


Functionalized Graphene Platforms for Anticancer Drug Delivery

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Abstract: Two-dimensional nanomaterials are emerging as promising candidates for a wide range of biomedical applications including tissue engineering, biosensing, pathogen incapacitation, wound healing, and gene and drug delivery. Graphene, due to its high surface area, photothermal property, high loading capacity, and efficient cellular uptake, is at the forefront of these materials and plays a key role in this multidisciplinary research field. Poor water dispersibility and low functionality of graphene, however, hamper its hybridization into new nanostructures for future nanomedicine. Functionalization of graphene, either by covalent or non-covalent methods, is the most useful strategy to improve its dispersion in water and functionality as well as processability into new materials and devices. In this review, recent advances in functionalization of graphene derivatives by different (macro)molecules for future biomedical applications are reported and explained. In particular, hydrophilic functionalization of graphene and graphene oxide (GO) to improve their water dispersibility and physicochemical properties is discussed. We have focused on the anticancer drug delivery of polyfunctional graphene sheets.

Keywords: two-dimensional nanomaterials, graphene, functionalization, anticancer drug delivery, photothermal therapy

Introduction

Cancer is a general name for a group of more than 100 diseases and one of the most serious health risks that is the second-leading cause of death worldwide behind cardiovascular disease.^{1–5} Cancer is usually caused by abnormal proliferation of different cells in the body that differ significantly in the complexity of treatment. Abnormal cell proliferation leads to tumor formation that can be benign or malignant. A benign tumor (non-cancerous) is not cancerous and remains confined to its original site and does not metastasize to other regions of the body. However, a malignant tumor (cancerous) is an invasive tumor and spreads through the bloodstream or lymphatic system throughout the body. Benign tumors can usually be removed by surgery, but malignant tumors are often resistant to current treatments and are much more dangerous because of their ability to invade and metastasize to different parts of the body.^{6,7} Many research studies have focused on finding new strategies to reduce the side effects of conventional therapies.^{8–10} Despite its drawbacks and limitations, chemotherapy plays a significant role in cancer treatment.¹¹ One of the main challenges associated with chemotherapy is low bioavailability of chemotherapeutic agents and drug-resistant tumor cells.^{12–14} Nanomaterials, due to their unique physicochemical properties, including shape,

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surface, size, and optical properties, are able to target cancerous tissue and cross the biological barriers with minimal side effects.^{8,15,16} Different types of nanomaterials such as organic nanoparticles (polymeric micelles, liposomes, and dendrimers) inorganic nanoparticles (quantum dots, carbon nanotubes, magnetic and metal nanoparticles), 2D nanomaterials (graphene and its derivatives, molybdenum disulfide, boron nitride, black phosphorus nanosheets, transition-metal dichalcogenides, transition metal oxides, metal organic frameworks, layered double hydroxides), nanocomposites, and nanogels have been used for this purpose.^{17–28} To address these problems, anticancer drug delivery systems based on two-dimensional nanomaterials are developed and their ability to target anticancer drugs into tumors is investigated.²⁹ Graphene-based nanomaterials due to their excellent physicochemical and biological properties including high loading capacity, photothermal property, and fast cellular uptake have been used to improve current chemotherapies.^{30–33} In this review, we have focused on the functionalized graphene sheets as nanocarriers to

transport therapeutic agents into tumors along with a brief discussion on the challenges and future trends in this field.

Graphene Platforms: Structure, Chemistry, and Toxicity

Graphene is a two-dimensional honeycomb network with sp^2 carbon atoms. Each atom is bonded to neighboring carbons by σ -bond and out of plane p orbitals are extended over the whole structure. Graphene could be considered as the main backbone of various allotropes of carbon including fullerene, zero dimension (0D), nanotubes, one dimension (1D), and graphite, three dimensions (3D)³⁴ (Figure 1). The unique physicochemical, optical, electrical, and mechanical properties of graphene make it a suitable platform for various applications such as energy storage,^{35,36} sensors,^{37–39} biological and medical applications,^{39–46} cancer therapy,^{47,48} functional devices,^{49–51} and drug delivery.^{52–54} High thermal and electrical conductivity, high elasticity and flexibility, and large surface area are some graphene properties superior to other nanomaterials.^{55,56} Due to its outstanding properties

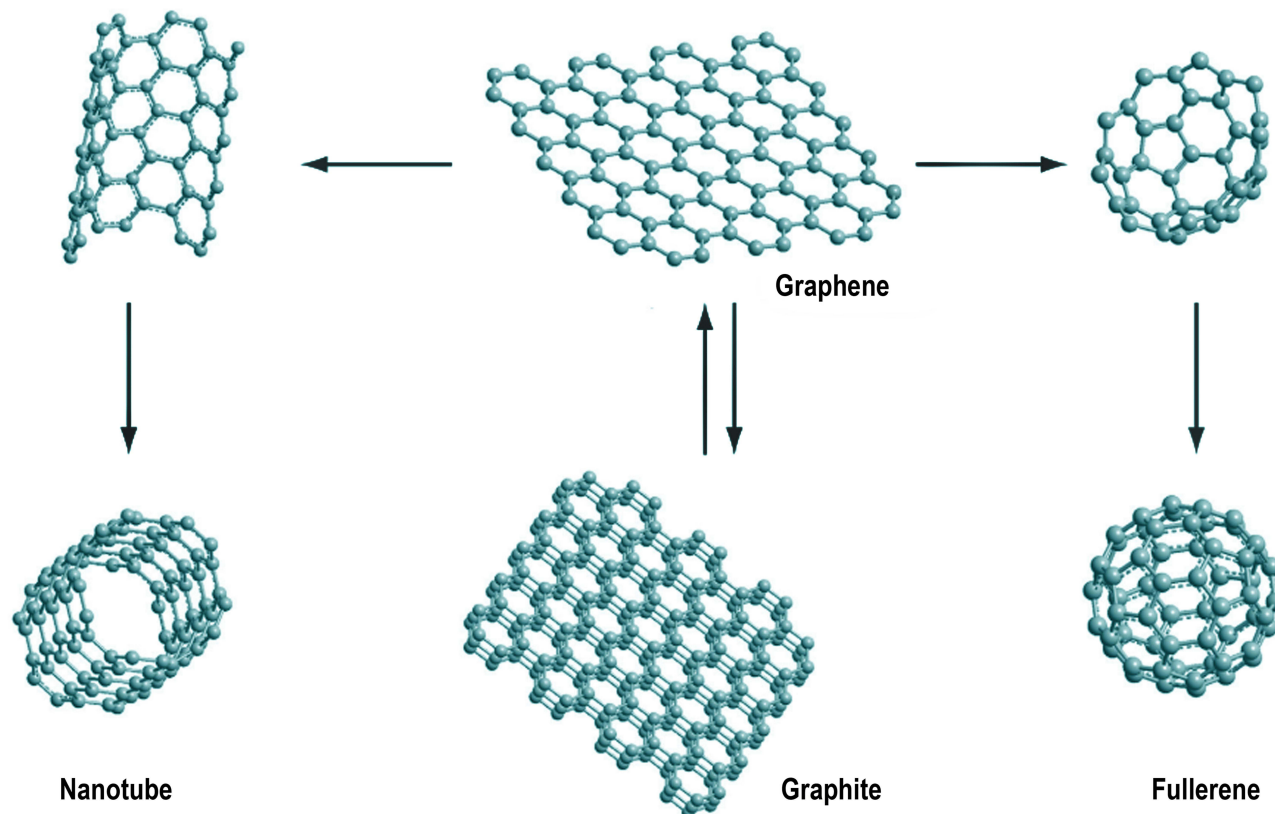


Figure 1 Graphite and different allotropic forms of carbon.

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such as photothermal property, oxidative reactivity, and low price, graphene can be used as an appropriate platform for drug delivery. Also, layer structure of graphene represents a high loading capacity for therapeutic agents.⁵⁷ Despite the extraordinary properties of graphene, one of the main drawbacks of using it for drug delivery is the low dispersibility of this compound in aqueous solutions. Oxidation to graphene oxide (GO), production of reduced graphene oxide (rGO) or functionalization by hydrophilic functional groups are the main strategies to overcome this problem (Figure 2). GO, an oxidized derivative of graphene, consists of a large number of oxygen containing functionalities such as epoxide, hydroxyl, and carboxylic acid. While epoxide and hydroxyl groups are placed in the basal plane, carboxylic groups are placed along the edges. These functional groups improve dispersibility of GO in water. rGO has much less epoxy due to reduction and it shows a low dispersibility in aqueous solutions.

However, one of the main concerns regarding biomedical applications of graphene is the intrinsic toxicity and health risk of this compound.^{58–61} The toxicity of graphene-based nanomaterials mainly depends on different factors including size, surface charge, shape, number of layers, surface functional groups, and particulate state.^{58,62–64} While some studies showed no toxicity and side effects of graphene on mouse cells, others indicated considerable toxicity for graphene.^{65–67} This discrepancy come back to the variation in the structure of graphene derivatives and necessitates more extensive studies to conclude on the toxicity of graphene and its derivatives. Therefore, before any medical applications, a deep understanding of the toxicological profile of graphene-based nanomaterials is required. Cellular studies have shown that

graphene and its derivatives can destroy the structures of the cells. For example, graphene caused plasma membrane damage in Hep G2 cells and induced disintegrate the mitochondrial membrane in a dose-time and shape-dependent manner.^{68,69} Moreover, graphene-based nanomaterials led to DNA fragmentation and chromosomal aberrations in human mesenchymal stem cells and cause side effects in normal cells such as immune system cells.^{70,71} Graphene causes apoptosis by inducing mitogen-activated protein kinases and the transforming growth factor- β -related signaling pathways.⁷² Graphene-based nanomaterials have shown dose-dependent hemolytic activity and aggregated graphene particles have shown considerable toxicity. Some studies have shown that graphene and its derivatives increase intracellular ROS and cause cytotoxicity and induce oxidative stress through which proteins, DNA, and lipid destruction have been damaged.^{73–77}

Robert Langer and co-workers played with the functionality of graphene oxide and studied the toxicity effects of different types of graphene oxide on mice. The aim was to find a possible relationship between the amount of oxygen containing functional groups and biocompatibility of graphene oxide. Their results showed that by injecting graphene oxide, this substance becomes a mass in the body. The team found that the mice's body excreted graphene oxide over time.

