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REVIEW

Carbon Nanomaterials in Biomedicine: Opportunities and Toxicological Concerns

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Abstract: Carbon nanomaterials have garnered significant interest from researchers ac*ROS*s various disciplines, primarily due to their high specific surface area, versatile surface chemical modifications, and exceptional optical properties. Notable carbon nanomaterials include graphene, carbon nanotubes, and carbon quantum dots, each exhibiting distinct potential applications within the biomedical domain. Extensive research over the years has positioned these diverse carbon nanoparticles as promising candidates for drug delivery, cancer diagnosis and therapy, tissue engineering, and biosensing, among other applications. Nonetheless, the issue of toxicity associated with carbon nanomaterials presents a pressing challenge that necessitates resolution. Empirical studies indicate that the size, aggregation state, and surface functionalization of carbon nanotubes can influence the biotoxicity and immunotoxicity of carbon nanoparticles within biological systems, thereby impacting their clinical translation and application. To advance the application and clinical translation of carbon nanomaterials within the biomedical field, this review will focus on carbon quantum dots, carbon nanotubes, graphene nanoparticles, and other carbon-based nanomaterials. It will provide a comprehensive summary of their application progress in the biomedical sector, as well as an analysis of their biotoxicity and immunotoxic responses. This synthesis aims to facilitate the clinical translation and application of carbon nanomaterials.

Keywords: biomedical applications, biotoxicity, biocompatibility, carbon nanomaterials, immunotoxicity

Introduction

With the growing demand for nanotechnology ac*ROS*s various sectors, including medicine,[1] agriculture,[2] and industry,[3] the field has experienced rapid advancements. Among these developments, carbon nanomaterials have garnered significant attention due to their exceptional physical and chemical properties[4–6] This expanding family of nanomaterials includes carbon nanotubes,[7] graphene,[8] fullerenes,[9] and carbon dots,[10] all of which are composed of sp^2hybridized carbon atoms arranged in a hexagonal lattice. This unique structure endows carbon nanomaterials with distinctive optical, electrical, and biological characteristics[11–13] As a result, they find applications in diverse fields, particularly in biomedicine, where they are extensively utilized for biological imaging[14–16] fluorescence sensing[17–19] controlled drug release[20–22] and tumor diagnosis and treatment[23–25] Their excellent biocompatibility and low cytotoxicity underscore their promising potential for future applications[26–33] (Figure 1).

In addition to synthetic carbon-based nanomaterials, naturally occurring carbon nanoparticles, such as those ranging from 1 to 100 nanometers in size, can be generated through the combustion of fuels like methane[34] and propane.[35] These environmentally exposed carbon nanoparticles have been demonstrated to facilitate the production of oxygen free radicals[36,37] induce cellular damage[38,39] and trigger inflammatory responses.[40] Consequently, numerous researchers

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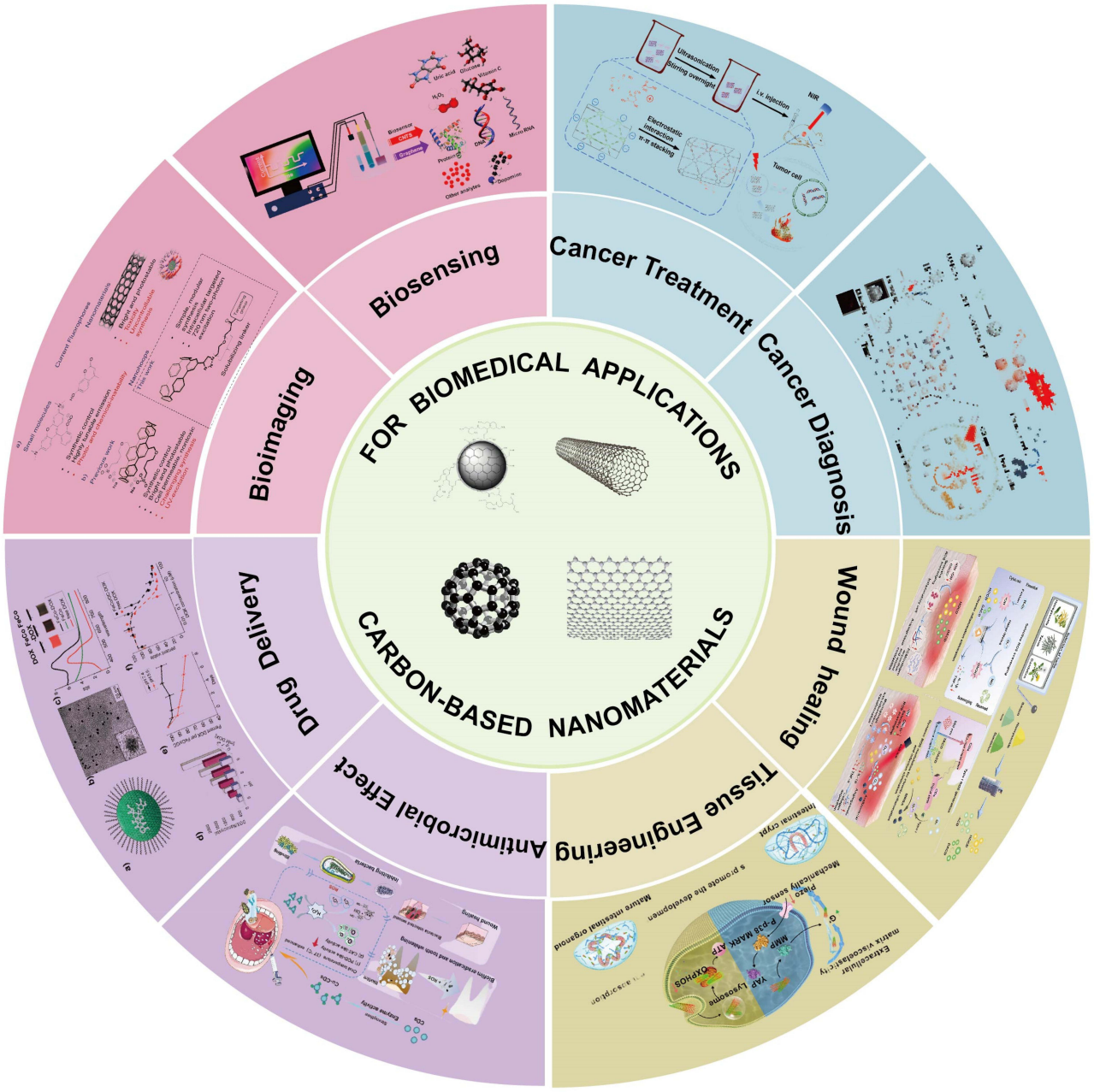


Figure 1 Application of carbon nanomaterials in the biomedical field.

have recognized that prolonged exposure to synthetic carbon nanomaterials may similarly harm the human body, akin to natural nanoparticles. Furthermore, synthetic carbon nanomaterials may exhibit greater toxicity than their natural counterparts. This increased toxicity is attributed to the complex processes, such as surface functional modification, frequently employed during the artificial synthesis of carbon nanomaterials to enhance their performance or biological activity.[41]

During these processes, chemical reagents may persist within carbon nanomaterials and subsequently enter the organism's peripheral circulation. Consequently, conducting comprehensive and systematic research on the biological toxicity of carbon nanomaterials is essential to enhance their application p*ROS*pects in the biomedical field[42–44] The immune system plays a crucial role in maintaining homeostasis within the body by performing several essential functions, including the surveillance, identification, and elimination of foreign pathogens, as well as the removal of

aging or damaged cells and organelles, and cancerous tissue cells. This system is particularly significant in peripheral blood, tissues, and mucous membranes[45,46] When carbon nanomaterials are introduced into a biological context, they inevitably interact with the immune system. These nanomaterials can exert a substantial impact on immune function, occasionally triggering inflammatory responses and heightened immune activity.[47] If nanomaterials exhibit high immunogenicity but insufficient immunoreactivity, they may provoke the aggregation of immune cells, such as B cells, T cells, macrophages, and neutrophils, around the nanomaterials, potentially resulting in the formation of granulomatous lesions.[48] Consequently, it is imperative to assess the immunotoxicity of nanomaterials through in vivo testing.[49–51]

In this paper, the author provides a comprehensive overview of the applications of carbon nanomaterials, including zero-dimensional carbon dots[52,53] one-dimensional carbon nanotubes[54,55] and two-dimensional graphene[56–58] within the field of biomedicine. The discussion encompasses their utilization in biological imaging, fluorescence sensing, drug delivery, tissue engineering, and tumor diagnosis and treatment, among other areas. Notably, three-dimensional carbon nanomaterials have been less extensively studied due to their unique structural characteristics and uncertain biological properties. Despite the promising potential of carbon nanomaterials in biomedicine, their application is constrained by several limitations, including biological toxicity, immunotoxicity, and biodegradability concerns. These challenges currently restrict the use of carbon nanomaterials to the laboratory stage, with limited translation into clinical practice. Consequently, this paper also reviews the existing knowledge on the biological toxicity of carbon nanomaterials, providing a theoretical foundation for future research in this domain.

Application of Different Carbon Nanomaterials in the Biomedical Field

Carbon nanomaterials are frequently categorized based on their dimensionality and the geometric configuration of carbon atoms. Currently, these materials can be broadly classified into four categories: zero-dimensional carbon dots, fullerenes, and nanodiamond particles; one-dimensional carbon nanotubes and carbon nanofibers; two-dimensional graphene; and three-dimensional structures such as fullerene and diamond nanocrystalline films.[59] Despite being composed solely of carbon atoms, each type exhibits distinct molecular architectures. For instance, graphene typically manifests as a single-layer sheet, whereas fullerenes are often spherical or ellipsoidal. These structural variations significantly influence the functional properties of carbon nanomaterials[60,61] As research in this field advances, it has been discovered that carbon nanomaterials exhibit varying proportions of sp^2 and sp^3 hybridized carbon bonds, depending on the method of carbon hybridization. This variability endows carbon nanomaterials with enhanced crystallinity and versatile modification potential, enabling both covalent and non-covalent modifications with other atoms or groups. Such characteristics underpin the diverse biological activities associated with carbon nanomaterials.[62–64]

Application of Carbon Quantum Dots in Biomedicine

Carbon quantum dots (CQDs) are a kind of zero-dimensional carbon nano-material, which has attracted the attention of researchers in many fields because of their good physical and chemical properties. At first, carbon dots were accidentally discovered by Xu et al[65] when purifying single-walled carbon nanotubes by arc discharge. Later, carbon dots were synthesized by soot from candle burning, and carbon dots were separated and purified by polyacrylamide gel electrophoresis. However, the yield of carbon dots obtained by this method is not high. To solve this problem, researchers have developed other advanced synthesis methods and purification and characterization methods to improve the yield and quality of carbon dots (as shown in Table 1).[66–72]

As research on carbon dots continues to advance, scholars have identified several notable characteristics, including excellent optical properties[72,73] low cytotoxicity,[74] high biocompatibility,[75] and favorable biological interactions.[76] Consequently, carbon dots are increasingly being utilized in the biomedical field. Their potential is particularly promising in fluorescence sensing applications. For instance, Zhu et al[77] synthesized nitrogen-doped carbon dots (N-CDs) using polyaminophenylhydrazine as a precursor via the hydrothermal method. These carbon dots can aggregate within HeLa cells and exhibit a red fluorescence in response to pH changes, thereby enabling the detection of intracellular pH variations. Simultaneously, researchers like Raveendran and Kizhakayil[78] synthesized fluorescent carbon dots for HeLa cells using L-glutamic acid and dopamine as precursors through high-temperature heating. However, these carbon dots exhibit green fluorescence upon excitation, responding to changes in cellular pH, which constrains their applicability in

Table 1 Common Synthesis Methods of Carbon Quantum Dots

Precursor	Synthetic Method	Application	Advantages	Disadvantages	Ref.
Resols	Irradiation for 15 min photocatalysis 28 14.9% resols template pyrolysis by functionalized silica colloid spheres	Bioimaging	Uniform particle size and excellent water dispersibility	Too complex preparation process	[66]
L-ascorbic acid	Electrochemical oxidation	Antibacterial	–	–	[67]
Selenocystine	Hydrothermal treatment	Free radical scavenging	Simple; safe and efficient	–	[68]
Curcumin	Reflux at 180 °C for10 hz	Tumor theranostic	Superior bioavailability and permeability	–	[69]
EDTA-2Na PEI	Hydrothermal treatment	Wound healing	–	–	[70]
Thioureapenetrated ZIF	Pyrolysis	Fluorescence sensing	–	–	[71]
Screen-printed carbon electrodes	Electrochemical oxidation	Cell bioimaging and solid-state electrochemiluminescence	–	–	[72]

the biomedical field. This limitation arises because the inherent blue fluorescence of biological tissues may interfere with the excitation of green fluorescence. Additionally, the similarity in wavelengths between blue light and green fluorescence further complicates the fluorescence sensing process.

In their pursuit of novel anti-tumor strategies, Bai et al,[79] including researchers from Yulong Bai's team, utilized lysine, o-phenylenediamine, and sulfuric acid as precursors to synthesize sulfur and nitrogen co-doped carbon dots (S, N-CDs) with red-shifted absorption properties via the hydrothermal method. When excited by near-infrared (NIR) light, these carbon dots exhibit pH-responsive fluorescence specific to lysosomes and tumor tissues. Concurrently, the fluorescent probe demonstrates the ability to target and eradicate tumors through photodynamic therapy while performing sensing functions. Experimental investigations revealed that the oxygen production efficiency is 27%, and the photothermal conversion efficiency reaches 34.4%, surpassing the performance of conventional single nitrogen atom-doped carbon dots.

