Review Article

CARBON NANOTUBES: APPLICATIONS IN CANCER TREATMENT

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ABSRACT:

Carbonnanotubes production used for applications in energy storage, automotive parts, boat hulls, sporting goods, water filters, thin-film electronics, coatings, actuators and electromagnetic shields. CNTs exhibit dimensional and chemical compatibility with biomolecules, such as DNA and proteins. CNTs enable fluorescent and photoacoustic imaging, as well as localized heating using near-infrared radiation. CNTs have been successfully applied in pharmacy and medicine due to their high surface area that is capable of adsorbing or conjugating with a wide variety of therapeutic and diagnostic agents. CNTs have been also assayed for gene therapy, immunotherapy, tissue regeneration and diagnosis of different ailments.
Keywords: Carbonnanotubes, gene therapy, immunotherapy, tissue regeneration.

INTRODUCTION:

Carbon nanotubes (CNTs), in particular, have been introduced in pharmacy and medicine for drug delivery system in therapeutics since the beginning of the 21st century. Carbon nanotubes (CNTs) are allotropes of carbon, made of graphite and constructed in cylindrical tubes with nanometer in diameter and several millimeters in length. Their impressive structural, mechanical, and electronic properties are due to their small size and mass, their strong mechanical potency, and their high electrical and thermal conductivity[1]. CNTs have been successfully applied in pharmacy and medicine due to their high surface area that is capable of adsorbing or conjugating with a wide variety of therapeutic and diagnostic agents (drugs, genes, vaccines, antibodies, biosensors, etc.). CNTs are able to adsorb or conjugate with a wide variety of therapeutic molecules (drugs, proteins, antibodies, DNA, enzymes, etc.). They have been proven to be
an excellent vehicle for drug delivery by penetrating into the cells directly and keeping the drug intact without metabolism during transport in the body[2–5]. It has been first applied to bind antineoplastic and antibiotic drugs to carbon nanotubes for cancer and infection treatments, respectively. Then, other linkages of biomolecules (genes, proteins, DNA, antibodies, BioMed Research International vaccines, biosensors, cells, etc.) to CNTs have been also assayed for gene therapy, immunotherapy, tissue regeneration and diagnosis of different ailments [6–10].

STRUCTURE:

Carbonic structures can form diverse shapes and configurations both within compounds and as elementary substances. The numerous carbon forms identified to date include naturally occurring minerals (such as graphite, diamond and coal) and fullerenes (such as buckyballs, grapheme and carbon nanotubes), which can be artificially synthesized and have more recently been found in nature.

Graphene is a flat monolayer of carbon atoms arranged in a two-dimensional hexagonal lattice (Fig. 1)[8-10] Moreover, single or multiple graphene sheets can be folded into cylindrical structures, to give single-walled (SWCNTs) and multi-walled (MWCNTs) CNTs and into carbon nanofibers (CNF).[8-10] SWCNTs consist of a single graphene cylinder with diameter varying between 0.4 and 2 nm, and usually occur as hexagonal close-packed bundles (Fig. 2). MWCNTs consist of two to several coaxial cylinders, each made of a single graphene sheet surrounding a hollow core. The outer diameter of MWCNTs ranges from 2 to 100 nm.[8-10]

Nowadays, MWNTs and SWNTs are produced mainly by three techniques: arc-discharge, laser-ablation and catalytic growth. The synthesized nano tube samples are characterized by means of Raman, electronic and optical spectroscopies.[10,11]

SWCNT	**MWCNT**
1. Single layer of graphene	**1**. Multiple layer of graphene
2. Catalyst is required for synthesis	**2**. Can be produced without catalyst
3. Bulk synthesis is difficult.	**3**. Bulk synthesis is easy
4. More defection during functionalization	**4**. Less defection, but difficult to improve
5. Purity is poor	**5**. Purity is high
6. Less accumulation in body.	**6**. More accumulation in body
7. Easy characterization and evaluation.	**7**. Difficult characterization and evaluation
8. Easily twisted	**8**. Difficult to twist