Researchers have used standard arrays to study the toxicity effects of graphene oxide and have shown that concentrations less than 1 mg/mL do not show considerable toxicity effects but higher concentrations are toxic to the body. Administration of GO in mice has resulted in chronic toxicity and death from pulmonary granuloma. In addition, dose-dependent pulmonary toxicity, granulomatous lesions, pulmonary edema fibrosis, and inflammatory

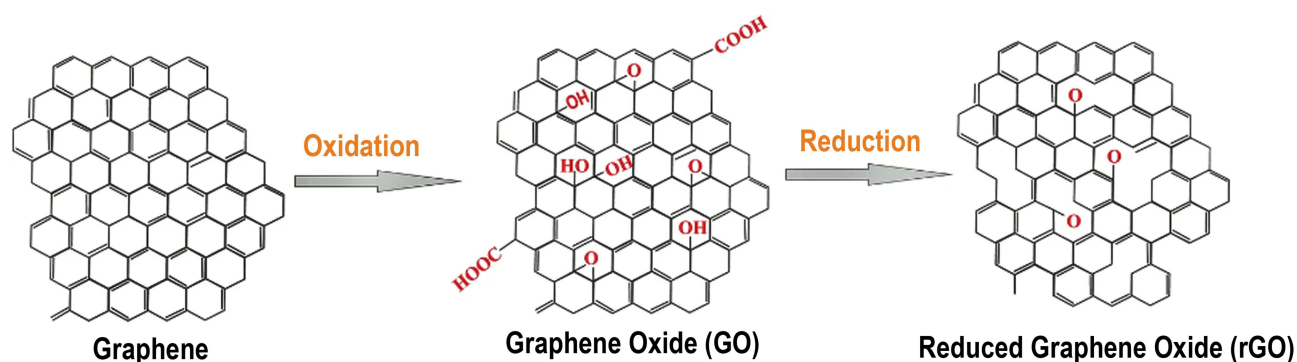


Figure 2 Structure of graphene and its oxidized derivatives.

Notes: Reproduced with permission from Priyadarsini S, Mohanty S, Mukherjee S, Basu S, Mishra M. Graphene and graphene oxide as nanomaterials for medicine and biology application. *Journal of Nanostructure in Chemistry*. 2018;8:123–137.⁴¹ Copyright © 2018, The Authors. Creative Commons CC BY (<https://creativecommons.org/licenses/by/4.0/legalcode>).

cell infiltration have also been observed after administration of GO. A pulmonary inflammatory response was also observed in rats after administration of graphene with BSA.^{78–81}

Functionalization of graphene with different functional groups can potentially improve the bioavailability, circulation lifetime and anticancer property of this material.^{82,83} As previously mentioned, one way to achieve this goal is functionalization of graphene surface by suitable polymers.⁸⁴ Modification of graphene surface by polymers enhances biocompatibility and circulation times of graphene in vivo. PEG is the most studied polymer for the modification and improvement of biological properties of graphene derivatives. Conjugation of PEG onto graphene sheets reduces toxicity and increases stability of graphene under physiological conditions.^{85,86} According to the hematological analysis and histological examinations, nanographene modified PEG do not cause appreciable toxicity at dose (20 mg/kg) in a period of 3 months.⁸⁷

Pharmacokinetics and clearance of graphene nanomaterials from the body has been studied but it needs extensive investigations to achieve a deep understanding of the long-term toxicity of these materials.^{88,89} The physicochemical properties of graphene derivatives including size, surface charge, surface chemistry, and shape impact their pharmacokinetics dramatically.⁹⁰ Transmission electron microscope (TEM), Raman spectroscopy, isotopic labeling, and rare-earth elements labeling are some of the methods available for tracking these materials in body.^{87,91–93} For example, Liang et al used the La/Ce dual elemental labeling method to track the bioaccumulation, transfer, and clearance of polyvinylpyrrolidone (PVP) modified GO in vivo.⁹⁴ They showed that injected PVP/GO mainly accumulate in the lungs, liver, and spleen, then pass through the glomerular filtration barrier (GFB) of the kidney and can be cleared, likely by both renal and fecal excretion. Similar results have been reported for injected PEGylated ¹²⁵I-labeled nanographene sheets.⁸⁷ Injected PEGylated graphene are accumulated in the reticuloendothelial system and gradually cleared from the bloodstream through their sequestration by cells of the mononuclear phagocyte system.

Graphene-Polymer Platforms; Synthesis and Physicochemical Properties

For many biological applications and in order to improve the functionality and dispersibility of graphene,

surface of this nanomaterial should be modified and functionalized. Surface modification of graphene platforms using biocompatible polymers endow new properties and effectively improve their performances for biomedical applications. Taking advantage of the huge conjugated π -systems, high specific surface area, and useful functionality, graphene platforms can be used as novel nanocarriers for different therapeutic agents.^{95–98} Incorporation of polymeric systems into the graphene structure allows tailoring these platforms into new multifunctional systems to deliver a variety of moieties such as therapeutic, targeting, and diagnostic agents.^{97,99} Non-covalent and covalent functionalization are two major strategies for the modification of graphene and its derivatives.^{100–106}

Graphene derivatives can be covalently modified by covalent attachment of polymers through addition of free radicals or dienophiles to their C=C bonds. Macromolecules can also be conjugated to GO through silanization, amidation, esterification, and cycloaddition reactions.^{107,108} However, challenges have to be addressed regarding non-destructive and covalent functionalization of graphene derivatives, as the methods previously mentioned cause disruption of sp^2 network and electronic and optoelectronic features of these graphene-based platforms.^{109,110} We have previously developed a non-destructive covalent method for the controlled functionalization of nanographene sheets through nitrene [2+1] cycloaddition reaction based on azidodichloro-triazine at ambient conditions.^{111,112} This strategy allows the controlled non-destructive functionalization of graphene with different polymers and (macro)molecules through conjugated triazine groups and opens up new avenues to construct complex devices for future biomedical applications¹¹² (Figure 3).

Non-covalent functionalization by supramolecular interactions including, π - π stacking, hydrogen bonding, and van der Waals force is another strategy for the modification of graphene and its derivatives. While this approach preserved the π -conjugation and the electronic properties of graphene-based materials, it is unstable and functional groups can be detached upon changes in the environmental conditions.^{107,108}

In the past several years, various types of graphene-polymer platforms have been developed and investigated as nanocarriers for therapeutic agents. Poly(ethylene glycol) (PEG),^{43,113–115} polyethylenimine (PEI),^{116,117} chitosan,^{118,119} and hyaluronic acid (HA)^{120,121} are

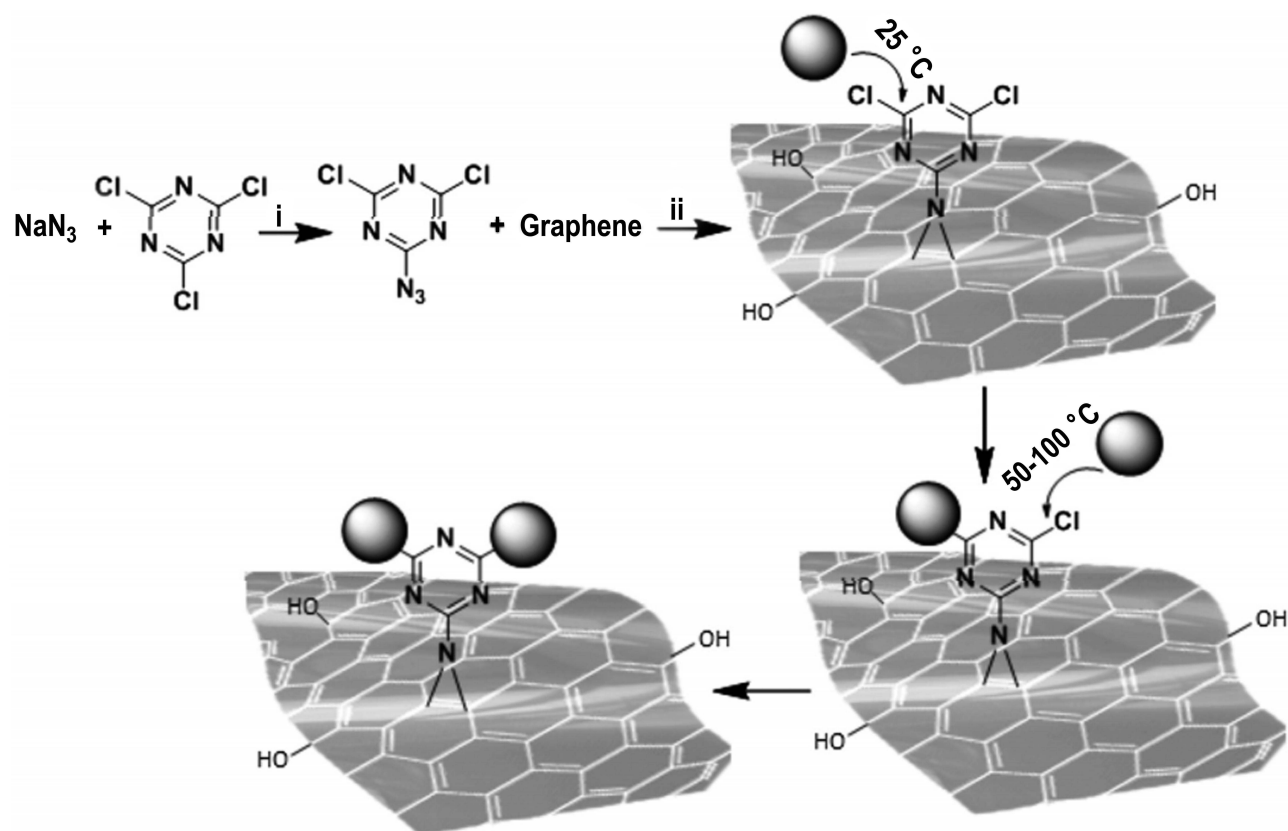


Figure 3 The controlled functionalization of nanographene sheets through nitrene [2+1] cycloaddition reaction at ambient conditions.

Notes: The nucleophilic substitution of chlorine atoms in triazine groups with different polymers and (macro)molecules results in new platforms with defined structures. Reproduced with permission from Gholami MF, Lauster D, Ludwig K, et al. Functionalized graphene as extracellular matrix mimics: toward well-defined 2D nanomaterials for multivalent virus interactions. *Adv Funct Mater.* 2017;27:1606477.¹¹² Copyright 2017, Advanced Functional Materials.

common polymers that are employed for surface functionalization of graphene derivatives. Dendrimers and hyperbranched polymers, including polyamidoamine^{100,122} and polyglycerol^{9,33,100,123} are other types of polymeric systems that are commonly used in this field. Polymers significantly improve the physicochemical properties, solubility, stability, biocompatibility, and drug loading capacity of graphene.

