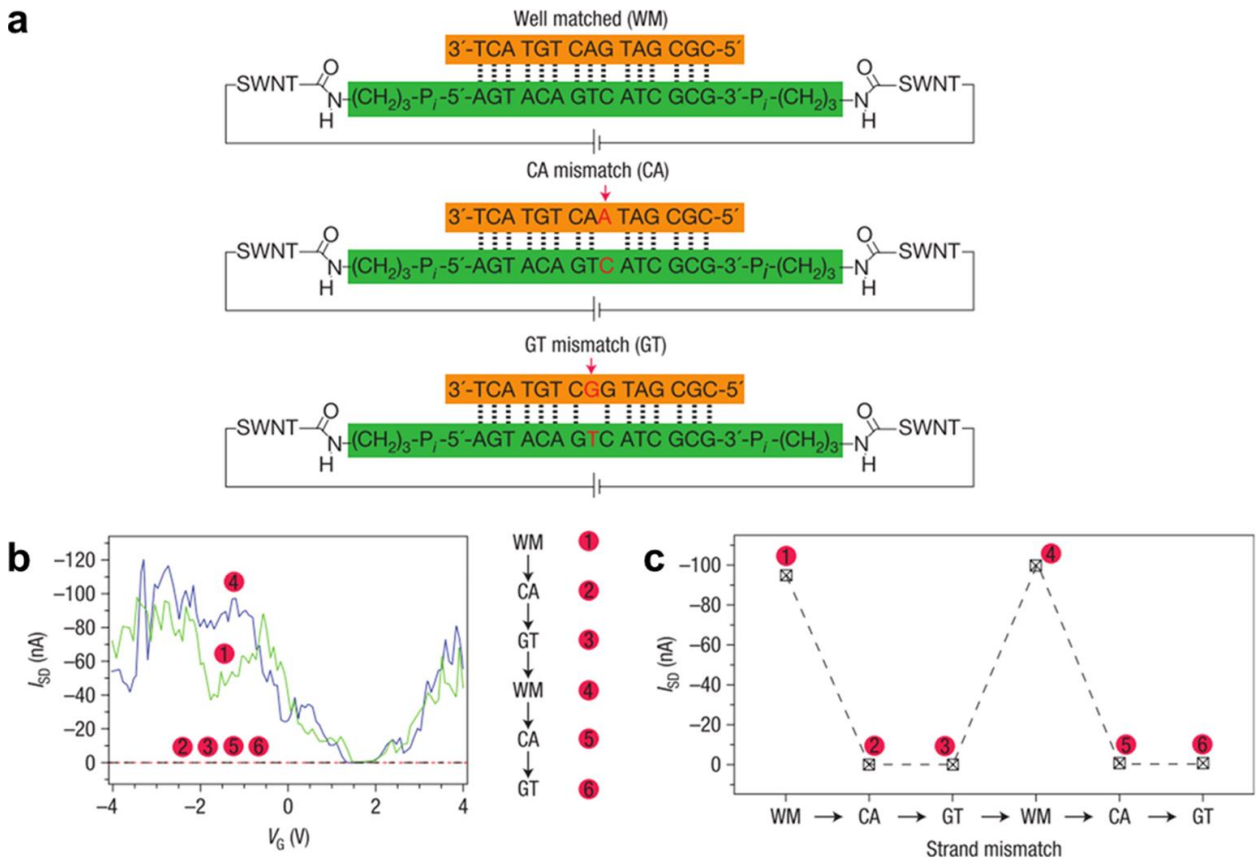
a
Well matched (WM)
3′-TCA TGT CAG TAG CGC-5′
SWNT
(CH2)3-Pi-5′-AGT ACA GTC ATC GCG-3′-Pi-(CH2)3
SWNT
CA mismatch (CA)
3′-TCA TGT CAA TAG CGC-5′
SWNT
(CH2)3-Pi-5′-AGT ACA GTC ATC GCG-3′-Pi-(CH2)3
SWNT
GT mismatch (GT)
3′-TCA TGT CGG TAG CGC-5′
SWNT
(CH2)3-Pi-5′-AGT ACA GTC ATC GCG-3′-Pi-(CH2)3
SWNT
b
ISD (nA)
VG (V)
WM
CA
GT
WM
CA
GT
c
ISD (nA)
WM → CA → GT → WM → CA → GT
Strand mismatch