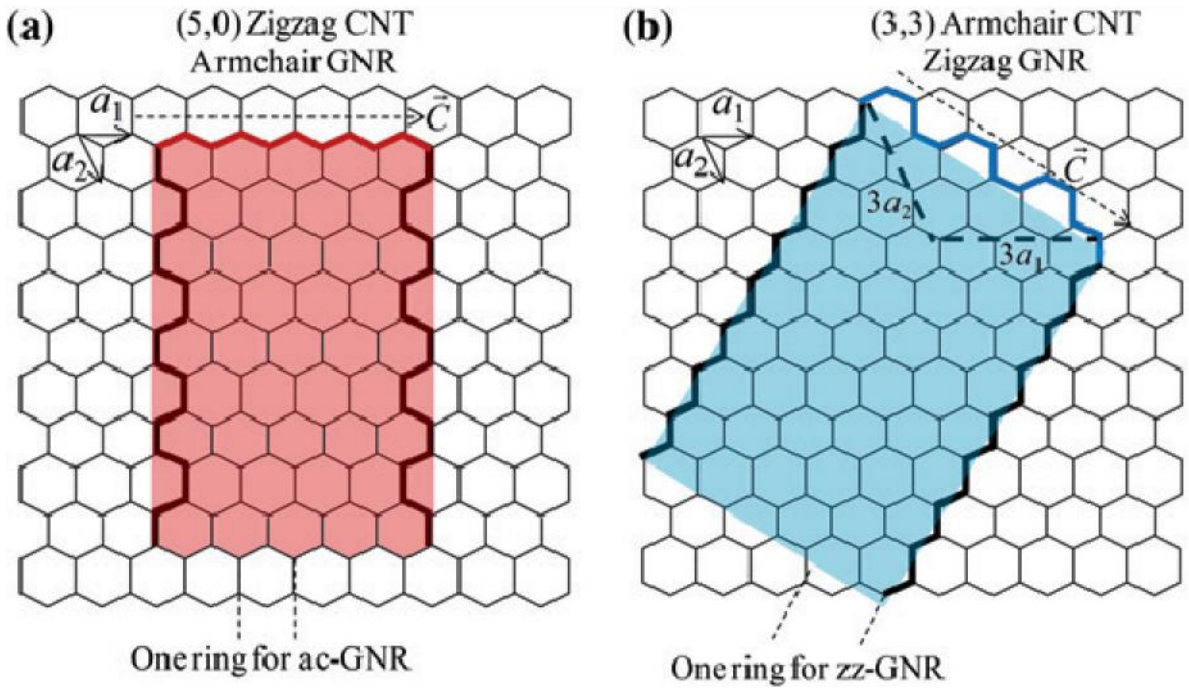

Fig 1: Schematic view of CNT made from graphene sheet a zigzag and b armchair CNT

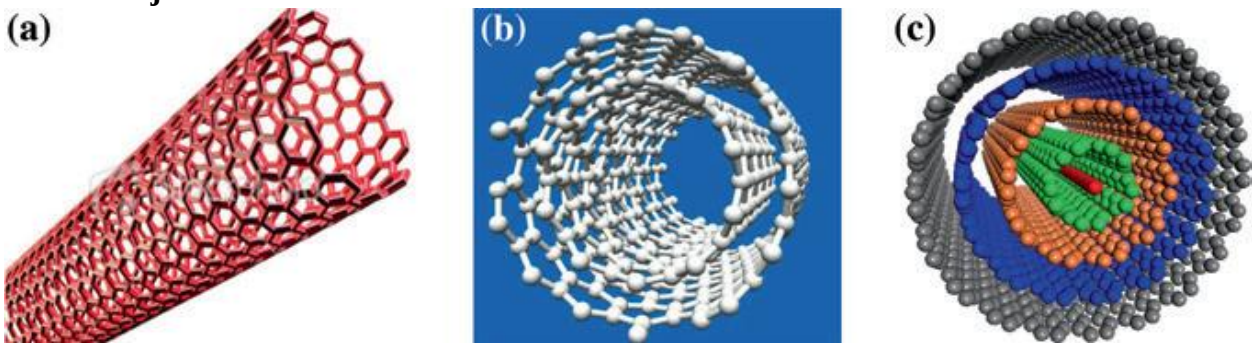

Fig 2: Basic structures of a single-walled, b double-walled, and c multi-walled CNTs

PRODUCTION AND WORKPLACE EXPOSURE TO CNTS:

Different techniques have been developed to produce nanotubes in appropriate amounts, including arc discharge, laser ablation, high-pressure carbon monoxide disproportionation and chemical vapor deposition (CVD).[5]A water-cooled surface may be included in the system to collect the nanotubes. The laser ablation method yields around 70% and produces primarily SWCNTs with a controlled size determined by the reaction temperature.[12] In plasma torch method, a gas mixture com- posed of argon, ethylene, and ferrocene is introduced into a microwave plasma torch, where it is atomized by the atmospheric pressure plasma, which has the form of an intense 'flame'. During CVD, a substrate is prepared with a layer of nickel, cobalt, and iron particles. The substrate is heated to approximately 700°C.[12, 13] To initiate the growth of nanotubes, two gases are bled into the reactor: a process gas (such as ammonia, nitrogen, or hydrogen) and a carbon-containing gas (such as acetylene, ethylene, ethanol, or methane.[13,14]

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KEY PROPERTIES OF CARBON NANOTUBES:

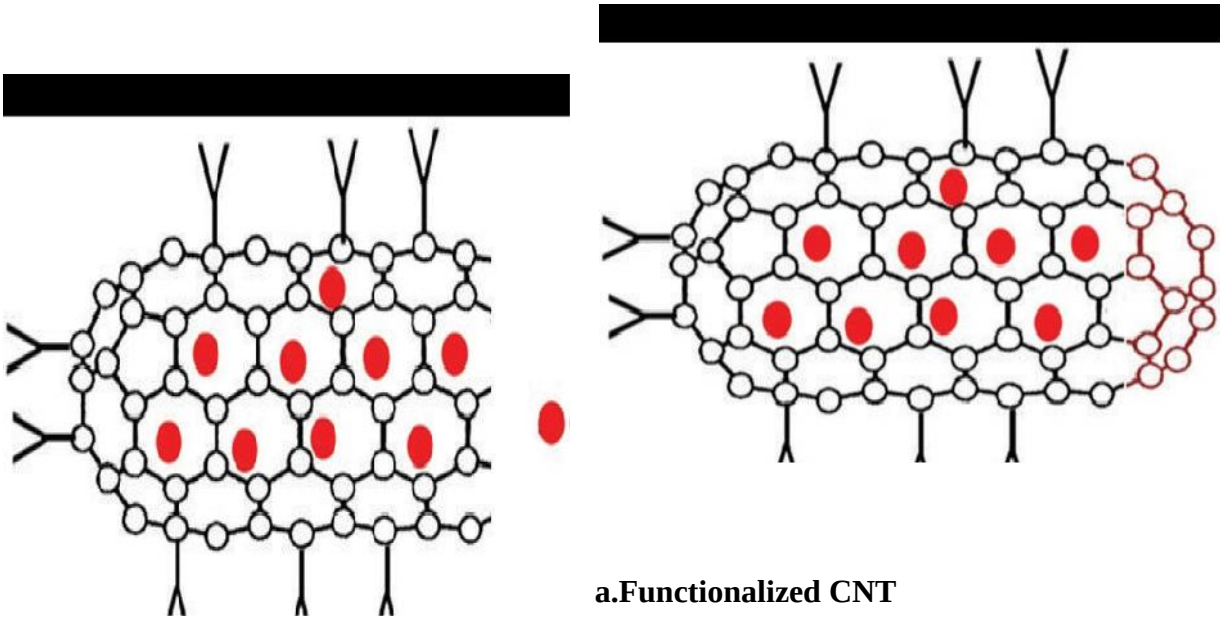
Carbon Nanotubes are an example of true nanotechnology. They are less than 100 nanometers in diameter and can be as thin as 1 or 2 nm. They are molecules that can be manipulated chemically and physically in very useful ways. They open an incredible range of applications in materials science, electronics, chemical processing, energy management, and many other fields.[8-10] Some properties include

- Extraordinary electrical conductivity, heat conductivity, and mechanical properties.
- They are probably the best electron field-emitter known, largely due to their high length-to-diameter ratios.
- As pure carbon polymers, they can be manipulated using the well-known and the tremendously rich chemistry of that element.

Some of the above properties provide opportunity to modify their structure and to optimize their solubility and dispersion. These extraordinary characteristics give CNTs potential in numerous applications.