Graphene-Polymer Platforms in Drug Delivery

Cancer is a major cause of death worldwide and prevention or therapy of this disease is one of the biggest health challenges nowadays. Chemotherapy has been used extensively to treat many types of cancer; however, it is limited by different factors including multidrug resistance, systemic toxicity, immunogenicity, and bioavailability. These limitations could be overcome by drug delivery systems.^{124–126}

Among drug delivery systems and breakthroughs, graphene and its derivatives have been abundantly used for a wide range of biomedical applications owing to their sheet-like structure, high specific surface area, and ease of functionalization.^{99,127,128} Due to the availability of different functionalization strategies and taking advantage of the multifunctionality of graphene and its derivatives, various drug delivery systems with controllable biological properties can be prepared. Functionalization of graphene derivatives with various polymers could potentially improve their reactivity, biocompatibility, circulation times in vivo and anticancer capacity. Graphene-polymer platforms with high drug loading capacity have opened up new opportunities in the development of novel drug delivery systems for various biomedical applications, where conventional graphene and polymer alone cannot meet all requirements.^{32,129–131}

Functionalization of graphene and its derivatives with PEG have been extensively used for the construction of anticancer drug delivery systems.¹¹³ Liu et al initially

reported PEG-decorated GO as a nanocarrier to effectively deliver anticancer drugs. They exploited non-covalent interactions to load anticancer hydrophobic drugs and found that the combination of PEG with graphene-based materials can effectively improve biocompatibility, cellular uptake, bioavailability, physiological stability, therapeutic efficacy, and circulation time of drugs in bloodstream.¹³² On the other hand, PEGylation of graphene reduces aggregates of graphene in RES organs (lungs, liver, spleen, and kidney) as well as its retention and toxicity. Similarly, in another report, 6-armed PEG-functionalized graphene oxide-based nanocarrier has been reported to deliver anticancer drugs such as oridonin and methotrexate (MTX).¹³³ Synthesis of PEG-grafted GO and loading of drugs has been performed via amidation and π - π stacking, respectively. This complex (oridonin or MTX@GO-PEG) exhibited higher cellular uptake and anticancer activity against CAL27 tumor cell in comparison with free drugs. PEGylated graphene has also been developed as dual-drug (DOX and platinum) delivery system with a higher efficiency than the single-drug system.¹¹³ The results of these studies showed that the combination of drugs efficiently overcomes the cancer drug resistance and improves their anti-cancer effect. This drug delivery system demonstrated less toxicity and damage to normal cells compared to DOX and platinum-free drugs. Interactions of PEGylated graphene with drugs have been adjustable by polymer chain length.^{134,135} In another study, PEGylation of GO using PEG copolymer conjugated to multiple pyrenes increased percentage of PEG on GO surface and simultaneously reduce GO to rGO. In-vitro assays of this study revealed that graphene with PEG content higher than 75% and longer PEG chain showed better physicochemical properties than their analogs with shorter PEG chains.¹³⁴ The combination of PEG with other polymers such as hyaluronic acid, polyethyleneimine, and chitosan have also been intensively investigated in order to improve therapeutic effects of graphene-drug platforms.^{34–38,136}

PEI a cationic polymer is another type of widely explored polymers for the surface modification of graphene-based materials.^{116,137,138} It was found that bare PEI with high molecular weight induced high cytotoxicity due to high cellular uptake and low biodegradability, while its hybridization with carbon materials resulted in a low cytotoxicity. Commonly, PEI is able to form a complex with graphene derivatives via electrostatic interactions and amination methods. PEI-graphene are cationic platforms

with multiple advantages including high hydrophilicity, biocompatibility, strong binding to nucleic acids, effective cell uptake, and thermal stability. We report that co-delivery of therapeutic genes and chemotherapy downregulates tumor cell resistance to anticancer drugs and overcome multidrug resistance (MDR).^{139,140} PEI-conjugated graphene has been developed for co-delivery of DOX drug and p53 tumor suppressor gene in order to inhibit HeLa cell growth. Owing to presence of PEI cationic polymer and synergistic effect of drug and gene, DOX/GO-PEI/p53 complex has been efficiently internalized into HeLa cells via endocytosis and has exhibited higher growth inhibition than the single drug/gene delivery system.¹⁴¹ In 2019, Mallick et al developed an interesting polymer-graphene platform based on self-assembled PEI covered graphene oxide nanoparticle (PEI-GTC-NP) for codelivery of cisplatin and topotecan into mitochondria. This platform is able to target drugs into mitochondria of cancer cells effectively. Reactive oxygen species (ROS) were generated at specific sites in mitochondria, which in turn led to apoptosis of cancer cells (Figure 4).¹¹⁶ Topotecan have been loaded on GO by π - π stacking to visualize nanomaterial in cancer cell's mitochondria by fluorescence emission. Cisplatin was also applied as chemotherapy medication to treat cervical cancer. Localization of PEI-GTC-NPs into cancer cell resulted in mitochondrial membrane perforation. MTT assay indicated that the half maximal inhibitory concentration (IC_{50}) for nanoparticles in the absence of PEI (GTC-NPs) is higher than PEI-GTC-NPs. This nanoparticle with positive surface charge and suitable size has been able to penetrate into mitochondria of cancer cells specifically and has shown good potential for treatment of cancer.

Natural biopolymers owing to their low toxicity, biodegradability, renewability, environmental sensitivity, and biocompatibility are also promising materials to improve the biological properties of graphene-based materials.^{142–145} Chitosan with anticancer activity and as a pH sensitive polymer has been widely employed in the synthesis of polymer-graphene hybrids.^{146–148} The produced multifunctional scaffolds have exhibited high loading capacities and functional binding sites for different types of drugs and targeting ligands.^{147–149} Moreover, graphene-chitosan platforms have been widely studied as a pH-sensitive nanovehicle for the targeted release of drugs into cancer cells. Graphene oxide-chitosan hybrids have been developed by Dhanavel and co-workers for the controlled delivery of 5-Fluorouracil (5-FU) and curcumin (CUR). These systems have been synthesized

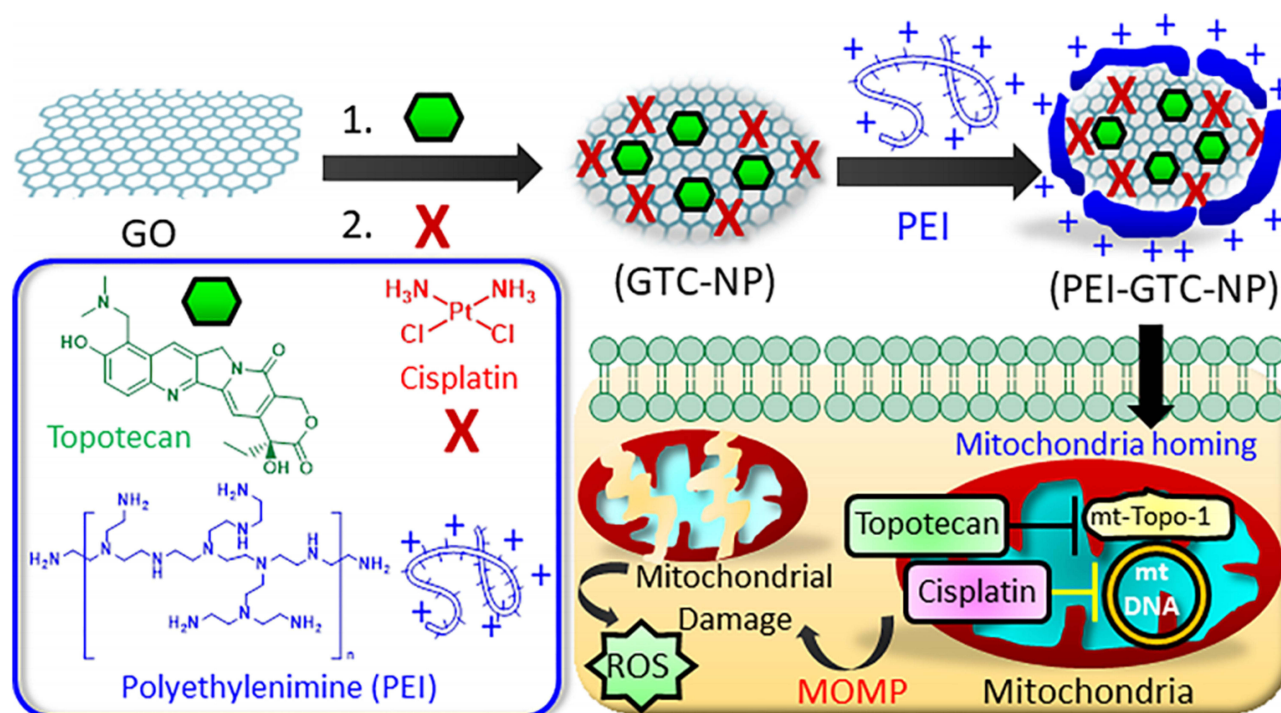


Figure 4 GO with PEI coverage coloaded with cisplatin and topotecan for mitochondria targeting of cancer cells.

Notes: Reproduced with permission from Mallick A, Nandi A, Basu S. Polyethylenimine coated graphene oxide nanoparticles for targeting mitochondria in cancer cells. *ACS Applied Bio Mater.* 2018;2:14–19.¹¹⁶ Copyright 2019, American Chemical Society.

by conjugation of chitosan to GO nanosheet through tripolyphosphate as a crosslinker. Chitosan/reduced graphene oxide (CS/rGO) has displayed pH-dependent drug release behavior. In 2018, Zhao et al reported a chitosan-graphene drug delivery system. It was a core-shell structure containing graphene oxide nanoparticles (GONs) as core and chitosan as surface charge-reversible shells, which was deposited on graphene core via self-assembly (Figure 5).¹⁵⁰ Doxorubicin (DOX) via the non-covalent interactions (π - π stacking) bound to the large π conjugated system of GO and chitosan shells prevents premature secretion of loaded DOX in the medium. Due to the lower pH in cancerous tissue, the coated chitosan was separated, thus accelerating the release of DOX. The charge of these nanomaterials changes from negative at pH= 7.4 in the bloodstream to positive at pH 6.5 in the tumor tissue. Chitosan-graphene platform showed advantages over the usual drug delivery systems including high drug loading capacity (DL), great encapsulation efficiency (EE), long-time circulation in bloodstream, improved cellular uptake, and adjustable controlled release of anticancer therapeutics.