Due to their excellent biocompatibility, carbon dots are frequently employed by researchers as drug delivery systems in vivo for the treatment of tumors and infectious diseases, in addition to their roles in biological imaging and fluorescence sensing[80–82] *Pseudomonas aeruginosa*, a normal flora on the human body surface, exhibits resistance to most commonly used antibiotics as a result of its prolonged symbiosis with the human host. However, it can proliferate and cause severe infections when the immune system is compromised or nutritional status is poor, making it a challenging nosocomial pathogen. In a study by Jian et al.[83] A nanocomposite (Arg-CQDs/pCur) was synthesized by polymerizing carbon dots derived from arginine (Arg) and curcumin (pCur). The targeted drug delivery platform demonstrates a specific therapeutic effect against *Pseudomonas aeruginosa*, exhibiting superior efficacy compared to curcumin alone. Concurrently, the incorporation of curcumin significantly enhances the biocompatibility of the composite, primarily due to curcumin's pharmacological properties, including anti-inflammatory and antioxidant effects.[84]

In a related study, Zavareh et al[85] synthesized a 5-fluorouracil chitosan carbon dots aptamer (5-FU-CS-CQD-Apt) system. This drug delivery system encapsulates the chemotherapeutic agent 5-fluorouracil within chitosan-carbon dots for the targeted treatment of breast cancer, addressing the challenge of multidrug resistance, which is exacerbated by the prolonged heterogeneous evolution of malignant tumors. The findings indicated a reduction in the *Bcl-2*/*Bax* ratio in *MCF-7* cells, suggesting that the proliferation of breast cancer cells was inhibited following treatment with 5-FU-CS-CQD-Apt. This composite drug delivery system thus demonstrates potential anti-tumor activity[81] (Figure 2).

In conclusion, carbon quantum dots, a category of nanomaterials characterized by a broad array of raw materials and straightforward synthesis and modification techniques, have garnered significant attention due to their exceptional optical properties, favorable biocompatibility, and minimal biotoxicity. The synthesis methodologies are primarily categorized into top-down and bottom-up approaches, encompassing techniques such as electrochemical oxidation, laser ablation, pyrolysis, microwave-assisted, and hydrothermal methods. The variety of synthesis and modification techniques expands the potential applications of carbon quantum dots. For instance, the hydrothermal synthesis method allows for the production of carbon quantum dots doped with various heteroatoms through the reaction of different compounds with

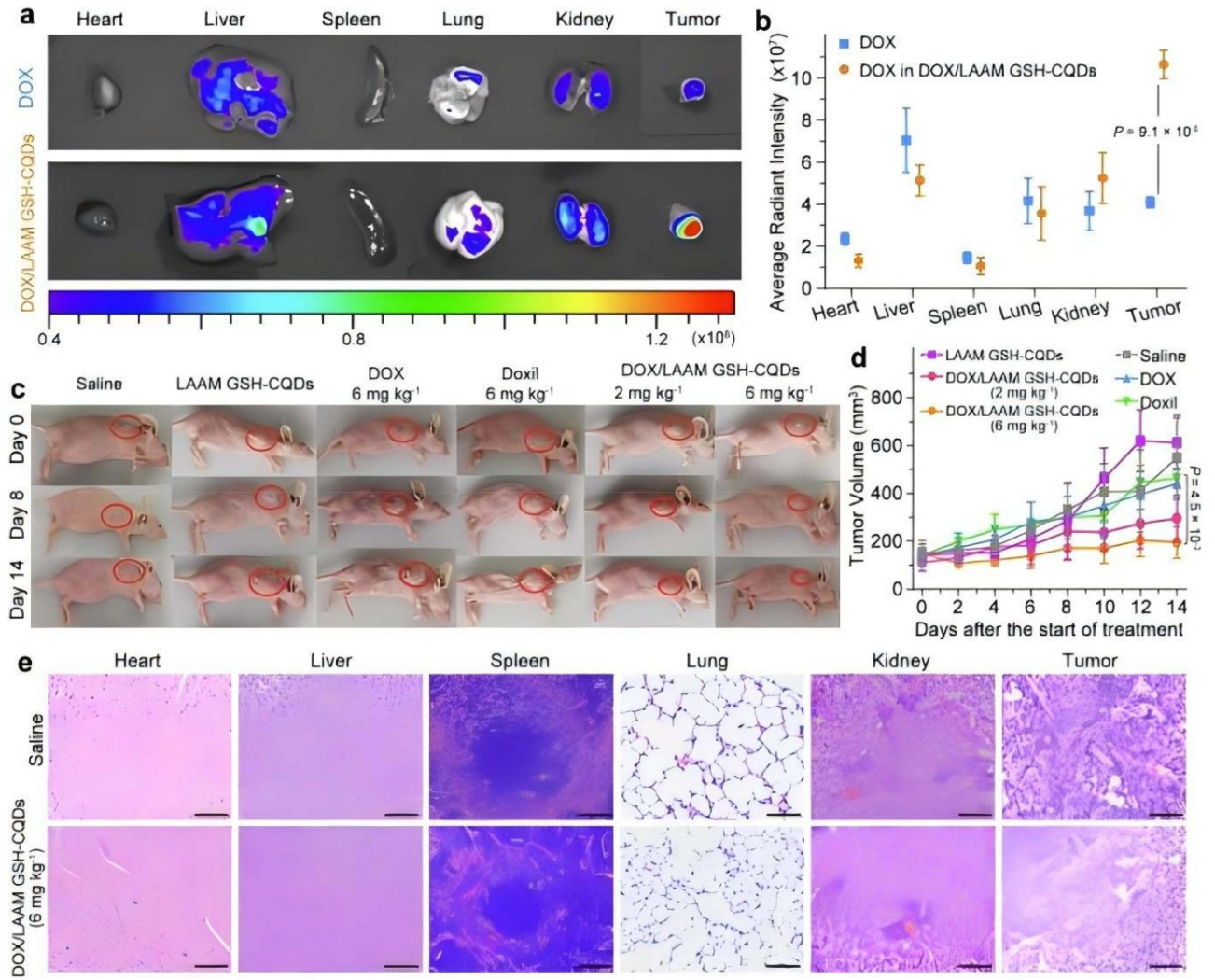


Figure 2 LAAM GSH-CQDs for DOX delivery. (**a**) Fluorescence imaging acquired from the DOX biodistribution in Kunming mice bearing HeLa tumors of major organs and tumor at 7 h post injection of DOX or DOX/LAAM GSH-CQDs. (**b**) Fluorescence intensity determined from the DOX biodistribution in Kunming mice bearing HeLa tumors of major organs and tumor at 7 h post injection of DOX or DOX/LAAM GSHCQDs. Data are expressed as mean ± SD (n = 3 mice). Statistical analysis was performed using two-tailed unpaired Student's t-tests. (**c**) Representative photos of A549-tumor-bearing nude mice after receiving the DOX, Doxil or DOX/LAAM GSHCQDs at a dose equivalent to 6 mg kg−1 DOX, DOX/LAAM GSH-CQDs at a dose equivalent to 2 mg kg−1 DOX treatments, saline, and LAAM GSH-CQDs. (**d**) Changes in tumor volume over time of A549-tumor-bearing nude mice after receiving the DOX, Doxil or DOX/LAAM GSH-CQDs at a dose equivalent to 6 mg kg−1 DOX, DOX/ LAAM GSH-CQDs at a dose equivalent to 2 mg kg−1 DOX treatments, saline, and LAAM GSH-CQDs. Data are expressed as mean ± SD (n = 3 mice). Statistical analysis was performed using two-tailed unpaired Student's t-tests. (**e**) Histological evaluation of tumor and major organs from A549-tumor-bearing nude mice after different treatments. The scale bars represent 50 μm. Reprinted with permission from ref 86. Copyright 2025 Nature.

citric acid, among others. These carbon quantum dots exhibit diverse residue modifications and charge distributions, influencing their biomedical applications. The diversity of these synthesis approaches not only impacts the physico-chemical properties of carbon quantum dots but also determines their potential applications in biomedical fields. For example, nitrogen-doped carbon quantum dots demonstrate remarkable selectivity and sensitivity in cell imaging and iron ion detection.

With the continued advancement of carbon quantum dot nanomaterials, numerous researchers have initiated the synthesis of biomass-derived carbon quantum dots utilizing the active constituents of natural pharmaceuticals as carbon sources. Biomass-derived carbon quantum dots have emerged as a focal point of research, primarily due to their environmentally friendly synthesis processes and cost-effectiveness. These carbon quantum dots, derived from biomass, are highly promising for applications in bioimaging and drug delivery. Furthermore, the methods of synthesis and surface modification of carbon quantum dots significantly influence their utility in cancer therapy. Through functionalization and

doping, carbon quantum dots can facilitate targeted drug delivery and enhance anti-tumor therapeutic efficacy. For instance, the modification of folic acid molecules on a carbon quantum dot nano-delivery platform significantly enhances the accumulation and targeting capabilities of carbon quantum dots in proximity to tumors. Furthermore, the integration of carbon quantum dots with other noble metal nanoparticles, such as gold nanoparticles, exploits the nano-enzyme activity inherent in nanomaterials to facilitate the decomposition of peroxides and the generation of oxygen within the tumor-induced microenvironment. This approach aims to mitigate the inadequate photodynamic therapeutic efficacy resulting from the hypoxic conditions characteristic of the tumor microenvironment. The diverse synthesis and modification techniques available for carbon quantum dots provide a robust foundation for their extensive application in the field of biomedicine. Future research should investigate the impact of various synthesis strategies on the properties of carbon quantum dots to develop nanomaterials with enhanced functionality and broader application potential.

Applications of Carbon Nanotubes in Biomedicine

Carbon nanotubes, encompassing single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs), represent some of the pioneering forms of carbon nanomaterials. As early as 1994, the synthesis of carbon nanotubes via the arc discharge method was documented.[86] Nevertheless, this technique is inadequate for the large-scale industrial production of carbon nanotubes.[87] Consequently, alternative synthesis methods, such as laser ablation and chemical vapor deposition, have been developed. These methods facilitate large-scale production and yield carbon nanotubes with enhanced functional properties compared to those produced by the arc discharge method[88,89] Extensive research on synthesized carbon nanotubes has revealed their exceptional mechanical flexibility and electrical conductivity, rendering them suitable for application in numerous critical industries and technologies. In comparison to zero-dimensional carbon nanomaterials, such as carbon quantum dots, carbon nanotubes exhibit superior potential for industrialization and commercialization.[90–92]

With the progression of modern physics, molecular electronics has experienced significant development and maturation. Molecular electronic devices, characterized by their high sensitivity, rapid response, and low detection thresholds, have been utilized ac*ROS*s various research domains.[93] Long-term investigations have revealed that single-walled carbon nanotubes (SWCNTs) do not undergo significant photobleaching in the near-infrared region when dispersed in aqueous solvents. Furthermore, they do not exhibit increased scattering, absorption, or autofluorescence.[94] These findings indicate that SWCNTs possess superior optical imaging and sensing capabilities within the near-infrared spectrum. Moreover, the selection of excitation light from the near-infrared region effectively mitigates the phototoxicity commonly associated with visible light fluorescence excitation. Consequently, carbon nanotubes exhibit a level of biocompatibility that is often absent in other fluorescent sensing materials, rendering them an excellent candidate for applications in fluorescent sensing and biological imaging[95–97] Subsequent studies have demonstrated that the integration of carbon nanotubes into molecular electronic devices significantly reduces overpotential and enhances sensitivity.[98]

Based on these findings, carbon nanotube composite devices have been utilized for the detection of biomolecules, including proteins,[99] DNA,[100] RNA, and cytokines.[101] For instance, Huang et al[102] synthesized magnetized carbon nanotubes using Fe_3O_4 and multi-walled carbon nanotubes (MWCNTs) as raw materials. Concurrently, they immobilized the antibody for carbohydrate antigen *CA19-9* onto the magnetized carbon nanotubes. This composite detection system was subsequently integrated with a flow-measuring biosensor to detect *CA19-9* protein in blood samples. The results of the study demonstrated that the detection threshold of the magnetized carbon nanotube system for *CA19-9* was 30 U/mL, which is below the established cutoff value of 37 U/mL for *CA19-9*. This indicates that carbon nanotubes exhibit significant efficacy in the detection of bioactive substances. Monitoring the content of *CA19-9* in the body will help to prompt the occurrence of cancer in the digestive system of the body, because after the atypical proliferation of some cells, especially gastrointestinal cells, Dedifferentiation will occur, and the expression of *CA19-9* will increase obviously, so it is quite necessary to develop a new biosensor with higher sensitivity for *CA19−9*.[103]

Furthermore, beyond their applications in molecular electronics, carbon nanotubes present significant potential in the field of tissue engineering. Tissue engineering, a subset of regenerative medicine, aims to construct biocompatible cell scaffolds that promote the rapid integration of extracellular matrix components, such as collagen, fibronectin, and proteoglycans, during cellular tissue regeneration, thereby establishing a cellular framework[104–106] Tissue engineering has attracted considerable

attention and anticipation from researchers as an emerging field due to its potential to create nanoscale structures that emulate natural tissues, thereby addressing specific intrinsic fissure injuries within the body.[107] For instance, Assali et al.[108] Employed polyethylene glycol as a molecular linker to noncovalently modify carbon nanotubes and pyrene groups, resulting in the formation of functionalized carbon nanotubes (f-CNTs). These f-CNTs were applied to damaged areas of the body, significantly enhancing the conductivity of collagen-based constructs in *3T3* cells. This finding suggests that the noncovalently modified carbon nanotube material holds substantial promise for applications in cytoskeleton and tissue regeneration. Similarly, researchers such as Xifeng Liu[109] utilized ultrasonic treatment to synthesize water-soluble single-stranded deoxyribonucleic acid (ssDNA) and carbon nanotube composites (ssDNA@CNT). These synthesized nanocomposites were then coated onto aminated poly(propylene fumarate) (PPF) scaffolds for potential use in bone injury and regeneration. The carbon nanotube coating on the scaffold can not only provide more adhesion sites for osteoblasts to promote cell proliferation, but also promote cell proliferation, alkaline phosphatase (*ALP*) and bone bridge by using the good conductivity of carbon nanotubes[110] (Figure 3).