Properties of Carbon Nanotubes:

The structure of a carbon nanotube is formed by a layer of carbon atoms that are bonded together in a hexagonal (honeycomb) mesh. This one-atom thick layer of carbon is called graphene, and it is wrapped in the shape of a cylinder and bonded together to form a carbon nanotube. Nanotubes can have a single outer wall of carbon, or they can be made of multiple walls (cylinders inside other cylinders of carbon).[8-11] Carbon nanotubes have a range of electric, thermal, and structural properties that can change based on the physical design of the nanotube.



a.Functionalized CNT

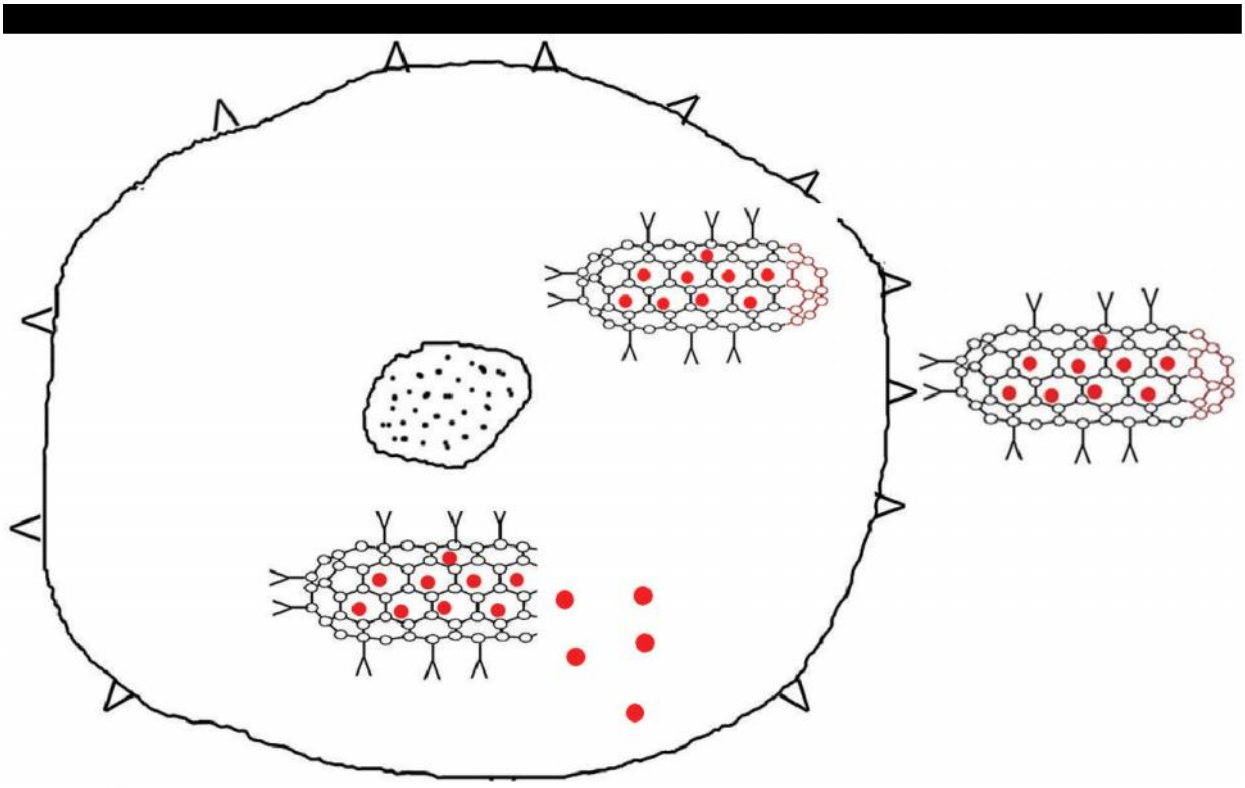


Figure 3: Schematic illustration of the drug delivery process. (a) CNT surface is linked with a chemical receptor (Y) and drugs (·) are loaded inside, (b) open end of CNT is capped, (c) drug-CNT carrier is introduced in the body and reaches the target cells due to chemical receptor on CNT surface, (d) cell internalizes CNT by cell receptors (V) via endocytosis pathway for example, (e) cap is removed or biodegrades inside the cell, then drugs are released.