While CS has been widely explored in biomedical and environmental fields, there have been some limitations including insolubility at neutral pH and low rate of degradation.¹⁴⁸ These problems have been overcome by

combining CS with other biopolymers such as cellulose, dextrin, sodium alginate, and so on.^{151–154} Multilayers of biopolymers can be disposed of on graphene through various techniques.^{155,156} In a study, layer-by-layer (LbL) self-assembly technique has been explored for deposition of CS and dextrin on graphene surface.¹⁵⁷ In this process GO has been first modified with CS, followed by conjugation of dextrin (Dex) via electrostatic interaction with oppositely charged polyelectronic. The GO-CS/Dex conjugate has shown high drug loading capacity, physiological stability, and cellular uptake, compared with GO-CS. In another study, CS has been modified by poly(itaconic acid-copolymerized acrylic acid) in order to increase hydrophilic nature of chitosan.⁵³ This new combination has been used for the modification of GO-amine (AGO) with anticancer drug delivery application. CS-GO hybrid has been prepared via electrostatic interactions between chemically modified chitosan as an anionic polyelectrolyte and AGO which acts as a cationic polyelectrolyte.¹¹⁸ Omidi et al,¹¹⁹ Samadi et al,¹⁵⁸ and Lei et al¹⁵⁹ have also verified improvement of physicochemical and biological properties of graphene-chitosan composites through integration with other polymers.

HA is recognized as another important polysaccharide for the improvement of the biological properties of graphene-

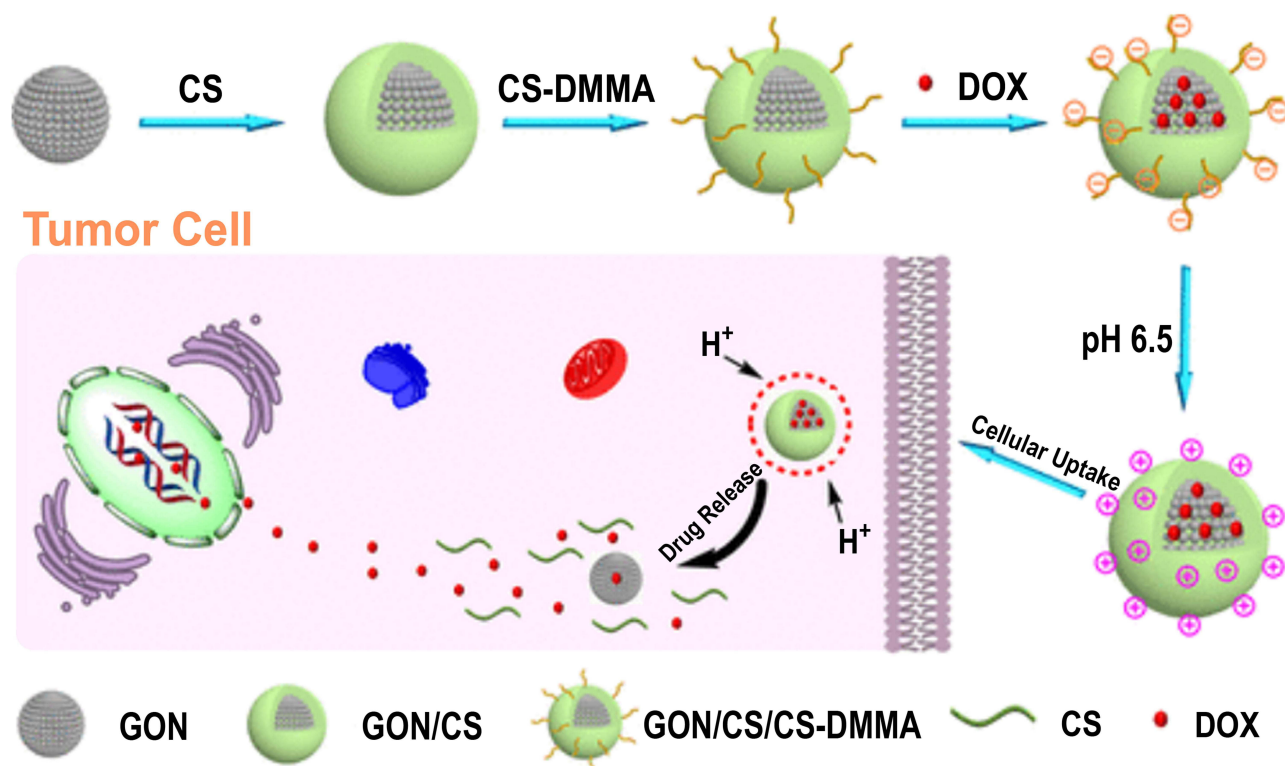


Figure 5 Schematic representation of the synthesis and cellular uptake of GO nanoparticle/chitosan hybrids as drug delivery system.

Notes: This system was sensitive to changes in pH through which intracellular DOX delivery was controlled. Reproduced with permission from Zhao X, Wei Z, Zhao Z, et al. Design and development of graphene oxide nanoparticle/chitosan hybrids showing pH-sensitive surface charge-reversible ability for efficient intracellular doxorubicin delivery. *ACS Appl Mater Interfaces*. 2018;10:6608–6617.¹⁵⁰ Copyright 2018, American Chemical Society.

based materials.^{121,160,161} Biomedical applications of HA and its usage for the production of anticancer drug delivery systems have been widely developed, due to its excellent biocompatibility, biodegradability, as well as strong binding affinity and selective targeting of tumor markers, especially the cluster determinant 44 (CD44) and hyaluronan receptor (HARE).^{162–164} Yin's group has prepared redox-sensitive hyaluronic acid-graphene oxide (HSG) composite and studied its ability to target HA-receptor overexpressing tumors and efficiency of redox-sensitive linkages to localize drugs at the target sites. This system was synthesized by conjugation of hyaluronic acid to GO nanosheet using disulfide linkages (HSG). HSG-DOX displayed accelerated release of DOX in acidic environments. Because high activity of hyaluronidase (HAase) in acidic conditions resulted in degradation of hyaluronic acid chains into small pieces and promoted release of DOX. Owing to high drug-loading capacity, photothermally controlled effects, specific targeting of HA receptors overexpressing tumors, and redox-dependent response, HSG-DOX showed amplified chemotherapeutic outcomes.¹⁶¹

Dendrimers and hyperbranched polymers, especially polyglycerol, are able to effectively improve biological properties

and biofunctionality of graphene sheets, as demonstrated in our previous studies.^{51,100,103,112,131,165–167} Our group implemented a new method for functionalization of graphene-based nanomaterials with hyperbranched polyglycerol.¹⁴ Thermally reduced GO was functionalized by triazine and consequently conjugated with hyperbranched polyglycerol through triazine functional groups. The polyglycerol-covered nanographene with mitochondria-targeted ligands and pH-triggered surface charges showed a high loading capacity and triggered release of DOX drug in the acidic environment (Figure 6). Owing to photothermal properties of nanographene, this multifunctional drug delivery system exhibited accelerated drug release and enhanced chemotherapeutic effect after NIR irradiation. The authors concluded that the high accumulation of smart multifunctional drug delivery system in mitochondria and nucleus, together with photothermal properties, were the reasons for the enhanced chemotherapeutic effects.¹⁴

Targeted Drug Delivery

One of the cancer treatment methods that has received a great deal of attention is targeted delivery in which anti-cancer drugs are transported to the target tissues specifically.

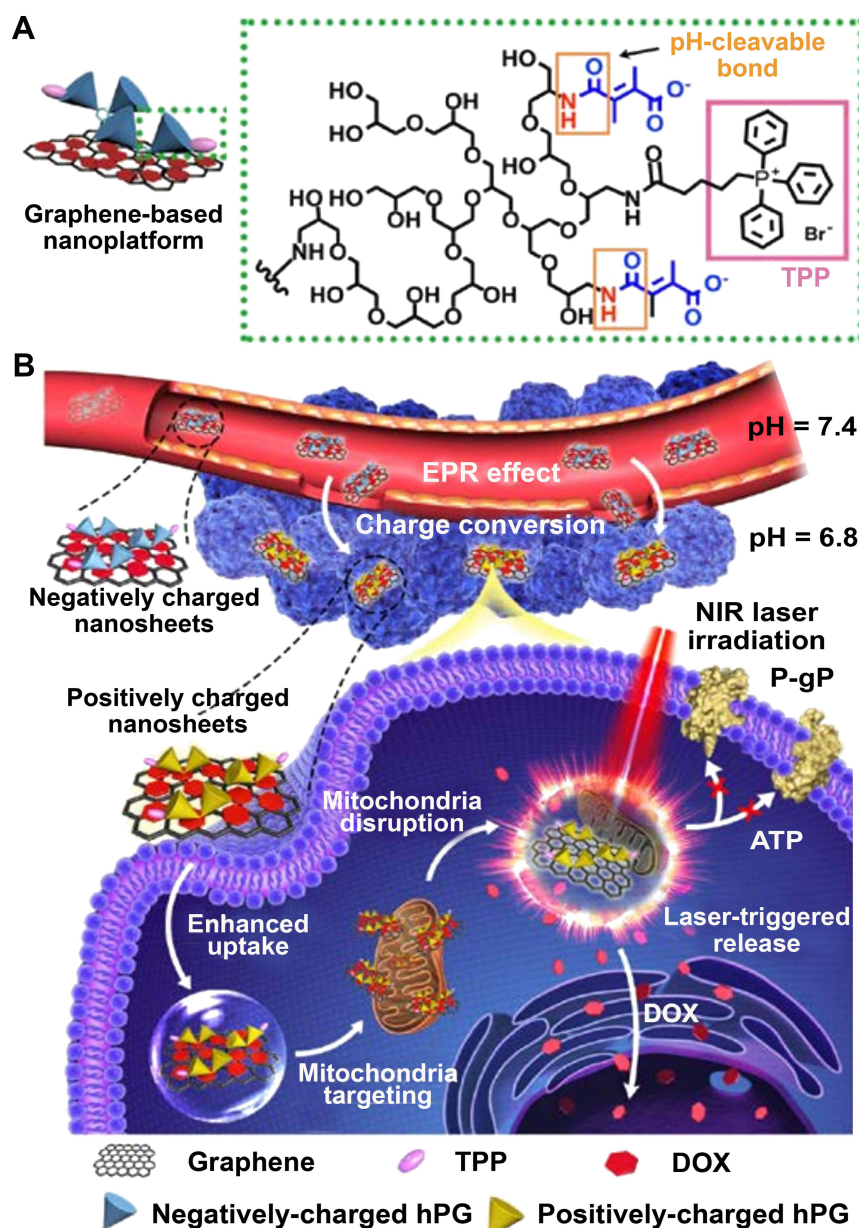


Figure 6 (A) The chemical structure of the polyglycerol-covered nanographene with the mitochondria-targeting ligands and charge conversional functional groups. (B) Multifunctional drug delivery system accumulates in mitochondria by targeting ligands and photothermal properties under NIR laser irradiation result in drug release and good therapeutic efficiency.