Applications of Graphene in Biomedicine

Graphene nanomaterials represent one of the most fundamental structures among carbon nanomaterials and are currently the thinnest known nanomaterials. This is primarily attributed to graphene's planar, sheet-like architecture, which is composed of single-atom-thick, sp2-bonded carbon atoms. This distinctive atomic configuration imparts graphene with exceptional optoelectronic properties, high thermal conductivity, and remarkable hydrophobicity[111–114] These singular physical and chemical characteristics have facilitated the utilization of graphene in diverse fields, including optoelectronic materials, energy chemistry, biomedical applications, and tissue engineering. Nevertheless, the structural attributes of graphene also pose certain challenges, such as its limited ability to form strong bonds with other materials due to the small size of its surface functional groups, and its propensity to aggregate rather than disperse, which is a consequence of its unique π-electron system.[115] In comparison to other carbon nanomaterials, graphene demonstrates lower cellular permeability and drug-loading capacity relative to smaller-sized carbon quantum dots, which possess higher specific surface areas. Additionally, graphene exhibits reduced adhesion at cellular sites when contrasted with carbon nanotubes.

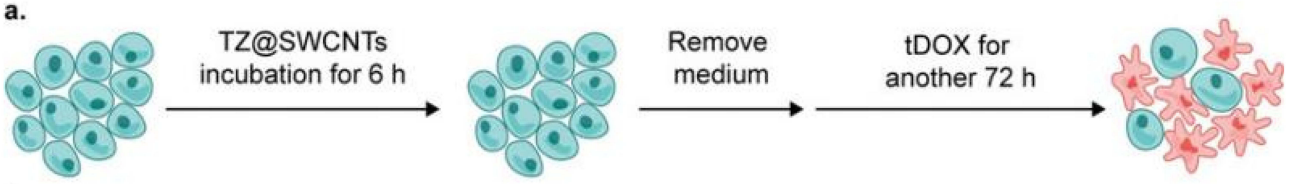
Nevertheless, graphene materials offer superior application potential and conversion performance compared to both carbon quantum dots and carbon nanotubes. The inherent limitations of graphene can be addressed through surface functionalization modifications[116–118] For instance, graphene-peptide nanocomposites have been employed as biosensors for detecting biomarkers or chemical markers within the body. Researchers, including Kikuo Komori,[119] have immobilized heme peptides on the surface of a graphene-carbon nanotube composite (CNTs/G), creating CNTs/G@HP for the amperometric sensing of hydrogen peroxide. The findings revealed that the micro-pores within the CNTs/G film facilitate the diffusion of hydrogen peroxide to the modified HP, thereby enhancing the catalytic cathodic current. Additionally, the catalytic current for the reduction of hydrogen peroxide on the CNTs/G@HP electrode is positively correlated with the surface coverage of HP.

The increasing incidence and mortality rates of oncological diseases, attributed to heightened life stress and an accelerated pace of life, pose a significant threat to public health.[120] Graphene materials, with their inherent photothermal properties, offer potential for tumor treatment through photothermal effects. For example, Yu et al[121] have developed a nanocomposite by immobilizing antiarrhythmic peptide 10 (AAP10) on polydopamine-functionalized reduced graphene oxide, resulting in AAP10-pDA/rGO. This nanocomposite facilitates photothermal damage in *MCF-7* tumor-bearing mice when stimulated by near-infrared light, thereby aiming to provide targeted therapy for breast cancer[81] (Figure 4).

Current Status and Difficulties of Preclinical Research on Carbon Nanomaterials

Following extensive exploration by researchers ac*ROS*s various disciplines, numerous application pathways and methodologies for carbon nanomaterials within the biomedical field have been progressively developed. This advancement not only significantly broadens the application p*ROS*pects and potential of carbon nanomaterials but also infuses new vitality into the field of biomedicine.[122] As an emerging class of biological nanomaterials, carbon dots have garnered considerable attention due to their favorable biocompatibility and exceptional optical properties. A substantial number of preclinical studies have been conducted by researchers to investigate the translational applications of carbon quantum

a.



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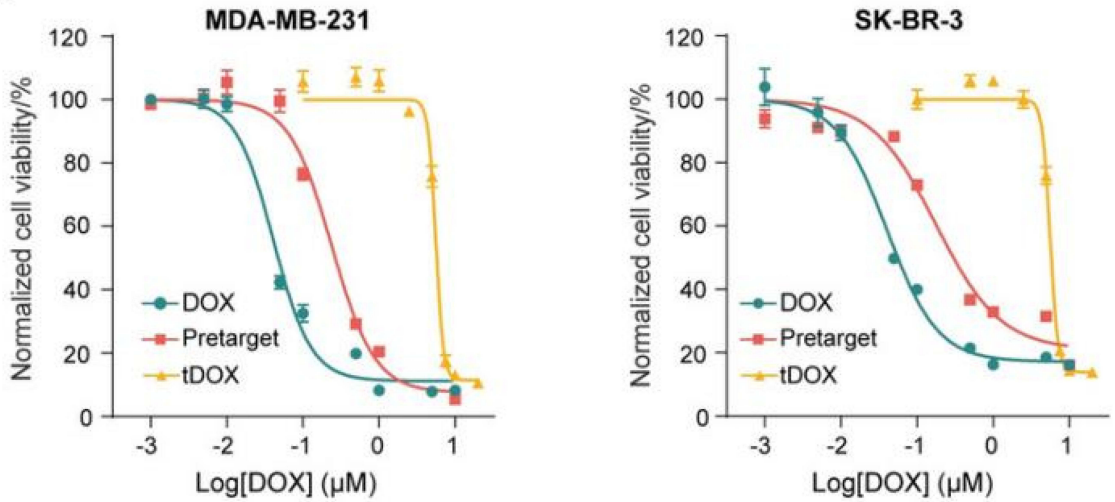

c.

EC50 / μM	DOX	Pretarget	tDOX
MDA-MB-231	0.041 ± 0.007	0.24 ± 0.06	5.59 ± 0.34
SK-BR-3	0.060 ± 0.010	0.23 ± 0.09	6.05 ± 0.48

d.

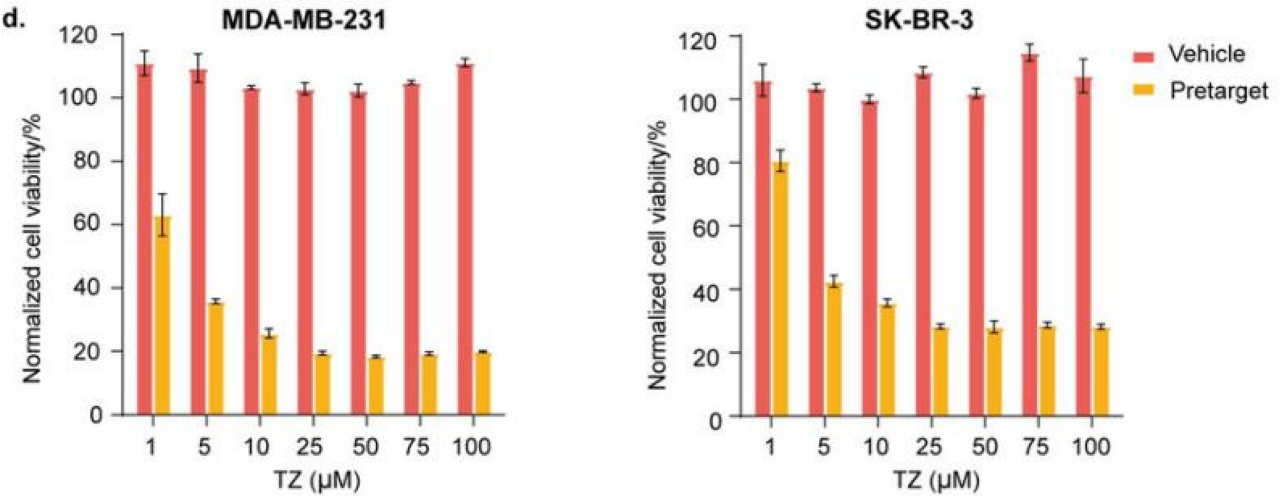

Figure 3 Pretargeted doxorubicin delivery in vitro. (**a**) Flowchart depicting TZ@SWCNTs pretargeting and subsequential tDOX treatment. (**b**) Cytotoxicity of DOX, prodrug tDOX and pretargeted strategy on MDA-MB-231 andSK-BR-3 breast cancer cells (n=3; error bars represent the STD). Blue and yellow lines indicate cells treated with DOX or tDOX of different concentration for 72 h. For Orange lines, cells were pretreated with TZ@SWCNTs (20 μM) for 6 h before replacing the media to complete medium with various concentration of tDOX for another 72 h. (**c**) Calculated EC50 (half-maximal effective concentration) values for DOX, prodrug tDOX and pretargeted strategy against MDA-MB-231 and SK-BR-3 breast cancer cells. (**d**) Cytotoxicity of the vehicle (TZ@SWCNTs, black bar) and pretargeted strategy (grey bar) on MDA-MB-231 and SK-BR-3 breast cancer cells (n=3; error bars represent the STD). Reprinted with permission from ref 111. Copyright 2020 John Wiley and Sons.

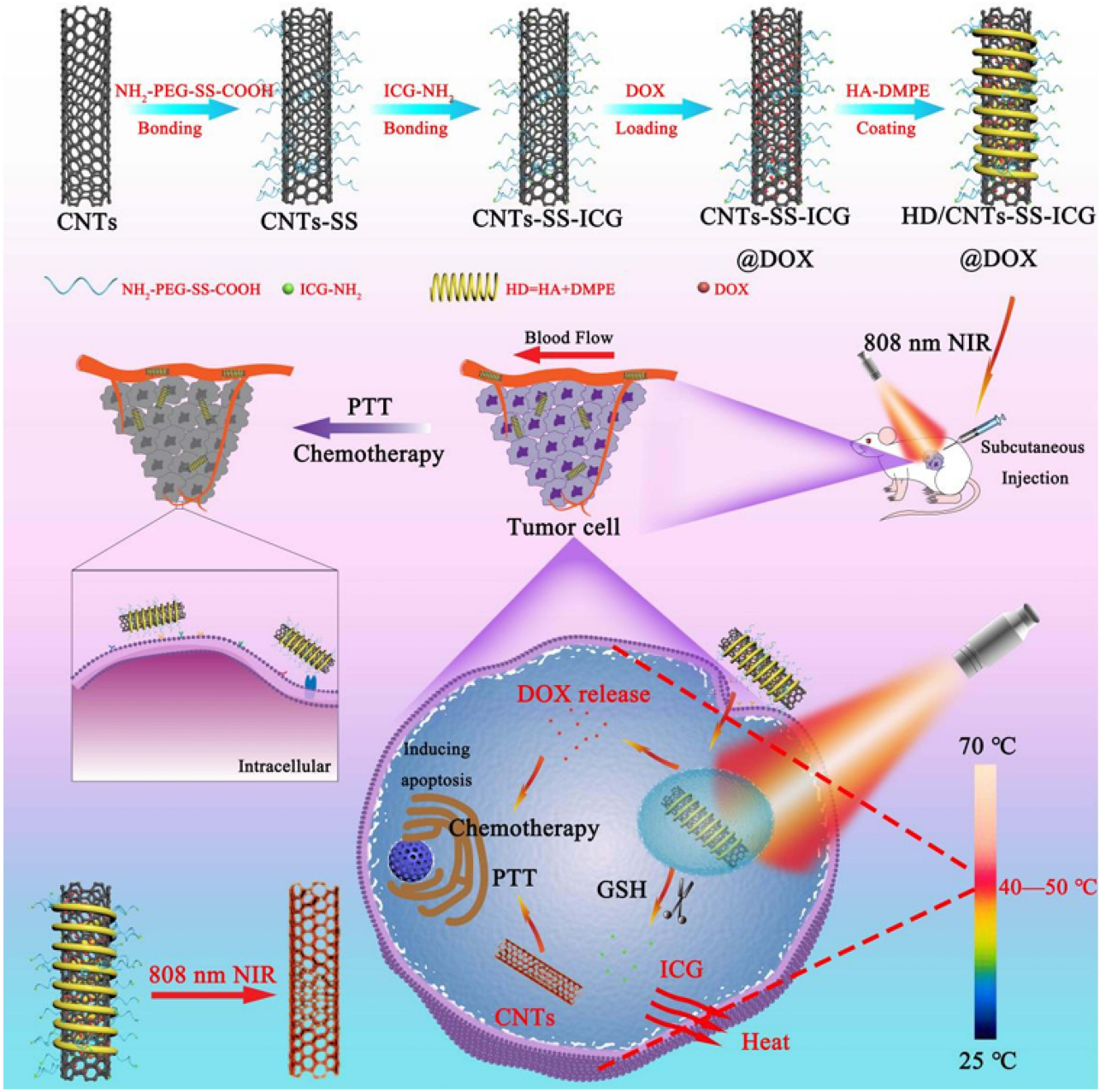

Figure 4 Schematic diagram of the preparation procedure and antitumor mechanism of HD/CNTs-SS-ICG@DOX DDS. A drug delivery system (HD/CNTs-SS-ICG @DOX) was developed by conjugating ICG-NH2 on the surface of CNTs through S-S, loading chemotherapy drug DOX inside the lumen, and finally coating the surface with targeting agent HD. Reprinted with permission from ref 123. Copyright 2024 MDPI.

dots in biomedicine. In these preclinical studies, the diverse synthesis methods of carbon quantum dots and the optimization of synthesis conditions are critical factors that directly influence their biomedical applications.[123] It has been demonstrated that carbon quantum dots synthesized via the hydrothermal method can self-assemble into carbon nanofilms at the air-liquid interface, facilitated by a metal catalyst. The electrochemical characteristics of the films were assessed using linear cyclic voltammetry and constant current charge-discharge tests, demonstrating superior electrical properties. Consequently, these films hold promise as potential materials for neurological applications aimed at mitigating the incidence and adverse outcomes of abnormal bioelectrophysiological conditions. This development suggests new opportunities for the utilization of carbon nanomaterials in biomedical fields.[124,125]

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Similar to carbon quantum dots, carbon nanotubes have been extensively utilized in drug delivery and bioimaging applications due to their distinctive physicochemical properties. Nonetheless, the pharmacokinetic characteristics of carbon nanotubes can be significantly enhanced through modifications with biocompatible agents such as liposomes, exosomes, and polyethylene glycol, thereby improving their applicability in the biomedical domain.[126] For instance, they have demonstrated successful application in preclinical research, particularly in tumor therapy and vaccination. These preclinical outcomes indicate the potential of modified CNTs as innovative multifunctional nanodrug delivery platforms.[127] However, current preclinical investigations reveal that the detection and tracking of CNTs within the circulatory system remain a significant challenge. Despite recent advancements in the in vivo detection technology of single-walled carbon nanotubes, numerous technical issues persist.[128] These challenges primarily encompass enhancing detection sensitivity and specificity, as well as achieving effective tracking within complex biological environments. Addressing these issues is essential for advancing the application of carbon nanotubes in the medical field.