Figure 7

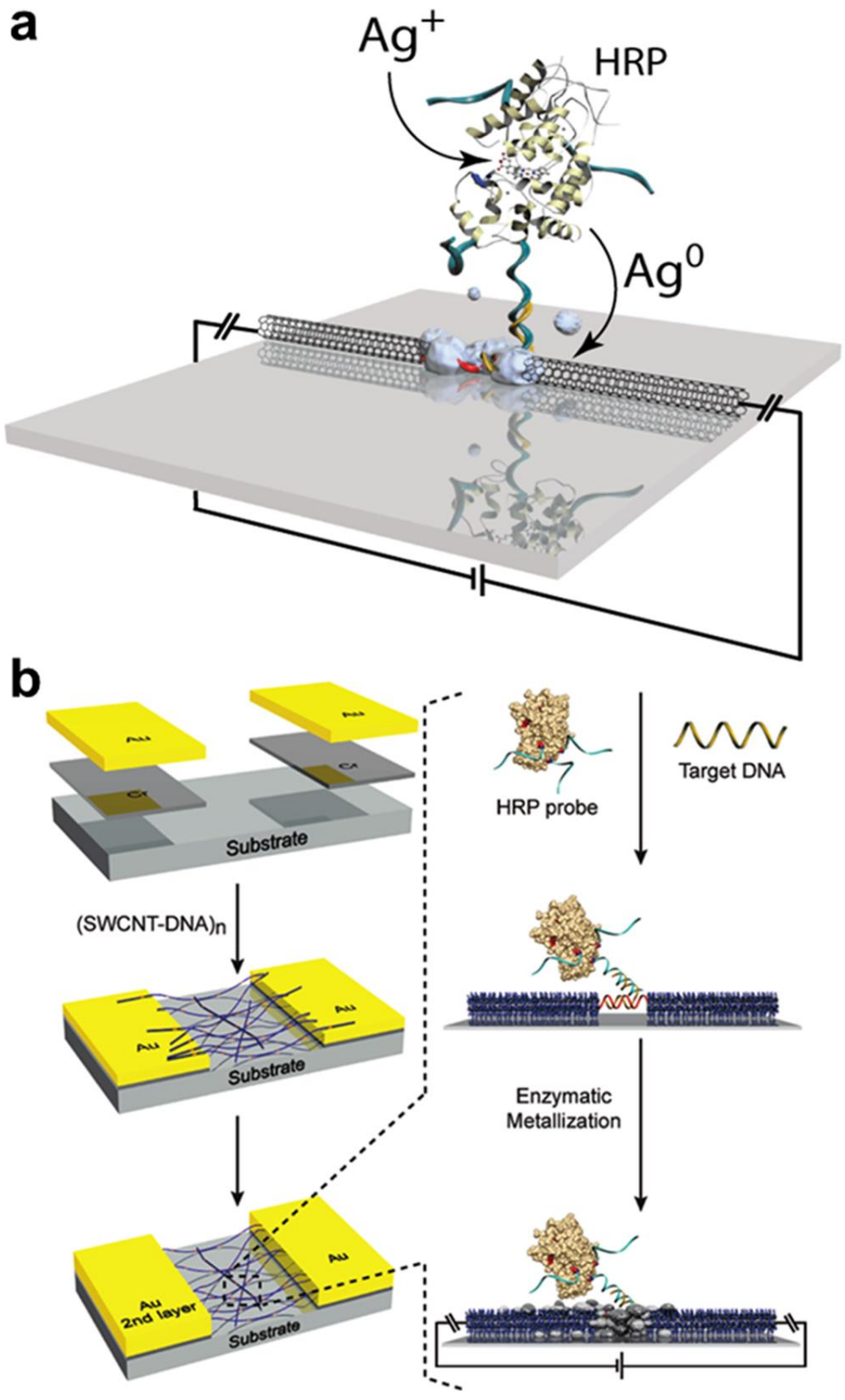
a
Ag+
HRP
Ag0
b
Au
Cr
Substrate
(SWCNT-DNA)n
Au
Au
Substrate
Au
Au
2nd layer
Substrate
HRP probe
Target DNA
Enzymatic
Metallization

Figure 8