Notes: Reproduced with permission from Tu Z, Qiao H, Yan Y, et al. Directed Graphene-based Nanoplatforams for hyperthermia: Overcoming multiple drug resistance. *Angewandte Chemie*. 2018;130:11368–11372.¹⁴ Copyright © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

The method is designed by attaching targeting agents to nanocarriers. Targeting drug delivery systems increases the localization of drugs at tumor sites and diminishes the side effects of chemotherapies. Accordingly, a drug delivery system with targeting ligands and good emission property in visible and infrared has been prepared by loading anticancer drugs onto NGO.¹⁶⁸ Zhang et al have developed GO as a drug delivery system by loading DOX and Camptothecin (CPT) on its surface and conjugation of folic acid to

transport cargos to the tumor sites. FA-conjugated NGO (FA-NGO) was able to target MCF-7 cells, and human breast cancer cells by interaction with FA receptors.⁶⁸ Some superparamagnetic nanocarrier based on attaching Fe₃O₄ as a magnetic nanocarrier on GO and aptamer (APT) as a targeting moiety for MCF-7 cancer cell is prepared and then, paclitaxel (PAC) is loaded as an anti-cancer drug. This system has shown advantages including biocompatibility, pH-responsivity, thermal stability, and high drug

loading capacity over similar nanocarriers.¹⁶⁹ A rGO-based system with the ability to deliver DOX to human breast adenocarcinoma cancer cells (MDA-MB-231) is also reported. In this system, a thiol maleimide containing catechol (dopa-MAL) is assembled on the surface of rGO by π - π stacking. Then, a cancer cell targeting cyclic peptide is attached to dopa-MAL. This nanostructure has shown a high efficiency against MDA-MB-231 cells with an $IC_{50}=58 \mu\text{g mL}^{-1}$ for DOX-loaded rGO/dopa-MAL-c (RGDfC), corresponding to an $IC_{50}=9.9 \mu\text{g mL}^{-1}$ for DOX in the matrix (Figure 7).¹⁷⁰

Hyaluronic acid (HA) is also used to target GO into cancer cells. GO with HA functionality (GO-HA) has been coloaded with DOX and paclitaxel (Ptx) and the obtained drug delivery system (GO-HA-DOX/Ptx) has been used for the efficient incapacitation of cancer cells.¹⁷⁰

Another target drug delivery system is designed based on dopamine (DA) functionalized nGO nanocarrier (DA-nGO). DA improves the delivery of methotrexate (MTX) as an anticancer cargo into target cells.¹⁷¹ Song et al have produced a targeted drug delivery system by loading Fe_3O_4 nanoparticle on the surface of GO and conjugation of lactoferrin (Lf) as a targeting ligand to this platform. The results have shown that this system (Lf@GO@ Fe_3O_4 @DOX) has the ability to deliver drugs into C6 glioma cells effectively.¹⁷²

Conjugation of polymers and targeting ligands onto the surface of graphene derivatives improves the therapeutic

efficiency of these platforms by increasing their loading capacity and decreasing their side effect as well as efficient localization of drug delivery systems in the targeted cells (Figure 8).¹⁷³

Smart Platforms

To overcome the limitations of conventional drug delivery systems such as poor tumor penetration, collateral damage to healthy tissues and uncontrollable drug release, stimuli-responsive drug delivery systems, in which therapeutic agents can be activated by endogenous or exogenous stimuli, have been developed.^{174,175} Graphene-based platforms can be excellent candidates in this regard, since they are sensitive to changes in tumor microenvironment/intracellular signals and response to physical stimuli factors.¹⁷⁵⁻¹⁷⁹

Due to the conversion of glucose to lactose, cancerous tissues are more acidic (pH 6.5–7.2) than both blood and healthy tissues (pH 7.4). Therefore, conjugation of pH-responsive ligands to the platforms results in controlled drug release at tumor sites.¹⁸⁰⁻¹⁸² Accordingly, graphene-polymer platforms with pH sensitive functional groups (COOH, $-NH_2$, and $-SO_3H$) have been widely explored to control the release of various therapeutic agents at tumor sites. An example of such systems has been recently reported by our group.¹⁴ Graphene-based drug delivery systems with charge conversional property was synthesized through functionalizing polyglycerol-covered nanographene sheets with 2,3-dimethylmaleic anhydride (GPTD) (Figure 6). The surface charge of this system

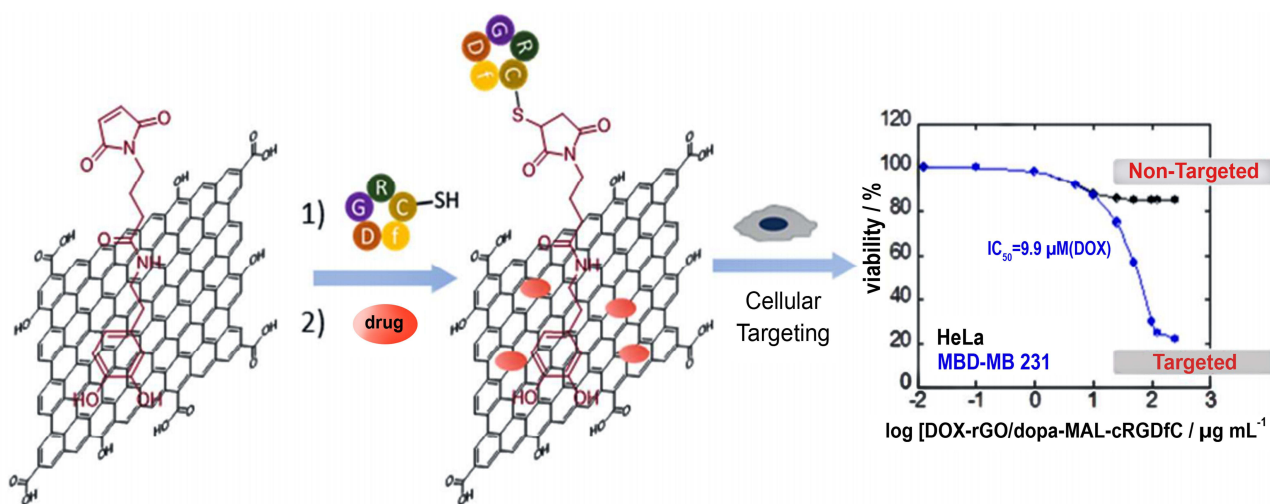


Figure 7 Functionalized rGO with thiol-maleimide containing catechol (dopa-MAL) as a targeted drug delivery system for DOX to destroy human breast adenocarcinoma cancer cells (MDA-MB-231).

Notes: Reproduced with permission from Oz Y, Barras A, Sanyal R, Boukherroub R, Szunerits S, Sanyal A. Functionalization of reduced graphene oxide via thiol-maleimide “click” chemistry: facile fabrication of targeted drug delivery vehicles. *ACS Appl Mater Interfaces*. 2017;9:34194–34203.¹⁷⁰ Copyright © 2017, American Chemical Society.

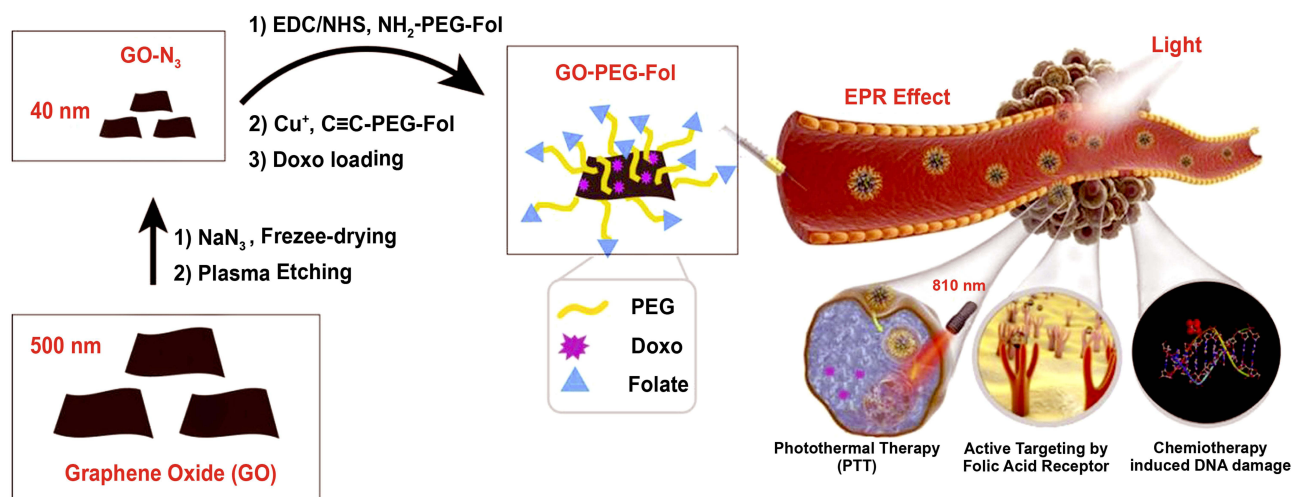


Figure 8 Synthesis of folic acid-functionalized PEGylated GO (GO-PEG-Fol), with small size and narrow size distribution ($\sim 30 \pm 5$ nm), and the ability of efficient converting NIR light into heat.