Graphene nanomaterials hold significant potential for application in preclinical research; however, they also encounter numerous challenges. The distinctive chemical structure, biological effects, and photoelectric properties of graphene and its derivatives have garnered considerable attention from researchers ac*ROS*s various disciplines, establishing them as a crucial component in the study of biological nanomaterials.[129] Leveraging these properties, graphene nanomaterials are particularly advantageous in the development and implementation of biosensors capable of efficiently detecting biomarkers and other target molecules, thereby facilitating the rapid diagnosis of diverse diseases. In preclinical investigations, graphene-based materials have been extensively utilized for pathogen detection and disease diagnosis, owing to their high sensitivity and versatility. Nonetheless, substantial obstacles remain to be addressed to advance the clinical translation of graphene nanomaterials. A significant challenge in contemporary research involves simplifying and standardizing the synthesis process while reducing costs, all without compromising the sensitivity and specificity of the materials. To facilitate extensive clinical applications, it remains essential to address issues related to reproducibility, stability, and biocompatibility within complex biological environments. Overcoming these challenges will advance the translation of graphene nanomaterials from laboratory research to clinical applications.[130,131]

In conclusion, while carbon nanomaterials have demonstrated promising applications in preclinical studies, they continue to encounter significant challenges in practical applications. Primarily, it is imperative to maintain stringent control over reaction conditions during the preparation process to ensure the uniformity and stability of the material. Additionally, the metabolic pathways and potential toxicity of carbon nanomaterials in vivo require further investigation. Future research should prioritize the optimization of the preparation process and the comprehensive exploration of their biological effects to facilitate a breakthrough in the application of carbon nanomaterials within the medical field. To advance the clinical translation of carbon nanomaterials, the subsequent section will provide a summary of their biotoxicity and inflammatory responses, thereby fostering progress in related research within the biomedical domain.

Biotoxicity of Carbon Nanomaterials

Owing to their distinctive physical and chemical properties, carbon nanomaterials present substantial potential for research and development ac*ROS*s various disciplines. Nonetheless, the growing demand for carbon nanomaterials in diverse sectors has resulted in an escalation of their industrial production, thereby broadening their applicability but also heightening the risk of human exposure through inhalation or dermal contact. Such exposures may pose potential risks to human health. Although no significant adverse effects have been documented thus far, this lack of evidence may be attributed to the limited application of carbon nanomaterials in fields that involve direct interaction with the human body, such as biomedicine, cosmetics, and the food industry[132–134] Carbon nanomaterials possess significant potential for application ac*ROS*s various domains. In the biomedical field, they can function as signal amplifiers in clinical detection techniques, such as electrocardiograms and electroencephalograms, serve as biosensors for the detection of diverse micro-substances within the body, and act as biological scaffolds in tissue engineering and regenerative medicine[135–137] Additionally, fullerenes and other carbon nanomaterials are frequently incorporated into cosmetic products, including moisturizers and shampoos,[138] and are utilized as preservatives and antimicrobial agents within the food industry.[139] These diverse applications suggest an increasing likelihood of human exposure to carbon nanomaterials in the future.

Consequently, to enhance the optimization and development of their potential applications, it is imperative to undertake long-term and systematic investigations into their biological toxicity.[140–142]

Cell Toxicity of Carbon Nanomaterials

As previously discussed, the biosafety and toxicity of carbon nanomaterials significantly influence their clinical translation and application. To advance the clinical translation and application of these materials and invigorate clinical diagnostics and therapeutics, it is imperative to assess their safety and toxicity. Consequently, Good Laboratory Practice (GLP) safety evaluation of carbon nanomaterials constitutes a critical research focus within the field of nanotechnology. Owing to their distinctive physicochemical properties and extensive application potential, carbon nanomaterials have emerged as a prominent research area. Nonetheless, their potential toxicity and implications for human health have also elicited considerable concern. Carbon nanomaterials demonstrate superior biocompatibility relative to most other nanomaterial types, resulting in reduced cellular and tissue damage as well as a diminished inflammatory response. Consequently, they are frequently employed as biomaterials in biomedical applications[143–145] However, the intrinsic functionality of carbon nanomaterials is often inadequate, necessitating functional modifications to achieve the desired biological effects. Minor variations during the processing and functional modification of carbon nanomaterials can significantly alter their properties. Factors such as localized and total charge, catalyst residues (commonly Fe, Co, and Ni), and slight variations in individual nanotube length are critical determinants influencing the biological functions and cytotoxicity of functionalized carbon nanotubes.[146,147]

Researchers, including Singh et al[148] have demonstrated that the type and density of charge on the surface of functionalized carbon nanotubes significantly influence the interaction effects between intracellular DNA and carbon nanotubes. Empirical evidence indicates that catalysts such as Fe, Co, and Ni, which are employed during the synthesis of carbon nanotubes, frequently remain embedded within the nanotubes and are subsequently introduced into the body. These residual catalysts facilitate the generation of oxygen free radicals from phospholipids, steroids, and DNA, thereby inducing oxidative stress and cellular damage. Notably, carbon nanotubes containing residual Co exhibit the highest level of cytotoxicity, causing pronounced chromosomal damage at a concentration of 4 μg/mL.[149]

In addition to carbon nanotubes, graphene nanomaterials have been shown to induce cellular damage, primarily through biological toxicity affecting the cell membrane.[150] It is well-established that cell membranes and organelle membranes predominantly comprise a phospholipid bilayer, characterized by hydrophilic phosphate heads and hydrophobic fatty acid tails, which facilitate the exchange of materials between intracellular fluids and the external environment. Beyond the phospholipid bilayer, cellular membranes also incorporate cholesterol, which plays a crucial role in maintaining membrane fluidity. Unmodified oxidized graphene materials can interact with cell membranes by extracting or removing cholesterol through hydrophobic interactions. This interaction results in decreased membrane fluidity and an increased likelihood of membrane rupture under the mechanical influence of oxidized graphene.[151,152]

Researchers Duan et al[151] demonstrated that graphene oxide is capable of extracting cholesterol from human alveolar epithelial cells (*A549*) and mouse macrophage cells (*Raw264.7*). The depletion or absence of cholesterol in the cell membrane results in a marked reduction in cell fluidity, thereby increasing the susceptibility of the cells to pore formation and ultimately leading to cell death. In a related study, Li et al.[153] Synthesized hydrated graphene oxide and hydroxylated graphene, subsequently examining their interactions with phospholipid membranes. Their research revealed that hydrated graphene oxide can induce oxidative stress processes, such as lipid peroxidation, within cell membranes, culminating in cellular damage or death. This phenomenon is attributed to the presence of superoxide radicals on the surface of hydrated graphene oxide, which instigate lipid peroxidation of unsaturated fatty acids in the cell membrane. In order to further promote the clinical translation of carbon materials, research on the mechanisms of toxicity of carbon materials has gradually emerged. The study demonstrates that graphene elicits reactive oxygen species (*ROS*) activation and induces cellular apoptosis in a manner dependent on *MAPK* and *TGF-β* signaling pathways.[154] Convergent evidence has established oxidative stress as a pivotal mechanism mediating carbon nanotube (CNT)-elicited cytotoxicity. Specifically, exposure to single-walled carbon nanotubes (SWCNTs) provokes oxidative stress in human epidermal keratinocytes, subsequently inducing cytotoxicity.[155] The incubation process triggers substantial *ROS* generation, culminating in cell death induction coupled with activation of the *NF-κB* and *p38* signaling pathways. Lysosomal dysfunction

may likewise constitute a pivotal mechanism underpinning carbon nanomaterial-induced cytotoxicity.[156] Wan et al[157] elucidated the underlying mechanism through which carbon nanomaterials induce cytotoxicity. Utilizing transmission electron mic*ROS*copy, *pEGFP-LC3* transfection assays, and immunoblotting to monitor autophagosome formation, the investigators revealed a significant attenuation of autophagic degradation. As is often observed in autophagic dysfunction, lysosomal impairment emerged concomitantly. Correspondingly, *FITC-dextran* staining experiments confirmed substantial lysosomal compromise in murine peritoneal macrophages following exposure to single-walled carbon nanotubes (SWCNTs) and graphene oxide. Single-walled carbon nanotubes (SWCNTs) provoke dose-dependent apoptotic cascades in *Raw264.7* macrophages through mitochondrial homeostatic collapse, concurrently suppressing adenosine triphosphate (*ATP*) biogenesis while amplifying reactive oxygen species (*ROS*) flux concomitant with upregulation of apoptosis-autophagy regulatory protein networks.[158]

Furthermore, the epoxy groups present on graphene oxide have the potential to generate radicals, thereby contributing to its inherent cytotoxicity. In addition to inducing cell death through interactions with membrane components such as cholesterol on the cell surface, research conducted by Pelin et al[159] has demonstrated that graphene materials, owing to their diminutive size and sharp edges, can readily penetrate the cell membrane. This penetration results in mechanical damage and subsequent leakage of cytoplasmic contents, ultimately culminating in cell death. Once internalized, graphene nanomaterials can disrupt mitochondrial function by diminishing the Mitochondrial Membrane Potential (MMP) and facilitating the release of Lactate Dehydrogenase (*LDH*), which ultimately leads to cell membrane damage. Similarly, studies have reported that graphene materials can compromise the integrity of cell or organelle membranes through the generation of reactive oxygen species, both extracellularly and within the cytoplasm. Notably, even at reduced concentrations, graphene materials can still inflict time-dependent cellular damage[160–163] (Figure 5).

In conclusion, this review addresses the safety evaluation and biotoxicity of carbon nanomaterials. The assessment of their toxicity is a multifaceted process influenced by various factors. Research indicates that the toxicity of carbon nanomaterials is intricately linked to their size, shape, surface functionalization, and other characteristics. For instance, zero-dimensional carbon quantum dots and one-dimensional carbon nanotubes, due to their large specific surface area and small size, can more readily penetrate the nucleus, leading to DNA damage, oxidative stress, protein stress, and other toxic reactions, thereby causing significant cellular damage[163,164] (Figure 6). These findings underscore the necessity of considering the structural and physicochemical properties of carbon nanomaterials in toxicity evaluations. Furthermore, the use of carbon nanomaterials in nanomedicine has raised safety concerns. Despite their promising potential in drug delivery and other applications, comprehensive safety data regarding their impact on human health remain inadequate.[165] Research has indicated that the inherent high reactivity and propensity for aggregation of carbon nanomaterials may

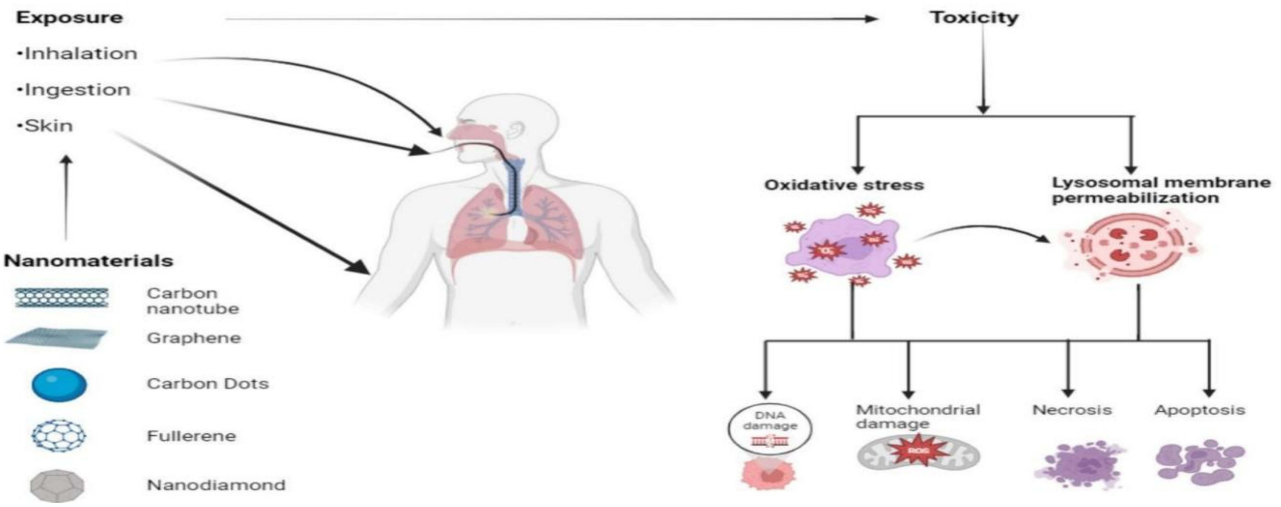

Figure 5 Schematic diagram of biological toxicity of carbon nanomaterials and inflammatory response to multiple tissues. Reprinted with permission from ref 165. Copyright 2024 Elsevier.