Strength:

Carbon nanotubes have a higher tensile strength than steel and Kevlar. Their strength comes from the sp^2 bonds between the individual carbon atoms. This bond is even stronger than the sp^3 bond found in

diamond. Under high pressure, individual nanotubes can bond together, trading some sp^2 bonds for sp^3 bonds. This gives the possibility of producing long nanotube wires. Carbon nanotubes are not only strong, they are also elastic.[8-10]

Electrical properties:

When the structure of atoms in a carbon nanotube minimizes the collisions between conduction electrons and atoms, a carbon nanotube is highly conductive. The strong bonds between carbon atoms also allow carbon nanotubes to withstand higher electric currents than copper. Electron transport occurs only along the axis of the tube.[8.9]

Thermal Properties:

The strength of the atomic bonds in carbon nanotubes allows them to withstand high temperatures. Because of this, carbon nanotubes have been shown to be very good thermal conductors.[8,9]

APPLICATIONS OF CARBONNANOTUBES:

1. Biomedical Applications:

A number of biomedical applications of CNTs are proposed including drug vectors, biomolecule, gene delivery to cells or organs, tissue regeneration, and biosensor diagnostics and analysis.[15-18] In fact, due to their high surface area, excellent chemical stability, and rich electronic polyaromatic structure. CNTs are able to adsorb or conjugate with a wide variety of therapeutic molecules (drugs, proteins, antibodies, DNA, enzymes, etc.) and to carry them near the targeted cell.[17-18]

2. Pharmaceutical Applications:

The main applications of CNTs in pharmacy and medicine include drug, biomolecule, gene delivery to cells or organs, tissue regeneration, and biosensor diagnostics and analysis.[14,15]

Drug is fixed on the surface or the inside of functionalized CNTs. The conjugate obtained is introduced into the animal body by classic ways (oral, injection) or directly to the target site through the use of a magnetic conjugate. The cell ingests the drug CNT capsule and finally the nanotube spills its contents into the cell and thus the drug is delivered [19-20].

The ability of CNTs to cross cell membranes for drug delivery are due to the simple hydrophobic interaction, π-π stacking interaction, electrostatic adsorption and covalent bonds in their structure, but also by adsorption into the hollow cylinder, which is conducive to increase the adsorptive capacity [19-21]. Besides, CNTs have a capacity not only to penetrate into the cells to promote the cellular uptake of therapeutic molecules but also to keep them intact during transportation and cellular penetration.[20,21]

3. Carbonnanotubes for Anticancer Therapy:

a) By Drug Delivery:

CNTs can be used as drug carriers to treat tumors [14-20]. The efficacy of anticancer drugs used alone is restrained not only by their systemic toxicity and narrow therapeutic window but also by drug resistance and limited cellular penetration. Because CNTs can easily across the cytoplasmic membrane and nuclear membrane, anticancer drug transported by this vehicle will be liberated in situ with intact concentration and consequently, its action in the tumor cell will be higher than that administered alone by traditional therapy.

Drugs can be linked with a magnetic CNT complex, obtained by fixing a layer of magnetite (Fe_3O_4) nanoparticle on the surface of the nanotubes. CNT drugs can be guided by an externally placed magnet to target a desired organ interested by the cancer cell localization sparing normal counterparts. Moreover, due to their tiny size and accessible external modifications, CNTs are able to cross the blood-brain barrier (BBB) by various mechanisms targeting for acting as effective delivery carriers to treat brain tumors.[19-21]

Many anticancer drugs have been conjugated with functionalized CNTs and successfully tested in vitro and in vivo such as epirubicin, doxorubicin, cisplatin, methotrexate, quercetin, and paclitaxel [14-21].
Chemotherapeutic agents can be bound to a complex formed by CNT and antibody against antigen over expressed on the cancerous cell surface. By the attraction of antigen-antibody, CNTs can be taken up by the tumor cell only before the anticancer drug is cleaved off CNTs; thus, targeting delivery is realized [19-21].
A water soluble SWCNT-Paclitaxel (PTX) conjugate has been found to be highly efficient in suppressing tumor growth when compared with free taxol in a murine 4T1 breast cancer cell model, likely for both the extended blood circulation and enhanced permeability and retention (EPR) effect by SWCNT.