Notes: GO-PEG-Fol is able to actively target MCF7 and MDA-MB-231 cells. Reprinted from *Materials Science and Engineering: C*, Vol 107, Mauro N, Scialabba C, Agnello S, Cavallaro G, Giammona G, Folic acid-functionalized graphene oxide nanosheets via plasma etching as a platform to combine NIR anticancer phototherapy and targeted drug delivery, Pages No. 110201 Copyright (2020), with permission from Elsevier.¹⁷³

changed from negative at pH 7.4 to positive at pH 6.8. Therefore, it was negatively and positively charged in the blood stream and tumor tissue, respectively. These unique features resulted in a longer-term circulation and increased permeability and retention (EPR) effect of drug delivery systems in body and better localization and controlled release of payloads at tumor sites. This multifunctional drug delivery system showed significant synergistic hyperthermia and chemotherapy effects and showed a high potential in multidrug resistance chemotherapy.¹⁴

Charge conversional graphene platforms are promising nanocarriers for site-specific delivery of drug because of their charge conversion at reduced pH.^{183–185} Our group reported a charge conversional graphene platform to promote cellular uptake of loaded drugs¹⁶⁶ (Figure 9). In this work, polyglycerol containing sulfate and amino groups were conjugated to GO surface, yielding charge-conversional systems. The protonation of hPG amine in the acidic environment accelerated the release of DOX due to repulsion between protonated DOX and hPG amine. On the other hand, due to weakening π - π stacking and hydrophobic interactions between the graphene-polymer platforms and doxorubicin, as well as increasing solubility of drug in acidic conditions, effective release of drug occurred in this condition.¹⁶⁶

It is known that antioxidant concentration (such as GSH) in intracellular microenvironment of tumor tissues (1–10 mM) is often higher than that in normal tissues (20

~ 40 μ M).^{186,187} This feature is important in the development of graphene-based smart systems. Internalized graphene-based platforms with disulfide bonds and redox properties are able to deliver drugs and release them at tumor sites efficiently. DOX has been linked to PEG/PCL copolymer via disulfide bonds and then decorated on graphene surface through hydrophobic interactions. The release of drugs from this system was controlled by redox factors such as GSH.¹⁸⁸

Apart from their ability to provide intracellular responsiveness, graphene platforms also have the capability to respond to some exogenous stimuli¹⁸⁹ including light and magnetic fields, which will be discussed later.

Graphene-Polymer Platforms in Bioimaging

Bioimaging techniques have a broad range of biomedical applications, from diagnosing diseases to investigating body tissues at the cellular level.¹⁹⁰ Previously, these techniques were mostly used in orthopedic diagnosis. Upon development of imaging tools and methods, other techniques such as magnetic resonance imaging (MRI), X-ray computed tomography (X-ray CT), ultrasound, radio wave technology etc. were also used in various medical fields.^{191,192} Bioimaging by both optical microscopy such as laser scanning confocal microscopy (LSCM) and electron microscopy such as liquid cell electron microscopy

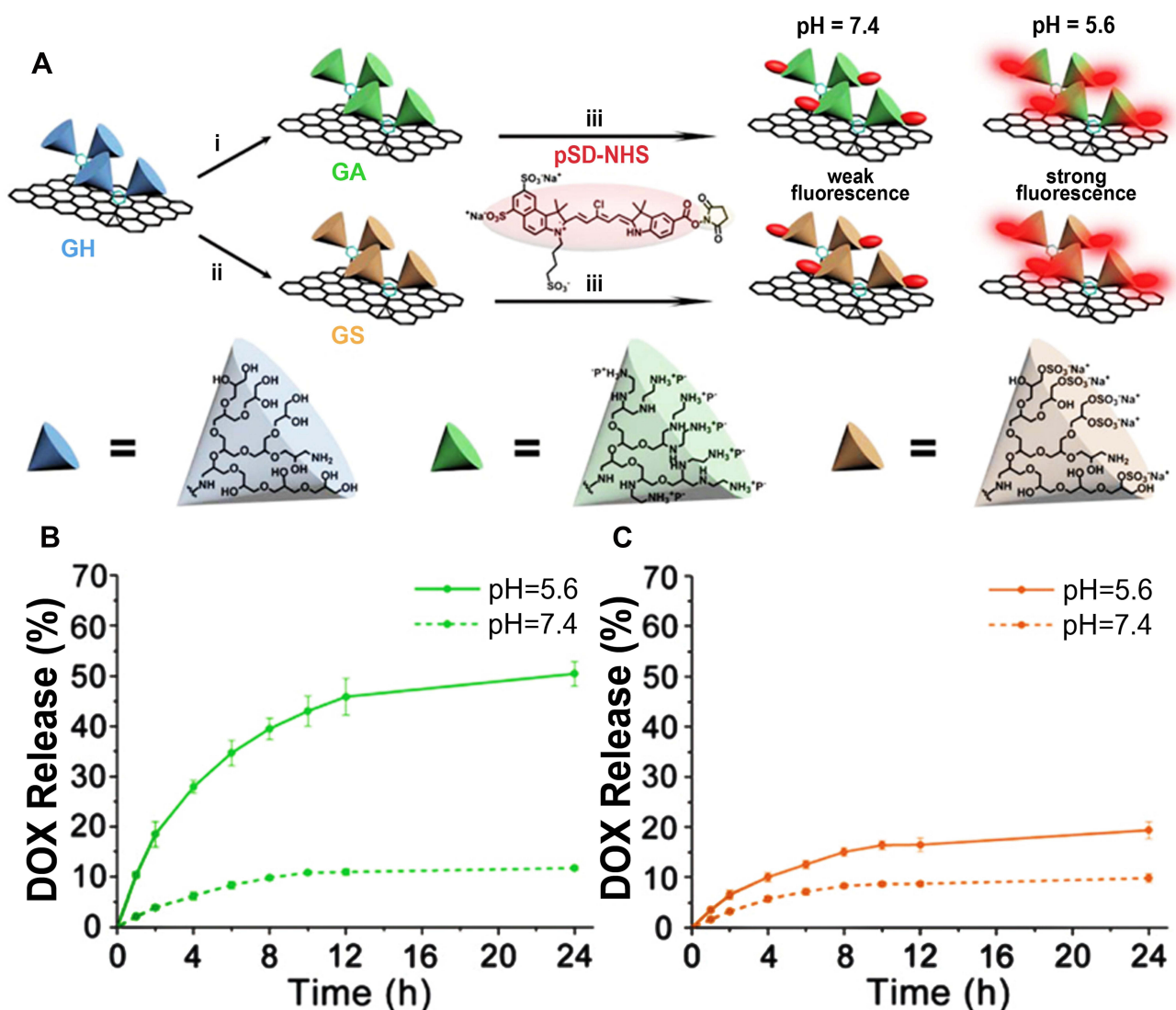


Figure 9 (A) Schematic representation of the synthesis of the polyglycerol amine functionalized graphene sheets (GA), polyglycerol sulfate-functionalized graphene sheets (GS) and conjugation of pH-sensitive dye to the GA and GS (GAD, GSD). Information regarding the synthesis these graphene platforms can be found in ref.¹⁶⁶ In vitro release profile of DOX from the GAD (B) and GSD (C) at 37 °C in various media.

Notes: Reproduced with permission of Royal Society of Chemistry from Tu Z, Wycisk V, Cheng C, Chen W, Adeli M, Haag R. Functionalized graphene sheets for intracellular controlled release of therapeutic agents. *Nanoscale*. 2017;9:18931–18939.¹³¹ Copyright 2017, Advanced Functional Materials; permission conveyed through Copyright Clearance Center, Inc.

(LC-EM) helps to evaluate living tissues with high magnifications.^{193,194} Graphene and its derivatives, due to their interesting optical properties, have shown a high potential in this research field.^{195,196} They can be used for bioimaging in two ways: i) by inherent optical properties such as fluorescence quenching and Raman signals, ii) by loading fluorophores and fluorescent drugs onto their surface.^{197,198}

Graphene due to its zero-bandgap energy is not photoluminescent but graphene derivatives such as GO possess a significant band-gap and show the photoluminescence property.¹⁹⁹ They emit a broad range of fluorescence from

ultra violet (UV) to NIR.²⁰⁰ One of the promising properties of graphene derivatives is their ability to quench most types of fluorescence materials.²⁰¹ These two features make graphene and its derivatives unique platforms for bioimaging. It is shown that charge transfer from the fluorophore to GO is the main reason for the fluorescence quenching and FRET (resonance energy transfer).^{202,203} Functionalization by a variety of materials, such as polymers, proteins, nucleic acids, peptides, and nanoparticles improves the physicochemical properties of graphene-based bioimaging probes.^{204–206} These compounds improve biocompatibility, loading capacity, water

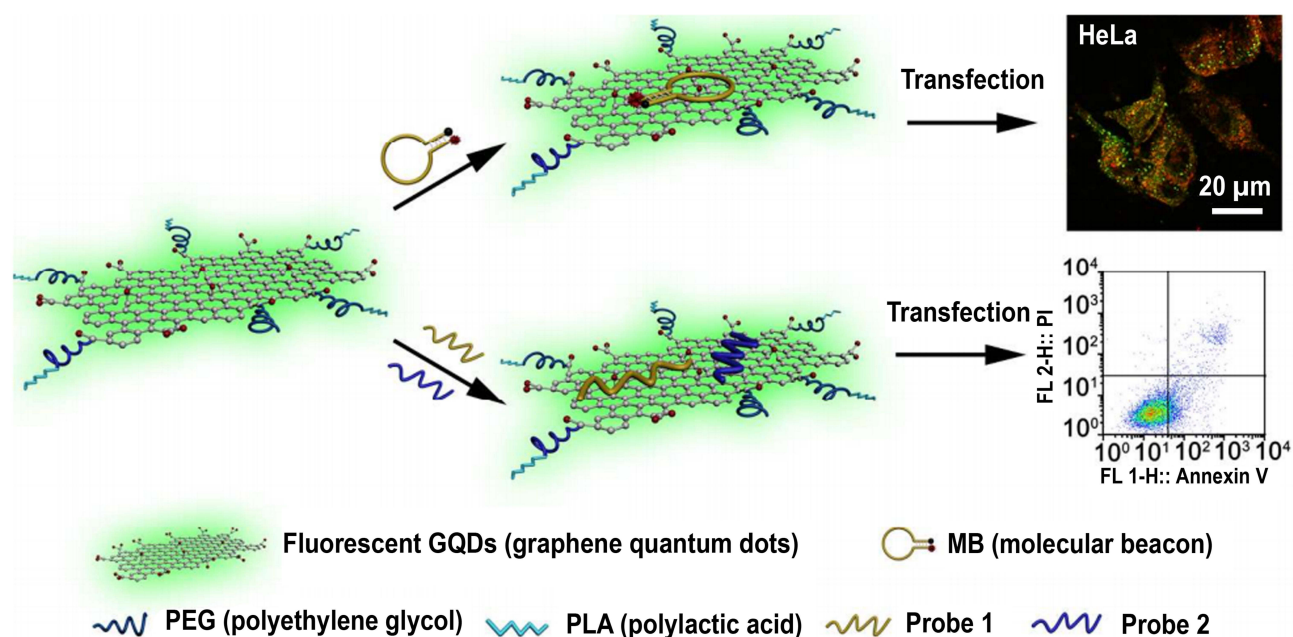


Figure 10 Schematic presentation of the functionalization of QDs by poly(l-lactide)-PEG and their application for cell imaging.