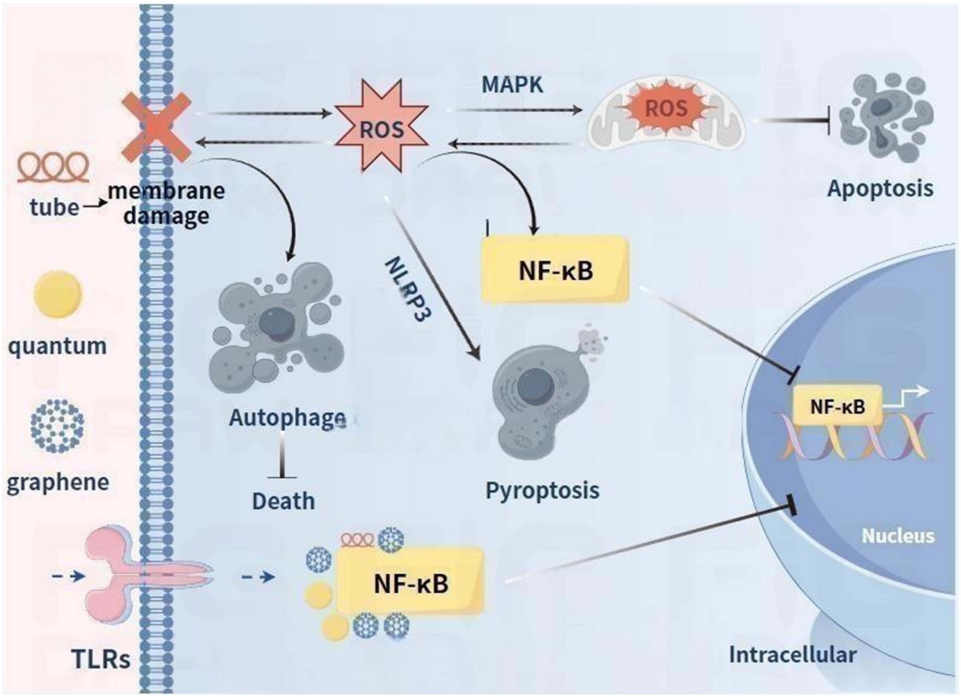

Figure 6 Possible mechanisms of cytotoxicity caused by carbon nanomaterials: ROS-activated MAPKs pathway; TLRs; NF-Kb; Apoptosis; Pyroptosis; Autophage.

result in genotoxicity, thereby posing significant challenges to their safety in medical applications.[166] Consequently, it is imperative to conduct a thorough evaluation of the safety of carbon nanomaterials in the development of safe and effective nanomedicine technologies. Strategies aimed at mitigating the toxicity of carbon nanomaterials have garnered considerable attention. By employing surface chemical modifications, the biocompatibility of carbon nanomaterials can be enhanced, thereby reducing their toxicity.[167] Furthermore, this approach offers valuable directions for future research in the domain of carbon nanomaterials, such as the establishment of standardized toxicity testing protocols and theoretical models to elucidate the mechanisms underlying the toxicity of carbon nanomaterials. Such research endeavors will provide crucial theoretical insights and practical guidance for the development of carbon nanomaterials with reduced toxicity and enhanced safety[168–170] To date, regulatory bodies such as the United States Food and Drug Administration (FDA) have finalized policies and regulations pertaining to the application of nanomaterials in cosmetics, food, and feed. The establishment of these official guidelines has undoubtedly facilitated advancements in the field of carbon nanomaterials and related areas[171,172] However, a definitive FDA standard for the application of nanomaterials in biomedicine has yet to be established. Within the realm of nanomedicine, carbon nanomaterials have been extensively investigated for applications in drug delivery and tissue engineering, owing to their distinctive physicochemical properties. Nonetheless, there remains a paucity of information regarding the safety of these materials, which is crucial for the development of safe and effective nanomedical technologies. Consequently, it is imperative for the FDA to consider the biodistribution and potential toxicological effects of these materials when formulating relevant policies.

Immunotoxicity of Carbon Nanomaterials

The immune system is a complex biological network composed of highly specialized cells and tissues, developed through extensive evolutionary processes and environmental adaptation. It primarily encompasses immune defense mechanisms designed to combat foreign pathogenic microorganisms, including bacteria,[173] viruses[174] and parasites.[175] Additionally, the immune system possesses a self-stabilization function that facilitates the clearance of senescent and damaged cells and organelles, thereby maintaining homeostasis. Furthermore, its surveillance function is critical for the identification and elimination of cells and tissues that have undergone malignant transformation, collectively supporting the maintenance of physiological equilibrium[176–178] Specialized cells that mediate immune responses are predominantly located

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in peripheral blood and mucosal tissues, rendering it inevitable for carbon nanomaterials present within or on the body to interact with the immune system.

Previous research has demonstrated that carbon nanomaterials are predominantly non-biodegradable within the human body, resulting in their prolonged presence in peripheral circulation or tissues.[179] During this period, carbon nanomaterials can interact with various biomolecules, thereby participating in physiological or pathological processes. Notably, these interactions often involve adaptive immune cells, such as macrophages and neutrophils, which may lead to the release of cytokines. This cytokine release has the potential to mediate cytokine storms. Consequently, the organism may experience either an enhanced or suppressed immune response, contingent upon the balance between pro-inflammatory and anti-inflammatory factors.[180–182]

As previously discussed, carbon nanotubes represent some of the earliest forms of carbon nanomaterials, with investigations into their immunotoxicity commencing as early as 2006 to assess their biocompatibility and potential immunotoxic effects. For example, research conducted by Dumortier et al[183] utilized a 1,3-dipolar cycloaddition reaction to functionalize carbon nanotubes and subsequently evaluated the immunotoxicity of these modified nanotubes on primary T cells and B cells derived from mice. The findings from this study demonstrated that the modified carbon nanotubes did not exhibit significant toxicity to primary lymphocytes from mice. Following this, several studies have reported that carbon nanotubes modified with polyethylene glycol, amidation, and phospholipids similarly showed no significant immunotoxicity to lymphocytes. Nonetheless, these studies possess notable limitations. As foreign entities and non-biological materials, carbon nanotubes are primarily subject to immune recognition and clearance by macrophages and neutrophils upon entering the body. Consequently, evaluating the toxicity of carbon nanotubes based solely on their impact on lymphocytes is insufficiently persuasive.

Elkodous et al.[184] Conducted a study on the interaction between pristine carbon nanotubes and macrophages, uncovering that carbon nanotubes can facilitate the release of various inflammatory cytokines by activating pathways associated with oxidative stress and caspases. This activation can lead to cytokine storms and inflammatory cascades within the body[184,185] Subsequently, numerous researchers have concentrated on the interaction effects between carbon nanotubes and adaptive immune cells. Their findings indicate that unfunctionalized carbon nanotubes can induce inflammation and promote apoptosis through toll-like receptor (*TLR*) pathways, as well as pathways involving *IL-6*, dendritic cell maturation, *TNF*, NF-κB, and *CXCR3, CCR5* ligands[186,187] To mitigate the immunotoxicity of carbon nanotubes, surface functionalization modifications such as phosphorylation, carboxylation, and polyethylene glycol modification can be employed. Long-term studies have demonstrated that anionic functionalization significantly reduces the immunotoxicity of carbon nanotubes and enhances their biocompatibility, whereas cationic functionalization increases cytokine concentrations in the body, leading to more severe inflammatory responses and potentially promoting fib*ROS*is[188–190]

In addition to concerns surrounding carbon nanotubes, the immunotoxicity and biocompatibility of graphene nanomaterials remain significant areas of investigation for researchers. A study by Sasidharan et al[191] examined the interactions between pristine and functionalized graphene nanomaterials with human macrophages, as well as their compatibility with the blood system. The study's findings suggest that functionalized graphene nanomaterials can substantially mitigate the immunotoxicity associated with pristine graphene, while both forms of graphene demonstrate excellent compatibility with blood. Further research indicates that the immunotoxicity of oxidized graphene is markedly lower than that of pure graphene materials. This reduction is attributed to the ability of oxidized graphene to inhibit complement production, thereby diminishing the recognition and chemotactic activity of the complement system against oxidized graphene and subsequently reducing the production of pro-inflammatory cytokines in the body.[192] The investigation into the modification of graphene material sizes aimed to assess their impact on immune function. The study's findings indicated that larger graphene flakes (1–10 μm) are more readily recognized, engulfed, and cleared by macrophages, whereas smaller graphene nanomaterials persistently stimulate immune cells to secrete cytokines.[193] This discovery challenges previous foundational understandings. Consequently, through extensive longitudinal studies, researchers have identified that small graphene particles can influence the expression of cytokines such as *TBX21* and *CD80*, activate leukocyte chemotactic pathways, and induce the expression of genes associated with *CXCL10* ligands and *CXCR3* receptors, thereby enhancing immune function and promoting apoptosis.[194]

Conclusion

Carbon nanomaterials, as an emerging class of biological nanomaterials, have garnered significant attention within the scientific community. This interest is attributed to their diverse forms, facile structural modification capabilities, expansive specific surface area, exceptional optical properties, and superior biocompatibility. These attributes endow carbon nanomaterials with substantial potential for applications in biomedicine, demonstrating remarkable versatility. Specific types of carbon nanomaterials, including carbon quantum dots, carbon nanotubes, and graphene nanoparticles, exhibit considerable promise in drug delivery, bioimaging, biosensing, and cancer diagnosis and treatment, owing to their distinctive physicochemical properties. For instance, carbon quantum dots are extensively utilized in bioimaging and drug delivery, benefiting from their favorable biocompatibility and low toxicity. Similarly, graphene and its derivatives excel in biosensing and bioimaging applications, with their high surface area and excellent electrical conductivity rendering them highly suitable for a broad spectrum of uses in these domains.Carbon nanomaterials have found applications ac*ROS*s various disciplines due to their exceptional biocompatibility, high specific surface area, and ease of synthesis. Certain applications have already been incorporated into industrial production processes. However, within the biomedical sector-specifically in contexts where carbon nanomaterials are administered into the peripheral bloodstream through intravenous injection or similar methods-comprehensive regulatory approval has not yet been secured. Nonetheless, the potential applications of carbon nanomaterials in areas such as bioimaging and fluorescence sensing continue to be substantial.[195–197]

Nevertheless, the biotoxicity associated with carbon nanomaterials warrants careful consideration. Empirical evidence indicates that the toxicity of carbon nanotubes is intricately linked to factors such as their size, shape, surface chemistry, exposure route, and purity. Furthermore, the primary mechanism underlying the toxicity of carbon nanotubes and graphene predominantly involves the induction of oxidative stress, which can precipitate cellular damage and provoke inflammatory responses. Consequently, researchers are actively investigating strategies, such as surface functionalization, to mitigate the toxicity of these materials. In the context of biomedical applications, the functionalization of carbon nanomaterials is a critical step in enhancing their biocompatibility and minimizing their toxicological impact. Functionalization not only improves the solubility and biocompatibility of carbon nanomaterials, thereby reducing their cytotoxicity, but also augments their drug loading capacity and targeted delivery capabilities. This enhancement results in increased efficacy and reduced adverse effects in drug delivery systems.

In conclusion, this paper presents a comprehensive review of the applications of carbon nanomaterials in the field of biomedicine, encompassing areas such as bio-fluorescent sensing, targeted drug delivery, tumor-specific diagnosis and therapy, and tissue regeneration engineering. The existing body of research demonstrates the extensive potential of carbon nanomaterials in biomedical applications. However, certain limitations, particularly concerning their biological toxicity and biocompatibility, warrant further investigation. These challenges underscore the need for future research directions in the domain of carbon nanomaterials. Furthermore, it is imperative to differentiate carbon nanomaterials from other biomedical materials by summarizing their unique advantages over other nanomaterials, thereby providing a compelling rationale for their clinical application. The author posits that, through sustained research and innovation by the scientific community, carbon nanomaterials will ultimately transition from laboratory research to clinical application, offering innovative solutions for biochemical detection, cancer treatment, and tissue rehabilitation.

Outlook

In recent years, the application of carbon-based nanomaterials in biomedical fields has attracted much attention. Carbon quantum dots and graphene nanomaterials and carbon nanotubes are widely used in bioimaging, drug delivery and cancer therapy due to their excellent optical and biocompatible properties. However, these materials still face some challenges in practical applications.

Firstly, despite the outstanding performance of carbon nanomaterials in drug delivery and bioimaging, their toxicity and biodistribution in different biological systems still need to be further investigated and optimized. So, To facilitate the transition of carbon nanomaterials from laboratory research to clinical trials and practice, it is imperative to thoroughly examine their biotoxicity and biocompatibility within the human body. As a result, numerous research groups have

concentrated on assessing the cytotoxicity and immunotoxicity of carbon nanomaterials. Studies have demonstrated that pristine carbon nanotubes, when recognized by macrophages, tend to aggregate intracellularly due to their intrinsic properties, leading to cellular damage and the induction of apoptosis. In vivo studies utilizing mouse models have shown that, following macrophage damage, carbon nanotubes can induce macrophage fusion, ultimately resulting in the formation of foreign-body granulomas. This indicates that the immunotoxicity of carbon nanotubes remains a critical concern, necessitating extensive surface and functional modifications for improvement. In terms of cytotoxicity, although functionalized carbon nanotubes exhibit reduced cytotoxicity, it is still affected by parameters such as length, size, and modification techniques[198–200] Research on the cytotoxicity of graphene materials has been progressively refined by researchers and is beginning to meet expectations. However, before the advancement of graphene materials to Phase IV clinical trials, further optimization of administration methods and dosages is required.[201,202]

Secondly, graphene nanoparticles have shown versatility in cancer therapy, but there are still technical bottlenecks in their large-scale production and consistent control. In addition, despite the excellent performance of graphene nanoparticles in photothermal therapy and drug delivery, their stability and efficacy in different biological environments still need to be further verified. It is pointed out that the size, morphology, and degree of surface functionalization of graphene CQDs have a significant impact on their interaction properties with the immune system, which requires precise control during synthesis.In addition to the observable and quantifiable immunotoxic effects, there is a notable paucity of studies examining the impact of carbon nanomaterials on the proliferation and differentiation of various immune cell types. Given their resistance to degradation within the biological milieu, these materials are likely to persist for prolonged durations, during which the generation, differentiation, and eventual localization of new immune cells in lymphatic tissues and other immune-related organs are inevitable. Consequently, it is imperative to investigate the effects of carbon nanomaterial accumulation on newly developed immune cells[203,204] Existing literature suggests that the morphology and dimensions of carbon nanomaterials can significantly affect the growth and differentiation of immune cells, thereby raising concerns regarding the potential compromise of immune system functionality in the context of infectious diseases or neoplastic conditions[205,206] Conversely, carbon nanomaterials possess the potential for functionalization to modulate inflammatory responses, which could be harnessed for therapeutic applications in the management of refractory infections or malignant tumors. The deployment of functionalized carbon nanomaterials in proximity to infection or tumor sites has the potential to enhance immune cell chemotaxis and modulate the polarization of tumor-associated macrophages and neutrophils within the tumor immune microenvironment. This approach may effectively diminish tumor immune evasion and mitigate bacterial multidrug resistance.[207–209]