b) As Antitumor Immunotherapy:

CNTs used as carriers can be effectively applied in antitumor immunotherapy[23,24]. This therapeutic consists of stimulating the patient's immune system to attack the malignant tumor cells. This stimulation can be achieved by the administration of a cancer vaccine or as therapeutic antibody as drug[25-28].

c) By Local Antitumor Hyperthermia Therapy:

The hyperthermia therapy using CNTs has been recently suggested as an efficient strategy for the cancer treatments. SWCNTs exhibit strong absorbance in the near-infrared region (NIR; 700–1100 nm). These nano-materials are considered as potent candidates for hyperthermia therapy since they generate significant amounts of heat upon excitation with NIR light [29-31].

4. Carbon Nanotubes for Infection Therapy:

Because of the resistance of infectious agents against numerous antiviral, antibacterial drugs or due to certain vaccine in efficacy in the body. Functionalized CNTs have been demonstrated to be able to act as carriers for antimicrobial agents[32,33].

5. Carbon Nanotubes for Gene Therapy by DNA Delivery:

Gene therapy is an approach to correct a defective gene which is the cause of some chronic or hereditary diseases by introducing DNA molecule into the cell nucleus. Some delivery systems for DNA transfer include liposomes, cationic lipids and nanoparticles such as CNTs recently discovered[15,17]. When bound to SWCNTs, DNA probes are protected from enzymatic cleavage and interference from nucleic acid binding proteins, consequently, DNA-SWCNT complex exhibits superior biostability and increases self-delivery capability of DNA in comparison to DNA used alone [4,17].

6. Antimicrobial applications:

Functionalized CNTs can be used in vaccination procedures. CNTs were shown to activate cells deriving from the innate immune system, such as monocytes, macrophages, and dendritic cells. Microarray profiling of a monocytic cell line, THP-1, showed that CNTs, both functionalized and non functionalized, activate several genes involved in monocyte response to infection or vaccination, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), among others.[17-19]

7. Carbon Nanotubes as Antioxidants*:*

The last two decades, has there beenan explosive discovery of their roles in the developmentof diseases, and also of the health protective effects ofantioxidants [34,35]. Nevertheless, the potential role of CNTs asfree-radical scavengers is still an emerging area of research. Some scientists have recently reported that CNTs and in particular carboxylated SWCNTs are antioxidants in nature and may have useful biomedical applications for prevention of chronic ailments, aging, and food preservation [36].

8. Carbon Nanotubes as Biosensor Vehicles for Diagnostic and Detection:

A biosensor is an analytical device, usedfor the detection of an analyte that combines a biological component with a physicochemical detector. The use of CNTsin biosensing nanotechnology is recent and represents a mostexciting application area for therapeutic monitoring and invitro and in vivo diagnostics.

9. Carbon Nanotubes for Enantioseparation of Chiral Drugs and Biochemical:

In pharmaceutical industries, 56% of thedrugs currently in use are chiral products and 88% ofthe last ones are marketed as racemates consisting of anequimolar mixture of two enantiomers [36]. Recently, USFood and Drug Administration (FDA) recommended theassessments of each enantiomer activity for racemic drugsin body and promoted the development of new chiral drugs as single enantiomers[36]. Therefore, a wide range of new technologies for chiral separation has been developed, among them carbon nanotechnology.

10. Carbon Nanotubes for Solid Phase Extraction of Drugs and Biochemicals:

Nonfunctionalizedor functionalized CNTs have been investigatedas Solid phase Extraction (SPE) adsorbents used alone or in conjugation with classical SPE sorbents (C18 silica, XAD-2 copolymer) for the analytical extraction of drugs, pesticides or natural compounds in different media such as biological fluids, drug preparations, environment, plants, animal organs.

11. Other applications:

The linkages of other biomolecules such as genes, proteins, DNA and biosensors to CNTs have been also assessed for gene therapy and tissue regeneration.CNTs can effectively transport the genes inside mammalian cells, maintaining their integrity.[22-23]

DNA-SWCNT complex exhibits superior biostability and increased self-delivery capability of DNA in comparison to DNA used as free moieties. CNTs can interact directly with DNA through Van der Waals and hydrophobic forces.[23]

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