Notes: A strong signal for the functionalized QDs can be seen in HeLa cells. Low toxicity has also been observed for this material. Gene probes were loaded onto the surface of functionalized QDs with π - π interaction. The uptake of probes by HeLa cells can be controlled by the intrinsic photoluminescence of QDs, while the fluorescence of the gene probe applied to identify the target is used to monitor gene regulation. Probe 1 is an inhibitor probe of miRNA-21 and probe 2 is survivin antisense oligodeoxynucleotide. Reproduced with permission from Dong H, Dai W, Ju H, et al. Multifunctional poly (l-lactide)-polyethylene glycol-grafted graphene quantum dots for intracellular microRNA imaging and combined specific-gene-targeting agents delivery for improved therapeutics. *ACS Appl Mater Interfaces*. 2015;7:11015–11023.²⁰⁸ Copyright © 2015, American Chemical Society.

solubility, specificity, or sensitivity of graphene-based platforms and improve their performance as bioimaging tools.²⁰⁷ Dong et al have developed a multifunctional graphene quantum dots-polymer for cell imaging.²⁰⁸ They have used poly(L-lactide) (PLA) and PEG-grafted GQDs for microRNAs imaging analysis (Figure 10). Functionalization of GQDs with these polymers has created a nanocomposite with stable photoluminescence over a wide range of pH, which is extremely important for cell imaging. The results of cell experiments have shown low cytotoxicity and high biocompatibility for this nanocomposite, qualifying it for future bioimaging investigations.

Graphene-Polymer Platforms in Photothermal and Photodynamic Therapy

Graphene and its derivatives are able to absorb NIR laser irradiation and generate heat efficiently. Therefore, they have been widely used as photosensitizing agents for photothermal therapy. This technique in combination with chemotherapy shows synergistic therapeutic effect.^{209–214} Cheon et al have developed a combinational photochemotherapy to enhance therapeutic efficacy of DOX.²¹⁵ The bovine serum albumin (BSA)-functionalized rGO (BSA-rGO) nanosheets have

exhibited a high loading efficiency for DOX and absorbance of NIR light (5.5 W/cm^2 , 808 nm for 300 s). Due to the increased medium temperature at the tumor site under NIR irradiation, drug has been released from BSA-rGO-DOX and low viability of brain tumor cells with reduced chemotherapy side effects has been observed (Figure 11).

Moreover, photochemotherapy of DOX loaded PEGylated GO nanosheets and DOX loaded PEGylated mesoporous carbon nanospheres (MCN) against 4T1 cells is investigated. MCN-PEG/DOX and GO-PEG/DOX have shown less toxicity against 4T1 cells than free DOX. However, when these systems are irradiated by NIR laser (1.0 W/cm^2) for 3 min, an increase in toxicity has been observed. Additionally, due to higher photothermal conversion efficiency (η) and drug release rate, MCN-PEG/DOX has shown higher anticancer effect than DOX/GO-PEG.²¹⁶

A photothermal agent based on folic acid-CS functionalized graphene oxide (FA-CS-GO) with high photostability and tumor-targeting ability has been reported by Jun et al.²¹⁷ The hybridization of GO and CS-FA hinders the aggregation of GO, promotes cellular uptake and light absorption in this platform, and enhances the PTT effects of FA-CS-GO. The surface temperature of tumors treated with FA-CS-GO

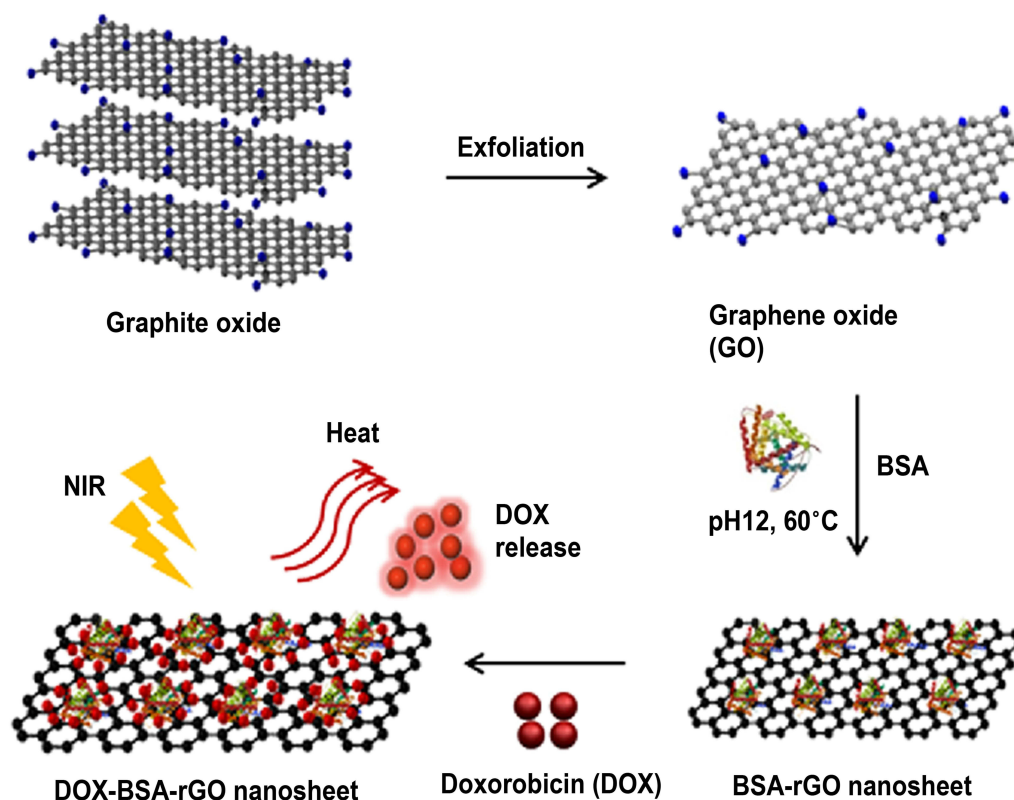


Figure 11 Schematic representation of the synthesis of DOX-BSA-rGO as a light sensitive drug delivery system for chemo-photothermal therapy.

Notes: Albumin is attached onto the surface of exfoliated GO and DOX is loaded onto the surface of BSA-rGO nanosheets. This system has enhanced therapeutic efficacy of DOX drug due to the synergic effect of chemotherapy and photothermal therapy. Reproduced with permission from Cheon YA, Bae JH, Chung BG. Reduced graphene oxide nanosheet for chemo-photothermal therapy. *Langmuir*. 2016;32:2731–2736.²¹⁵ Copyright © 2016, American Chemical Society.

increased to 57.6 °C under laser irradiation (2.0 W/cm²) within 5 min. The viability of tumors treated with FA-CS-GO + laser decreased dramatically, in comparison with laser irradiation in the absence of this platform.

The combination of graphene mediated PTT with immunotherapy has resulted in very promising results for the treatment of metastatic tumors. Fe₃O₄ nanoparticles (FNPs)/rGO/PEG (FNPs/rGO-PEG) nanocomposite are developed as multimodal agents for MRI-guided photothermal-immunotherapy. The combination of FNPs/rGO-PEG nanocomposite with NIR light through reduction of tumor macrophages and photothermal therapy has promoted antitumor immune response.²¹⁸ The surface tumor temperature in FNPs/rGO-PEG-injected mice has reached to 59°C after NIR laser irradiation (805 nm, 1 W cm²).²¹⁸

Photodynamic therapy (PDT) is an efficient method for tumor suppression. In this strategy, reactive oxygen species (ROS) are generated by photosensitizer (PS) upon visible light or laser absorption and destroy tumor cells at target sites.^{219,220} To control ROS generation and enhance cellular

uptake of photosensitizers, reactive agents including porphyrins, chlorins, and dyes are conjugated to graphene platforms.^{219,221,222} Moreover, multimodal therapies combined with PDT such as chemo-photodynamic therapy (PDT), immunotherapies-photodynamic therapy (PDT), and photothermal therapy (PTT)–photodynamic therapy (PDT) have been used for strong antitumor activity. Nanographene oxides (NGOs) with TPE (AIE) photosensitizers were synthesized as powerful tool for multimodal imaging-guided PDT.²²³ NGP-TPE red nanoparticles under 450 nm laser irradiation have shown a significant tumor inhibition both in vitro and in vivo. In another study, the chemo-PDT mediated by photosensitizer indocyanine green (ICG) and folic acid conjugated GO-PEG co-loaded with MTH1 inhibitor (TH287) and DOX has been developed for the targeted therapy of osteosarcoma tumor. MTH1 protein with controlled ROS production has been shown to be a highly synergistic chemo-photodynamic therapy.²²⁴

Furthermore, graphene quantum dots (GQDs) and graphene oxide quantum dots (GOQDs) with the size range of 1.5–5.5 nm have reduced skin cancer (B16F10) cells and

breast cancer (MCF-7) cell viability about 90% when combined with UV irradiation (365 nm) for 5 min.²²⁵

Graphene-Polymer Hybrids for Gene and Biomolecules Delivery

Some human diseases stem from defective genes. In gene therapy, effective treatments of genetic diseases, nucleic acids, and genetic materials are encapsulated by nanocarriers and delivered to the desired sites in the cell.²²⁶ Gene delivery is a process through which foreign DNA is transferred into target cells to express an exogenous gene.²²⁷ Due to low bioavailability and enzymatic degradation of DNA, it should be delivered to the cells by a suitable carrier. Gene delivery systems are categorized into: viral, non-viral, and oncolytic viral vectors.²²⁸ Viral gene delivery systems are composed of modified viruses which are not able to replicate. The most studied viral vectors for DNA delivery are including adenoviruses (AV), adeno-associated viruses (AAV), retroviruses (RV), lentiviruses (LV), and herpes simplex viruses (HSV). Their analogs for RNA delivery are human foamy virus (HFV), oncoretro-viral vectors, and lenti-viral vectors.²²⁹ Another type of gene delivery system is oncolytic viral vectors that represent an ideal platform for gene delivery. These viruses can occur either naturally or can be engineered as natural viruses in the laboratory.²³⁰ The first oncolytic virus was approved by the US Food and Drug Administration in 2015.²³¹ In contrast, non-viral vectors are an alternative to virus-based systems, although they have poor transfection efficiency compared to viral vectors. Non-viral vectors, such as polymers, show significantly lower cytotoxicity. They are able to carry large DNA molecules and can be produced cost-effectively in large quantity.^{232,233} These vectors are generally prepared by both chemical and physical methods. Physical methods are usually performed via physical force to increase permeability of the cell membrane. The most important physical methods are microinjection, electroporation, ultrasound, and gene gun.^{234,235} Chemical methods utilize cationic polymers, cationic lipids, liposomes, and cell-penetrating peptides to deliver genes into cells.^{236–238} Many gene delivery systems have been designed based on cationic polymers, such as PEI.^{239–241} Due to pH buffering capacity, this polymer is one of the most important non-viral polymeric vectors for gene delivery. This sustainable buffering capacity below physiological pH helps condense DNA to escape the endosomal barrier while avoiding lysosomal degradation.²⁴² PEI due to lack of degradability has high toxicity for biomedical applications. To solve this problem, a number of PEI polymers with

biodegradable segments in their backbone have been synthesized. Graphene is also used to design non-viral gene transfer systems. These systems have been proposed as efficient 2D non-viral gene transfer vectors, because their outstanding properties²⁴³ such as facile and versatile chemical functionalization, protection of nucleic acid from enzymatic degradation, and fast cellular uptake result in efficient gene transfection into the target cells.^{244–246} In order to improve the biocompatibility and bio-stability of graphene platforms as well as their ability for the efficient transfection of genes, they have been modified with various polymers and ligands.^{247,248}

There are a large number of studies regarding graphene-polymer platforms for gene delivery application. In 2018, an efficient non-viral gene delivery system was designed using PEI functionalized GO (GO-PEI) loaded with miR-7b by Dou et al which exhibited excellent transfection efficiency with low cytotoxicity.²⁴⁹ The results have shown that GO-PEI could efficiently deliver miR-7b plasmid into bone marrow macrophages. Animal study has demonstrated that preserved preosteoclast by GO-PEI-miR-7b enhanced bone vascularization in ovariectomized mice.