Finally, although carbon-based nanomaterials have shown great potential in biomedical applications, challenges in clinical translation remain. Further studies on the behavior of these materials in complex biological systems are needed to ensure their safety and efficacy.[210] For example, the application of carbon nanomaterials in tumor immune microenvironment provides a new breakthrough direction for tumor therapy. Tumor microenvironment (TME) is a key factor affecting the occurrence, development and outcome of tumors. Tumor-associated macrophages (*TAMs*) play an important role in the occurrence, development, invasion and metastasis of tumors, and have immunosuppressive ability. Carbon-based composite nanomaterials formed with carbon nanomaterials as a platform and other small molecular compounds or nanoparticles are emerging members of the carbon material family, which become ideal candidates for targeting TAMs due to their excellent optical properties, such as near-infrared imaging, photostability, photoluminescence performance, and good immune reactivity.[211] For example, copan-doped carbonitide nanocomposites (CNCu@HA) effectively eliminate tumors and initiate robust immune responses by inducing apoptosis, copper death, and immunogenic cell death (ICD) when triggered by near-infrared light. This material enhances the synergistic effect of chemodynamic therapy (CDT) and photodynamic therapy (PDT) by photothermal ablation of tumor cells while acting as a dual Fenton-like catalyst and photosensitizing agent to generate excess reactive oxygen species (*ROS*) and deplete glutathione (*GSH*).[212] This multi-level synergistic effect not only enhances the immune response, but also reshapes the tumor immune microenvironment, demonstrating significant anti-tumor effects. The membrane-coated hollow MnN-carbon nanocomposite (HMn-NC@M) reshaped the immunogenic tumor microenvironment through phototherapy and STING activation. The material is subjected to photothermal and photodynamic therapy under near-infrared light to induce immunogenic cell death (ICD), release tumor antigens and damp-associated molecular patterns (DAMPs), thereby triggering anti-tumor

immune responses and regulating the tumor microenvironment by decomposing hydrogen peroxide, alleviating hypoxia, depleting glutathione, and releasing Mn^{2+} ions.[213] These studies indicate that carbon-based nanomaterials hold great promise in the application of tumor immune microenvironment.

But it's worth noting,Our current comprehension of carbon nanomaterials and their interactions with biological molecules or tissue cells within organisms remains limited. Notably, different cell types exhibit distinct sensitivities to carbon nanomaterials; for example, primary cells and cultured tumor cells demonstrate varying levels of sensitivity. Consequently, before the application of carbon nanomaterials in tissue engineering, drug delivery, and fluorescent sensing, extensive long-term testing and analysis are imperative.[214] In the context of biotoxicity and biocompatibility, it is crucial to address not only the mechanisms of cellular damage but also the processes of intercellular communication and information transfer during these interactions. The incorporation of three-dimensional models utilizing human primary cells is essential, as it helps to identify significant yet frequently overlooked mutual influences in cell communication.[215–218]

Although there are many challenges in clinical translation, remarkable progress has been made in the biomedical applications based on carbon nanomaterials. These breakthroughs originate from rigorous research and innovative practice. At the same time, with the recent rapid development of artificial intelligence technology heralding a transformative era, the existence of these artificial intelligence assistants may promote the generation of new synthesis methods or new structural patterns of carbon nanomaterials through big data simulation core simulation, In order to promote the development of carbon nanomaterials in the fields of intelligent responsive carbon nanomaterials, immune microenvironment regulation, precision medicine application and so on. The author believes that with the joint efforts of many researchers from different fields, sooner or later, carbon nanomaterials will make breakthrough research progress, promote their clinical application transformation, and bring new possibilities to the clinical diagnosis and treatment process.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Yang X, Xu G, Liu X, et al. Carbon nanomaterial-involved EMT and CSC in cancer. *Rev Environ Health*. 2021;38(1):1–13. doi:10.1515/reveh-2021-0082
2. Chi H, Liu G. Carbon nanomaterial-based molecularly imprinted polymer sensors for detection of hazardous substances in food: recent progress and future trends. *Food Chem*. 2023;420:136100. doi:10.1016/j.foodchem.2023.136100
3. Manimegalai S, Vickram S, Deena SR, et al. Carbon-based nanomaterial intervention and efficient removal of various contaminants from effluents - A review. *Chemosphere*. 2023;312(Pt 1):137319. doi:10.1016/j.chemosphere.2022.137319
4. Xiong R, Sauvage F, Fraire JC, et al. Photothermal nanomaterial-mediated photoporation. *Acc Chem Res*. 2023;56(6):631–643. doi:10.1021/acs.accounts.2c00770
5. Jiwanti PK, Wardhana BY, Sutanto LG, et al. Recent development of nano-carbon material in pharmaceutical application: a review. *Molecules*. 2022;27(21):7578. doi:10.3390/molecules27217578
6. Castro KPR, Colombo RNP, Iost RM, da Silva BGR, Crespilho FN. Low-dimensionality carbon-based biosensors: the new era of emerging technologies in bioanalytical chemistry. *Anal Bioanal Chem*. 2023;415(18):3879–3895. doi:10.1007/s00216-023-04578-x
7. Ackermann J, Metternich JT, Herbertz S, Kruss S. Biosensing with fluorescent carbon nanotubes. *Angew Chem*. 2022;61(18):e202112372. doi:10.1002/anie.202112372
8. Wang C, Muni M, Strauss V. Graphene's role in emerging trends of capacitive energy storage. *Small*. 2021;17(48):e2006875. doi:10.1002/smll.202006875
9. Mashino T. Yakugaku zasshi. *J Pharm Soc Jpn*. 2022;142(2):165–179. doi:10.1248/yakushi.21-00188
10. He YF, Cheng K, Zhong ZT, et al. Carbon quantum dot fluorescent probe for labeling and imaging of stellate cell on liver frozen section below freezing point. *Anal Chim Acta*. 2023;1260:341210. doi:10.1016/j.aca.2023.341210
11. Nawaz F, Ali M, Ahmad S, et al. Carbon based nanocomposites, surface functionalization as a promising material for VOCs (volatile organic compounds) treatment. *Chemosphere*. 2024;364:143014. doi:10.1016/j.chemosphere.2024.143014

12. Jiang M, Wang Y, Li J, Gao X. Review of carbon dot-hydrogel composite material as a future water-environmental regulator. *Int J Biol Macromol*. 2024;269(Pt 1):131850. doi:10.1016/j.ijbiomac.2024.131850
13. Sun L, Zhao Y, Peng H, et al. Carbon dots as a novel photosensitizer for photodynamic therapy of cancer and bacterial infectious diseases: recent advances. *J Nanobiotechnol*. 2024;22(1):210. doi:10.1186/s12951-024-02479-4
14. Wijayanti NP, Permatasari FA, Damayanti S, et al. Toxicity assessment and bioimaging potential of carbon dots synthesized from banana peel in zebrafish model. *Narra J*. 2024;4(3):e1228. doi:10.52225/narra.v4i3.1228
15. Shen CL, Liu HR, Lou Q, et al. Recent progress of carbon dots in targeted bioimaging and cancer therapy. *Theranostics*. 2022;12(6):2860–2893. doi:10.7150/thno.70721
16. Hu J, Sun Y, Aryee AA, Qu L, Zhang K, Li Z. Mechanisms for carbon dots-based chemosensing, biosensing, and bioimaging: a review. *Anal Chim Acta*. 2022;1209:338885. doi:10.1016/j.aca.2021.338885
17. Liang H, Liu H, Tian B, Ma R, Wang Y. Carbon quantum Dot@Silver nanocomposite-based fluorescent imaging of intracellular superoxide anion. *Mikrochimica acta*. 2020;187(9):484. doi:10.1007/s00604-020-04359-8
18. Ratre P, Nazeer N, Kumari R, et al. Carbon-based fluorescent nano-biosensors for the detection of cell-free circulating MicroRNAs. *Biosensors*. 2023;13(2):226. doi:10.3390/bios13020226
19. Yuan L, Shao C, Zhang Q, Webb E, Zhao X, Lu S. Biomass-derived carbon dots as emerging visual platforms for fluorescent sensing. *Environ Res*. 2024;251(Pt 1):118610. doi:10.1016/j.envres.2024.118610
20. Kurniawan D, Mathew J, Rahardja MR, et al. Plasma-enabled graphene quantum dot hydrogels as smart anticancer drug nanocarriers. *Small*. 2023;19(20):e2206813. doi:10.1002/smll.202206813
21. Henna TK, Raphey VR, Sankar R, Ameena Shirin VK, Gangadharappa HV, Pramod K. Carbon nanostructures: the drug and the delivery system for brain disorders. *Int J Pharm*. 2020;587:119701. doi:10.1016/j.ijpharm.2020.119701
22. Nair A, Greeny A, Nandan A, et al. Advanced drug delivery and therapeutic strategies for tuberculosis treatment. *J Nanobiotechnol*. 2023;21(1):414. doi:10.1186/s12951-023-02156-y
23. Vahedi N, Tabandeh F, Mahmoudifard M. Hyaluronic acid-graphene quantum dot nanocomposite: potential target drug delivery and cancer cell imaging. *Biotechnol Appl Biochem*. 2022;69(3):1068–1079. doi:10.1002/bab.2178
24. Asai A, Konno M, Koseki J, Taniguchi M, Vecchione A, Ishii H. One-carbon metabolism for cancer diagnostic and therapeutic approaches. *Cancer Lett*. 2020;470:141–148. doi:10.1016/j.canlet.2019.11.023
25. Tang L, Li J, Pan T, et al. Versatile carbon nanoplatforms for cancer treatment and diagnosis: strategies, applications and future perspectives. *Theranostics*. 2022;12(5):2290–2321. doi:10.7150/thno.69628
26. Nie R, Zhang J, Jia Q, et al. Structurally oriented carbon dots as *ROS* nanomodulators for dynamic chronic inflammation and infection elimination. *ACS Nano*. 2024;18(33):22055–22070. doi:10.1021/acsnano.4c05266
27. Lovell TC, Bolton SG, Kenison JP, et al. Subcellular targeted nanohoop for one- and two-photon live cell imaging. *ACS Nano*. 2021;15(9):15285–15293. doi:10.1021/acsnano.1c06070
28. Liu M, Huang L, Xu X, et al. Copper doped carbon dots for addressing bacterial biofilm formation, wound infection, and tooth staining. *ACS Nano*. 2022;16(6):9479–9497. doi:10.1021/acsnano.2c02518
29. Tiwari JN, Vij V, Kemp KC, Kim KS. Engineered carbon-nanomaterial-based electrochemical sensors for biomolecules. *ACS nano*. 2016;10(1):46–80. doi:10.1021/acsnano.5b05690
30. Sherlock SP, Tabakman SM, Xie L, Dai H. Photothermally enhanced drug delivery by ultrasmall multifunctional FeCo/graphitic shell nanocrystals. *ACS nano*. 2011;5(2):1505–1512. doi:10.1021/nn103415x
31. Li Y, Lu J, Zhang J, et al. Phase-change nanotherapeutic agents based on mesoporous carbon for multimodal imaging and tumor therapy. *ACS Appl Bio Mater*. 2020;3(12):8705–8713. doi:10.1021/acsabm.0c01102
32. Jin J, Guo M, Liu J, et al. Graphdiyne nanosheet-based drug delivery platform for photothermal/chemotherapy combination treatment of cancer. *ACS Appl Mater Interfaces*. 2018;10(10):8436–8442. doi:10.1021/acsami.7b17219
33. Bao L, Cui X, Wang X, et al. Carbon nanotubes promote the development of intestinal organoids through regulating extracellular matrix viscoelasticity and intracellular energy metabolism. *ACS Nano*. 2021;15(10):15858–15873. doi:10.1021/acsnano.1c03707
34. Li Y, Li J, Yu T, et al. Rh/InGaN1-xOx nanoarchitecture for light-driven methane reforming with carbon dioxide toward syngas. *Sci Bull*. 2024;69(10):1400–1409. doi:10.1016/j.scib.2024.02.020
35. Cebadero-Domínguez Ó, Diez-Quijada L, López S, et al. in vitro toxicity of two functionalized reduced graphene oxide materials with potential application in food packaging. *Toxicol In Vitro*. 2025;102:105970. doi:10.1016/j.tiv.2024.105970
36. Forbot N, Bolibok P, Wiśniewski M, et al. Carbonaceous nanomaterials-mediated defense against oxidative stress. *Mini Rev Med Chem*. 2020;20(4):294–307. doi:10.2174/1389557519666191029162150
37. Yang M, Chen T, Chen X, et al. Development of graphitic carbon nitride quantum dots-based oxygen self-sufficient platforms for enhanced corneal c*ROS*slinking. *Nat Commun*. 2024;15(1):5508. doi:10.1038/s41467-024-49645-8
38. Ahmed OHM, Naiki-Ito A, Takahashi S, et al. A review of the carcinogenic potential of thick rigid and thin flexible multi-walled carbon nanotubes in the lung. *Nanomaterials*. 2025;15(3):168. doi:10.3390/nano15030168
39. Mansour AM, Khaled RM, Ferraro G, Shehab OR, Merlino A. Metal-based carbon monoxide releasing molecules with promising cytotoxic properties. *Dalton Trans*. 2024;53(23):9612–9656. doi:10.1039/d4dt00087k
40. Yamaguchi SI, Xie Q, Ito F, et al. Carbon nanotube recognition by human Siglec-14 provokes inflammation. *Nat Nanotechnol*. 2023;18(6):628–636. doi:10.1038/s41565-023-01363-w
41. Cebadero-Dominguez Ó, Díez-Quijada L, Puerto M, Prieto A, Cameán AM, Jos Á. In vitro evaluation of the toxicity mechanisms of two functionalized reduced graphene oxide derivatives. *Chem Biol Interact*. 2025;406:111359. doi:10.1016/j.cbi.2024.111359
42. He Q, Wu Z, Zhang L. Carbon dots as a new class of multifunctional nanomaterial in mesenchymal stem cells: opportunities and challenges. *J Mat Chem B*. 2023;11(16):3511–3536. doi:10.1039/d2tb02790a
43. Liu Y, Zhang L, Cai H, et al. Biomass-derived carbon dots with pharmacological activity for biomedicine: recent advances and future perspectives. *Sci Bull*. 2024;69(19):3127–3149. doi:10.1016/j.scib.2024.08.011
44. Garg R, Prasad D. Carbon dots and their interactions with recognition molecules for enhanced nucleic acid detection. *Biochem Biophys Res Commun*. 2023;680:93–107. doi:10.1016/j.bbrc.2023.09.033