GO-PEI nanostructure has been fabricated as a gene delivery and bioimaging vector by Kim et al.²⁵⁰ Polyethylenimine as a cationic polymer, which has been widely used as a non-viral gene delivery vector, is conjugated to GO surface to improve its interactions with negatively charged genes. Combination of branched PEI and GO results in a hybrid system with enhanced transfection efficiency and photoluminescence property for simultaneous gene delivery and bioimaging (Figure 12). Branched PEI exhibits high transfection efficiency due to enhanced cellular uptake and a high level of endosomal escape. However, due to the high cytotoxicity of high molecular weight branched PEI (HMWBPEI), their use as effective gene delivery systems is limited. In contrast, low molecular weight branched PEI (LMWBPEI) shows poor transfection efficacy, while it has low cytotoxicity. When LMW BPEI is conjugated to GO, it demonstrated good cellular uptake and transfection efficiency with low cytotoxicity. The gene transfection efficiency is evaluated using luciferase gene expression assays. The results exhibited a low gene transfection for the individual pristine GO and LMW BPEI and a high transfection for HMW BPEI and BPEI-GO. High transfection efficiency of BPEI-GO is due to the effect of LMW BPEI conjugated to GO and formation of a stable polyelectrolyte complex with plasmid DNA.

In general, it can be concluded that polymer-functionalized graphene-based carriers have been widely applied in

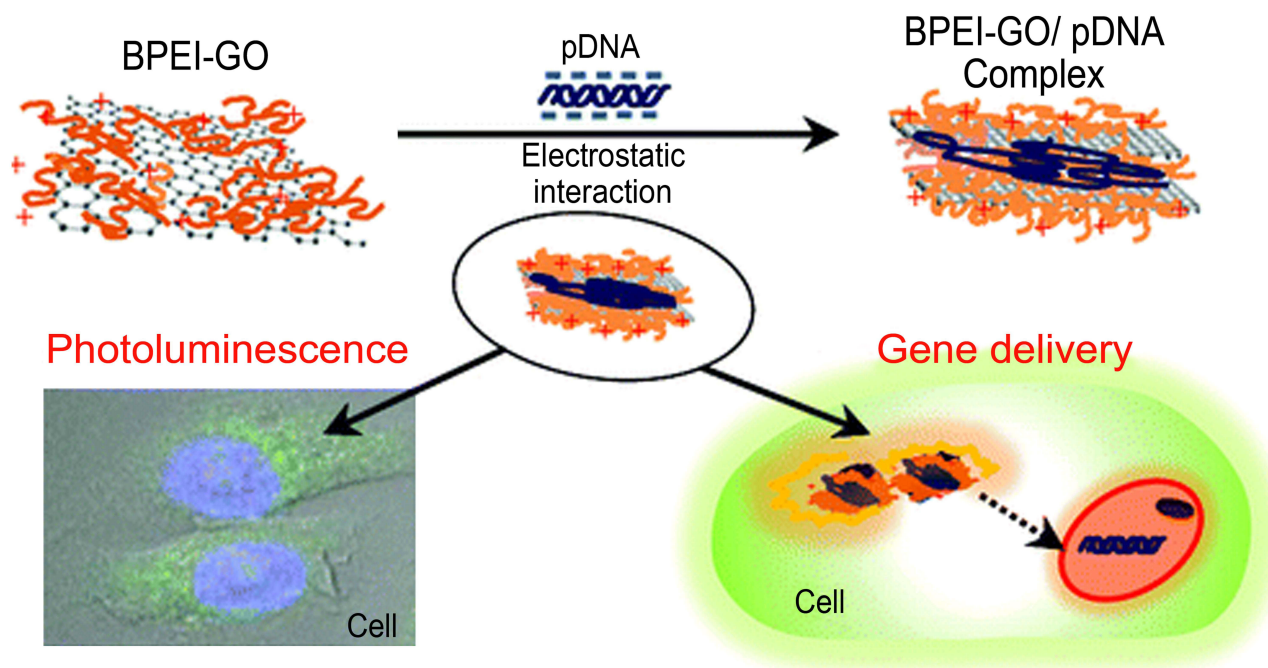


Figure 12 Schematic presentation of fabrication of GO-based gene delivery system through covalent attachment of LMW BPEI to this platform.

Notes: Conjugation of BPEI to GO enhances the photoluminescence properties of GO and improves the cellular uptake and transfection efficiency of the system. Therefore, BPEI-GO can be applied as bioimaging reagent and non-viral gene delivery vector simultaneously. Reproduced with permission from Kim H, Namgung R, Singha K, Oh IK, Kim WJ. Graphene oxide–polyethylenimine nanoconstruct as a gene delivery vector and bioimaging tool. *Bioconjug Chem.* 2011;22:2558–2567.²⁵⁰ Copyright © 2011, American Chemical Society.

gene delivery to treat various diseases including cancer,²⁵¹ osteoporosis,²⁵² and myocardial infarction.²⁵³ A variety of macromolecules including cationic polymers, dendrimers, chitosan, and peptides have been used to modify graphene derivatives for efficient gene transfection.^{254–256}

Graphene-Metal Platforms

Graphene derivatives with high surface area provide ideal platforms to immobilize various metal nanoparticles (MNPs) including Au, Fe, Pt, Gd, Pd, etc. in a sheet-like structure.^{257,258} Graphene/metal hybrids are investigated extensively for cancer therapy and imaging including photoacoustic imaging, PTT, thermomechanical, and surface enhanced Raman signals (SERS). Various approaches including in situ reduction, hydrothermal, electrochemical, physical vapor deposition, ex situ and wrapping MNPs have been reported to synthesize graphene/metal hybrids.²⁵⁹

In this regard, graphene-AuNPs hybrids have attracted a great deal of attention for various medical applications owing to their unique optoelectronic properties.^{260–262} Graphene-AuNPs hybrids are used as biosensors for the detection and diagnosis of cancer cells, due to their prominent surface plasmon resonance (SPR),²⁶³ NIR emission, quenching effect, adsorption of bioreceptors, enzyme mimicking

peroxidase activities, improved electron transfer rate, and conductivity of both graphene and AuNPs.²⁶⁴ Moreover, GO-AuNPs are reported as electrochemical immunosensors for detection of various cancer markers including CEA, CA125, P53, PSA, AFP, and Vascular endothelial growth factor (VEGF) 150.^{265–267} As an example, rGO/thionine/AuNPs hybrid has been used to fabricate immunosensors for the detection of cancer antigen 125 (CA125).²⁶⁸ This fabricated immunosensor has demonstrated low detection limits (0.01 U mL⁻¹), high reliability and accuracy. Moreover, various hybrids of GO-AuNPs are explored for fabrication of genobiosensors for detection of DNA, miRNA-21, and plasma miR-155.^{269–271} On the other hand, graphene/AuNPs are widely used for photothermal therapy (PTT) and photodynamic therapy (PDT) owing to the synergic effect of both components such as strong NIR optical absorption, high NIR light-to-heat conversion, and ROS production.^{272,273}

Magnetic graphene hybrids, particularly graphene/iron oxide, have shown synergistic therapeutic effect.^{274,275} It is demonstrated that graphene/Fe₂O₃ NPs hybrids can serve as MRI contrast and diagnosis agents.^{276,277} Besides efficient diagnostic applications, graphene/Fe₂O₃ NPs hybrids have been investigated as magnetically targeted drug delivery systems with simultaneous photothermal effect.^{278,279} Many

studies have shown that drug-loaded graphene/Fe₂O₃ systems can be effectively accumulated at the targeted tumor site by applying an external magnetic field.^{275,280,281} Moreover, under external magnetic field these systems have exhibited enhanced release of the drug at the targeted tumor site owing to heat generated by the Fe₃O₄ NPs and deformation of the nanocarrier. Based on these outcomes, magnetic graphene hybrids have been supposed as safe and excellent tools for imaging of cancer cells, drug delivery, and hyperthermia.^{279,282–285}

Lanthanide-based nanomaterials, particularly gadolinium, are another class of widely explored metals as contrast agents in MRI.^{286–288} Conjugation of gadolinium onto the surface of graphene-based materials endows new properties and enhances their magnetic, luminescence, and therapeutic properties. Due to its outstanding properties, graphene/GdNPs hybrid is one of the most promising nanomaterials for biomedicine applications including photodynamic/photothermal therapy, biosensing, and bioimaging.^{289,290}

Extensive studies have pointed out that Pd-based nanomaterials are excellent platforms for promoting the chemotherapeutic effects of graphene drug delivery systems. Tumor model studies have shown a high performance of graphene/PdNPs hybrids for diagnosis and treatment of cancers.^{291,292}

Conclusion

This review aims to explain the advantages and recent progresses in graphene-based platforms for different biomedical applications including drug and gene delivery as well as bioimaging. There is a great deal of attention to use graphene and its derivatives in biomedicine. However, an extensive study on the toxicity and health risks of this class of nanomaterials should be performed to diminish the risk of their long-term side effects. To achieve this goal, the key point is to produce a highly defined graphene family in terms of number of layers, surface area, and functionality.

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Disclosure

The authors reported no conflicts of interest for this work.

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