45. Liu Y, Liang G, Xu H, et al. Tumors exploit FTO-mediated regulation of glycolytic metabolism to evade immune surveillance. *Cell Metab*. 2021;33(6):1221–1233.e11. doi:10.1016/j.cmet.2021.04.001
46. Ribot JC, Lopes N, Silva-Santos B. γδ T cells in tissue physiology and surveillance. *Nat Rev Immunol*. 2021;21(4):221–232. doi:10.1038/s41577-020-00452-4
47. Di Ianni E, Møller P, Cholakova T, Wolff H, Jacobsen NR, Vogel U. Assessment of primary and inflammation-driven genotoxicity of carbon black nanoparticles in vitro and in vivo. *Nanotoxicology*. 2022;16(4):526–546. doi:10.1080/17435390.2022.2106906
48. Witkowska M, Florek E, Mrówczyński R. Assessment of pristine carbon nanotubes toxicity in rodent models. *Int J Mol Sci*. 2022;23(23):15343. doi:10.3390/ijms232315343
49. Svadlakova T, Holmannova D, Kolackova M, Malkova A, Krejsek J, Fiala Z. Immunotoxicity of carbon-based nanomaterials, starring phagocytes. *Int J Mol Sci*. 2022;23(16):8889. doi:10.3390/ijms23168889
50. Shuai C, Dong Z, Yang W, He C, Yang Y, Peng S. Rivet-inspired modification of carbon nanotubes by in situ-reduced ag nanoparticles to enhance the strength and ductility of Zn implants. *ACS Biomater Sci Eng*. 2021;7(12):5484–5496. doi:10.1021/acsbiomaterials.1c00931
51. Kinaret PAS, Ndika J, Ilves M, et al. Toxicogenomic profiling of 28 nanomaterials in mouse airways. *Adv Sci*. 2021;8(10):2004588. doi:10.1002/advs.202004588
52. Xiang L, An Z, Wu X, et al. Carbon dot-loaded apoptotic vesicles improve the liver kupffer cell-mediated antibacterial effect to synergistically alleviate sepsis. *ACS Nano*. 2024;18(26):16726–16742. doi:10.1021/acsnano.4c01780
53. Bu W, Shi Y, Huang X, et al. Rescue of nucleus pulposus cells from an oxidative stress microenvironment via glutathione-derived carbon dots to alleviate intervertebral disc degeneration. *J Nanobiotechnol*. 2024;22(1):412. doi:10.1186/s12951-024-02683-2
54. Chen C, Cheng J, Xiao Y, et al. Carbon nanotube-interconnected ruthenium phthalocyanine nanoparticles used for real-time monitoring of nitric oxide released from vascular endothelial barrier model. *Biosens Bioelectron*. 2024;250:116048. doi:10.1016/j.bios.2024.116048
55. Zhao P, Bai Y, Zhao C, et al. Multiwalled carbon nanotube-templated nickel porphyrin covalent organic framework for pencil-drawn noninvasive respiration sensors. *ACS Sens*. 2024;9(9):4711–4720. doi:10.1021/acssensors.4c01096
56. Zhang DY, Xu Z, Li JY, Mao S, Wang H. Graphene-assisted electron-based imaging of individual organic and biological macromolecules: structure and transient dynamics. *ACS Nano*. 2025;19(1):120–151. doi:10.1021/acsnano.4c12083
57. Mukherjee S, Mukherjee A, Bytesnikova Z, Ashrafi AM, Richtera L, Adam V. 2D graphene-based advanced nanoarchitectonics for electrochemical biosensors: applications in cancer biomarker detection. *Biosens Bioelectron*. 2024;250:116050. doi:10.1016/j.bios.2024.116050
58. Fabbri R, Scidà A, Saracino E, et al. Graphene oxide electrodes enable electrical stimulation of distinct calcium signalling in brain astrocytes. *Nat Nanotechnol*. 2024;19(9):1344–1353. doi:10.1038/s41565-024-01711-4
59. Zhao C, Kang J, Li Y, et al. Carbon-based stimuli-responsive nanomaterials: classification and application. *Cyborg Bionic Sys*. 2023;4:0022. doi:10.34133/cbsystems.0022
60. Amsden B. In vivo degradation mechanisms of aliphatic polycarbonates and functionalized aliphatic polycarbonates. *Macromol Biosci*. 2021;21(7):e2100085. doi:10.1002/mabi.202100085
61. Li M, Zhang C, Mao W, Jiang W. Carbon quantum dots modification reduces TiO2 nanoparticle toxicity in an aquatic food chain. *J Hazard Mater*. 2025;486:137115. doi:10.1016/j.jhazmat.2025.137115
62. Harik VM. Geometry of carbon nanotubes and mechanisms of phagocytosis and toxic effects. *Toxicol Lett*. 2017;273:69–85. doi:10.1016/j.toxlet.2017.03.016
63. Behi M, Gholami L, Naficy S, et al. Carbon dots: a novel platform for biomedical applications. *Nanoscale Adv*. 2021;4(2):353–376. doi:10.1039/d1na00559f
64. Wei ZQ, Shan WL, Li L. Post-modification of covalent organic framework functionalized aminated carbon nanotubes with active site (Fe) for the sensitive detection of luteolin. *Food Chem*. 2025;462:141063. doi:10.1016/j.foodchem.2024.141063
65. Xu X, Ray R, Gu Y, et al. Electrophoretic analysis and purification of fluorescent single-walled carbon nanotube fragments. *J Am Chem Soc*. 2004;126(40):12736–12737. doi:10.1021/ja040082h
66. Liu R, Wu D, Liu S, Koynov K, Knoll W, Li Q. An aqueous route to multicolor photoluminescent carbon dots using silica spheres as carriers. *Angew Chem Int Ed*. 2009;48(25):4598–4601. doi:10.1002/anie.200900652
67. Zhou J, Booker C, Li R, et al. An electrochemical avenue to blue luminescent nanocrystals from Multiwalled Carbon Nanotubes (MWCNTs). *J Am Chem Soc*. 2007;129(4):744–745. doi:10.1021/ja0669070
68. Li F, Li T, Sun C, Xia J, Jiao Y, Xu H. Selenium-doped carbon quantum dots for free-radical scavenging. *Angew Chem*. 2017;56(33):9910–9914. doi:10.1002/anie.201705989
69. Qi W, Liu Y, Dong N, et al. Multifunctional carbon quantum dots for monitoring and therapy of bacterial infected wounds. *Adv Healthcare Mater*. 2025;14(13):2403670. doi:10.1002/adhm.202403670
70. Tang Y, Chen Y, Liu Y, et al. Detection of Gastric Cancer-Associated d-amino acids and carcinoembryonic antigen by colorimetric and immuno ECL sensing platform based on the catalysis of N/S-doped carbon dots @ N-rich porous carbon nanoenzyme. *Anal Chem*. 2022;94(51):17787–17794. doi:10.1021/acs.analchem.2c03433
71. Xu Y, Liu J, Zhang J, et al. Chip-based generation of carbon nanodots via electrochemical oxidation of screen printed carbon electrodes and the applications for efficient cell imaging and electrochemiluminescence enhancement. *Nanoscale*. 2015;7(21):9421–9426. doi:10.1039/c5nr01765c
72. Isci R, Ibis O, Suna G, Unlu C, Ozturk T. Thienothiophene-based quantum dots: calibration of photophysical properties via carbon dot and biomolecular interactions. *Nanoscale*. 2025;17(22):13756–13766. doi:10.1039/d5nr00980d
73. Shirani MP, Rezaei B, Ensafi AA, Ramezani M. Development of an eco-friendly fluorescence nanosensor based on molecularly imprinted polymer on silica-carbon quantum dot for the rapid indoxacarb detection. *Food Chem*. 2021;339:127920. doi:10.1016/j.foodchem.2020.127920
74. Liu YY, Yu NY, Fang WD, et al. Photodegradation of carbon dots cause cytotoxicity. *Nat Commun*. 2021;12(1):812. doi:10.1038/s41467-021-21080-z
75. Manikandan V, Lee NY. Green synthesis of carbon quantum dots and their environmental applications. *Environ Res*. 2022;212(Pt B):113283. doi:10.1016/j.envres.2022.113283
76. Henna TK, Pramod K. S. Graphene quantum dots redefine nanobiomedicine. *Mater Sci Eng C Mater Biol Appl*. 2020;110:110651. doi:10.1016/j.msec.2020.110651

77. Zhu P, Gan Y, Lin K, et al. Dual-response detection of oxidized glutathione, ascorbic acid, and cell imaging based on pH/redox dual-sensitive fluorescent carbon dots. *ACS Omega*. 2020;5(9):4482–4489. doi:10.1021/acsomega.9b03730
78. Raveendran V, Kizhakayil RN. Fluorescent carbon dots as biosensor, green reductant, and biomarker. *ACS Omega*. 2021;6(36):23475–23484. doi:10.1021/acsomega.1c03481
79. Bai Y, Zhao J, Wang S, Lin T, Ye F, Zhao S. Carbon dots with absorption red-shifting for two-photon fluorescence imaging of tumor tissue pH and synergistic phototherapy. *ACS Appl Mater Interfaces*. 2021;13(30):35365–35375. doi:10.1021/acsami.1c08076
80. Li Z, Cheng H, Wang B, et al. Polylysine-modified near-infrared-emitting carbon dots assemblies: amplification of tumor accumulation for enhanced tumor photothermal therapy. *J Colloid Interface Sci*. 2024;668:132–141. doi:10.1016/j.jcis.2024.04.153
81. Xie W, Wang H, Xu H, et al. Sterically chained amino acid-rich water-soluble carbon quantum dots as a robust tumor-targeted drug delivery platform. *Nat Commun*. 2025;16(1):2716. doi:10.1038/s41467-025-57531-0
82. Liu H, Zhang T, Zheng M, Xie Z. Tumor associated antigens combined with carbon dots for inducing durable antitumor immunity. *J Colloid Interface Sci*. 2024;673:594–606. doi:10.1016/j.jcis.2024.06.101
83. Jian HJ, Anand A, Lai JY, et al. In situ hybridization of polymeric curcumin to arginine-derived carbon quantum dots for synergistic treatment of bacterial infections. *ACS Appl Mater Interfaces*. 2023;15(22):26457–26471. doi:10.1021/acsami.3c04316
84. Lin L, Chen X, Sun X, et al. MiR-125b-5p is targeted by curcumin to regulate the cellular antioxidant capacity. *Free Rad Res*. 2022;56 (9–10):640–650. doi:10.1080/10715762.2022.2162393
85. Zavareh HS, Pourmadadi M, Moradi A, Yazdian F, Omidi M. Chitosan/carbon quantum dot/aptamer complex as a potential anticancer drug delivery system towards the release of 5-fluorouracil. *Int J Biol Macromol*. 2020;165(Pt A):1422–1430. doi:10.1016/j.ijbiomac.2020.09.166
86. Stephan O, Ajayan PM, Colliex C, et al. Doping graphitic and carbon nanotube structures with boron and nitrogen. *Science*. 1994;266 (5191):1683–1685. doi:10.1126/science.266.5191.1683
87. Shiina S, Murohashi T, Ishibashi K, et al. Synthesis of Ultrahigh-Purity (6,5) carbon nanotubes using a trimetallic catalyst. *ACS Nano*. 2024;18 (35):23979–23990. doi:10.1021/acsnano.4c01475
88. Liu T, Zhu L, Liu K, et al. Diameter-controlled synthesis of carbon nanotubes using [2n]collarenes as rigid organic templates. *J Am Chem Soc*. 2024;146(47):32445–32451. doi:10.1021/jacs.4c08536
89. Hao C, Li M, Yang J, et al. Single-step PECVD synthesis of graphene@carbon nanotubes electrocatalyst. *Small Methods*. 2025;9(3):e2401101. doi:10.1002/smtd.202401101
90. Zhou H, Li W, Yu P. Carbon nanotubes-based nanofluidic devices: fabrication, property and application. *ChemistryOpen*. 2022;11(11): e202200126. doi:10.1002/open.202200126
91. Guo SY, Hou PX, Zhang F, Liu C, Cheng HM. Gas sensors based on single-wall carbon nanotubes. *Molecules*. 2022;27(17):5381. doi:10.3390/molecules27175381
92. Barrejón M, Zummo F, Mikhalchan A, et al. TEGylated double-walled carbon nanotubes as platforms to engineer neuronal networks. *ACS Appl Mater Interfaces*. 2023;15(1):77–90. doi:10.1021/acsami.2c16808
93. McCreery RL. Carbon-based molecular junctions for practical molecular electronics. *Acc Chem Res*. 2022;55(19):2766–2779. doi:10.1021/acs.accounts.2c00401
94. Nißler R, Ackermann J, Ma C, Kruss S. P*ROS*pects of fluorescent single-chirality carbon nanotube-based biosensors. *Anal Chem*. 2022;94 (28):9941–9951. doi:10.1021/acs.analchem.2c01321
95. Jeong H, Ryu S, Kim YN, et al. Easy, fast self-heating polyurethane nanocomposite with the introduction of thermally annealed carbon nanotubes using near-infrared lased irradiation. *Materials*. 2022;15(23):8463. doi:10.3390/ma15238463
96. Na Y, Zhang J, Zhang S, Liang N, Zhao L. Fluorescence sensor for zearalenone detection based on oxidized single-walled carbon nanohorns/N-doped carbon quantum dots-aptamer. *J Fluoresc*. 2024;34(6):2557–2569. doi:10.1007/s10895-023-03466-y
97. Ibrahim Y, Kamoun E, Abdel Moaty M, Mohy El Din M. Evaluation of carbon nanotubes-hydroxyapatite nanocomposites as bioactive implant coats radiated by near infrared laser. *Eur J Oral Sci*. 2022;130(4):e12873. doi:10.1111/eos.12873
98. Wang M, Wang T, Ojambati OS, et al. Plasmonic phenomena in molecular junctions: principles and applications. *Nat Rev Chem*. 2022;6 (10):681–704. doi:10.1038/s41570-022-00423-4
99. Jiang T, Zeng BF, Zhang B, Tang L. Single-molecular protein-based bioelectronics via electronic transport: fundamentals, devices and applications. *Chem Soc Rev*. 2023;52:5968–6002. doi:10.1039/d2cs00519k
100. Chen C, Huang Z. Tellurium-modified nucleosides, nucleotides, and nucleic acids with potential applications. *Molecules*. 2022;27(23):8379. doi:10.3390/molecules27238379
101. Liu Z, Liu F, Wang C, Li H, Xu Y, Sun S. Ratiometric electrochemical detection of interleukin-6 using electropolymerized methylene blue and a multi-walled carbon-nanotube-modified screen-printed carbon electrode. *Biosensors*. 2024;14(10):457. doi:10.3390/bios14100457
102. Huang Y, Wen Y, Baryeh K, et al. Lateral flow assay for carbohydrate antigen 19-9 in whole blood by using magnetized carbon nanotubes. *Mikrochimica acta*. 2017;184(11):4287–4294. doi:10.1007/s00604-017-2464-0
103. Thapa A, Soares AC, Soares JC, et al. Carbon nanotube matrix for highly sensitive biosensors to detect pancreatic cancer biomarker *CA19-9*. *ACS Appl Mater Interfaces*. 2017;9(31):25878–25886. doi:10.1021/acsami.7b07384
104. Zhang T, Zhang R, Zhang Y, et al. Silk-based biomaterials for tissue engineering. *Adv Colloid Interface Sci*. 2025;338:103413. doi:10.1016/j.cis.2025.103413
105. Qin L, Yang S, Zhao C, et al. P*ROS*pects and challenges for the application of tissue engineering technologies in the treatment of bone infections. *Bone Res*. 2024;12(1):28. doi:10.1038/s41413-024-00332-w
106. Yuan X, Zhu W, Yang Z, et al. Recent advances in 3D printing of smart scaffolds for bone tissue engineering and regeneration. *Adv Mater*. 2024;36(34):e2403641. doi:10.1002/adma.202403641
107. Patel DK, Dutta SD, Ganguly K, Kim JW, Lim KT. Enhanced osteogenic potential of unzipped carbon nanotubes for tissue engineering. *J Biomed Mater Res Part A*. 2021;109(10):1869–1880. doi:10.1002/jbm.a.37179
108. Assali M, Kittana N, Alhaj-Qasem S, et al. Noncovalent functionalization of carbon nanotubes as a scaffold for tissue engineering. *Sci Rep*. 2022;12(1):12062. doi:10.1038/s41598-022-16247-7
109. Liu X, George MN, Park S, et al. 3D-printed scaffolds with carbon nanotubes for bone tissue engineering: fast and homogeneous one-step functionalization. *Acta Biomater*. 2020;111:129–140. doi:10.1016/j.actbio.2020.04.047

110. Li H, Conde J, Guerreiro A, Bernardes GJL. Tetrazine carbon nanotubes for pretargeted in vivo "click-to-release" bioorthogonal tumour imaging. *Angew Chem*. 2020;59(37):16023–16032. doi:10.1002/anie.202008012
111. Rodríguez-Meana B, Del Valle J, Viana D, et al. Engineered graphene material improves the performance of intraneural peripheral nerve electrodes. *Adv Sci*. 2024;11(29):e2308689. doi:10.1002/advs.202308689
112. Cao X, Li S, Wang S, et al. Graphene-metal nanocrystal hybrid materials for bioapplications. *ACS Appl Mater Interfaces*. 2024;16 (39):51816–51825. doi:10.1021/acsami.4c11442
113. Yusuf J, Firdaus AHM, Sapuan SM, et al. Nanocellulose-graphene hybrid composites: fabrication, characterization, applications and environmental impact. *Int J Biol Macromol*. 2024;282(Pt 5):137244. doi:10.1016/j.ijbiomac.2024.137244
114. ElMorsy SM, Gutierrez DA, Valdez S, et al. Graphene acid quantum dots: a highly active multifunctional carbon nano material that intervene in the trajectory towards neurodegeneration. *J Colloid Interface Sci*. 2024;670:357–363. doi:10.1016/j.jcis.2024.05.072
115. Cao J, Wang Y, Jin L, et al. Aptamer and sodium alginate decorated graphene oxide composite material with ion responsiveness for low-density lipoprotein trapping. *J Chromatogr A*. 2024;1731:465166. doi:10.1016/j.chroma.2024.465166
116. Yao L, Chen A, Li L, Liu Y. Preparation, properties, applications and outlook of graphene-based materials in biomedical field: a comprehensive review. *J biomater sci Poly ed*. 2023;34(8):1121–1156. doi:10.1080/09205063.2022.2155781
117. Carrasco JA, Congost-Escoin P, Assebban M, Abellán G. Antimonene: a tuneable post-graphene material for advanced applications in optoelectronics, catalysis, energy and biomedicine. *Chem Soc Rev*. 2023;52(4):1288–1330. doi:10.1039/d2cs00570k
118. Chen J, Wang C, Li H, et al. Recent advances in surface modifications of elemental two-dimensional materials: structures, properties, and applications. *Molecules*. 2022;28(1):200. doi:10.3390/molecules28010200
119. Komori K, Terse-Thakoor T, Mulchandani A. Bioelectrochemistry of heme peptide at seamless three-dimensional carbon nanotubes/graphene hybrid films for highly sensitive electrochemical biosensing. *ACS Appl Mater Interfaces*. 2015;7(6):3647–3654. doi:10.1021/am508032p
120. Yu W, Lei Q, Yang L, et al. Contradictory roles of lipid metabolism in immune response within the tumor microenvironment. *J Hematol Oncol*. 2021;14(1):187. doi:10.1186/s13045-021-01200-4
121. Yu J, Lin YH, Yang L, et al. Improved anticancer photothermal therapy using the bystander effect enhanced by antiarrhythmic peptide conjugated dopamine-modified reduced graphene oxide nanocomposite. *Adv Healthcare Mater*. 2017;6(2). doi:10.1002/adhm.201600804
122. Li M, Yang L, An Y, et al. Selenium-doped carbon dots as a multipronged nanoplatform to alleviate oxidative stress and ferroptosis for the reversal of acute kidney injury. *ACS Nano*. 2025;19(18):17834–17849. doi:10.1021/acsnano.5c03415
123. Li J, Chu J, Chen Z, et al. Surface modification of biodegradable polymer enhances liver organoid attachment and integration forming a cholangiocyte monolayer. *Langmuir*. 2025;41(15):9839–9847. doi:10.1021/acs.langmuir.5c00257
124. Motamedi M, Madani F, Khosravani M, Adabi M. Preparation of surface-modified PLGA nanoparticles containing carbon quantum dots: insights from C6 cell line assays. *Nanomedicine*. 2025;20(12):1403–1416. doi:10.1080/17435889.2025.2504322
125. Cai J, Li B, Feng G, Zhang J, Fan H, Zheng B. Biomolecular interactions of carbon nanotubes with amyloid-β proteins. *J Mat Chem B*. 2025;13 (23):6664–6678. doi:10.1039/d5tb00153f
126. Son M, Mehra P, Nguyen FT, et al. Molecular recognition and in vivo detection of temozolomide and 5-aminoimidazole-4-carboxamide for glioblastoma using near-infrared fluorescent carbon nanotube sensors. *ACS Nano*. 2023;17(1):240–250. doi:10.1021/acsnano.2c07264
127. Chudoba D, Jażdżewska M, Łudzik K, Wołoszczuk S, Juszyńska-Gałązka E, Kościński M. Description of Release process of doxorubicin from modified carbon nanotubes. *Int J Mol Sci*. 2021;22(21):12003. doi:10.3390/ijms222112003
128. Bora H, Mandal D, Chandra A. High-performance, nitrogen-doped, carbon-nanotube-based electrochemical sensor for vitamin D3 detection. *ACS Appl Bio Mater*. 2022;5(4):1721–1730. doi:10.1021/acsabm.2c00094
129. Kansara V, Patel M. Exploring the role of graphene-metal hybrid nanomaterials as Raman signal enhancers in early stage cancer detection. *Talanta*. 2025;283:127185. doi:10.1016/j.talanta.2024.127185
130. Liang J, Wu Y, Zhang C, et al. Graphene-based nanomaterials in photodynamic therapy: synthesis strategies, functional roles, and clinical translation for tumor treatment. *Int J Nanomed*. 2025;20:8359–8392. doi:10.2147/IJN.S516606
131. Wu J, Bai X, Yan L, et al. Selective regulation of macrophage lipid metabolism via nanomaterials' surface chemistry. *Nat Commun*. 2024;15 (1):8349. doi:10.1038/s41467-024-52609-7
132. Li H, Zick ME, Trisukhon T, et al. Capturing carbon dioxide from air with charged-sorbents. *Nature*. 2024;630(8017):654–659. doi:10.1038/s41586-024-07449-2
133. Hadrup N, Vogel U, Jacobsen NR. Biokinetics of carbon black, multi-walled carbon nanotubes, cerium oxide, silica, and titanium dioxide nanoparticles after inhalation: a review. *Nanotoxicology*. 2024;18(8):678–706. doi:10.1080/17435390.2024.2431242
134. Zhang M, Fu G, Shi W, Feng X, Lens PNL, Zhang B. Microbial response to the chronic toxicity effect of graphene and graphene oxide nanomaterials within aerobic granular sludge systems. *J Hazard Mater*. 2024;477:135350. doi:10.1016/j.jhazmat.2024.135350
135. Kumar VB, Sher I, Rencus-Lazar S, Rotenstreich Y, Gazit E. Functional carbon quantum dots for ocular imaging and therapeutic applications. *Small*. 2023;19(7):e2205754. doi:10.1002/smll.202205754
136. Barrientos K, Arango JP, Moncada MS, et al. Carbon dot-based biosensors for the detection of communicable and non -communicable diseases. *Talanta*. 2023;251:123791. doi:10.1016/j.talanta.2022.123791
137. Tashakori-Miyanroudi M, Janzadeh A, Seifalian A, et al. Will carbon nanotube/nanofiber bring new hope for the treatment of heart damage? A systematic review. *Nanomedicine*. 2022;17(29):2189–2205. doi:10.2217/nnm-2022-0113
138. Santos AC, Morais F, Simões A, et al. Nanotechnology for the development of new cosmetic formulations. *Expert Opin Drug Delivery*. 2019;16 (4):313–330. doi:10.1080/17425247.2019.1585426
139. Moradi O. A review on nanomaterial-based electrochemical sensors for determination of vanillin in food samples. *Food Chem Toxicol*. 2022;168:113391. doi:10.1016/j.fct.2022.113391
140. Malina T, Poláková K, Hirsch C, Svoboda L, Zbořil R. Toxicity of carbon nanomaterials-towards reliable viability assessment via new approach in flow cytometry. *Int J Mol Sci*. 2021;22(14):7750. doi:10.3390/ijms22147750
141. Peng Z, Liu X, Zhang W, et al. Advances in the application, toxicity and degradation of carbon nanomaterials in environment: a review. *Environ Int*. 2020;134:105298. doi:10.1016/j.envint.2019.105298
142. Samak DH, El-Sayed YS, Shaheen HM, et al. Developmental toxicity of carbon nanoparticles during embryogenesis in chicken. *Environ Sci Pollut Res Int*. 2020;27(16):19058–19072. doi:10.1007/s11356-018-3675-6

143. Chua CYX, Liu HC, Di Trani N, et al. Carbon fiber reinforced polymers for implantable medical devices. *Biomaterials*. 2021;271:120719. doi:10.1016/j.biomaterials.2021.120719
144. Coyle JP, Derk RC, Kornberg TG, et al. Carbon nanotube filler enhances incinerated thermoplastics-induced cytotoxicity and metabolic disruption in vitro. *Part Fibre Toxicol*. 2020;17(1):40. doi:10.1186/s12989-020-00371-1
145. Cai T, Han Y, Li W, et al. Self-assembled electrochemically active biofilms doped with carbon nanotubes: electron exchange efficiency and cytotoxicity evaluation. *Sci Total Environ*. 2023;905:167006. doi:10.1016/j.scitotenv.2023.167006
146. Ghosh S, Dave V, Wal P. Therapeutic approach of carbon nanotube: revolutionize nanomaterial in biomedical and pharmaceutical sector. *J Food Drug Analy*. 2024;32(4):412–427. doi:10.38212/2224-6614.3531
147. Carrillo-Romero J, Mentxaka G, García-Salvador A, Katsumiti A, Carregal-Romero S, Goñi-de-Cerio F. Assessing the toxicity of metal- and carbon-based nanomaterials in vitro: impact on respiratory, intestinal, skin, and immune cell lines. *Int J Mol Sci*. 2024;25(20):10910. doi:10.3390/ijms252010910
148. Singh R, Pantarotto D, McCarthy D, et al. Binding and condensation of plasmid DNA onto functionalized carbon nanotubes: toward the construction of nanotube-based gene delivery vectors. *J Am Chem Soc*. 2005;127(12):4388–4396. doi:10.1021/ja0441561
149. Wick P, Manser P, Limbach LK, et al. The degree and kind of agglomeration affect carbon nanotube cytotoxicity. *Toxicol Lett*. 2007;168 (2):121–131. doi:10.1016/j.toxlet.2006.08.019
150. Devasena T, Francis AP, Ramaprabhu S. Toxicity of graphene: an update. *Rev Environ Contam Toxicol*. 2021;259:51–76. doi:10.1007/398_2021_78
151. Duan G, Zhang Y, Luan B, et al. Graphene-induced pore formation on cell membranes. *Sci Rep*. 2017;7:42767. doi:10.1038/srep42767
152. Pham VT, Truong VK, Quinn MD, et al. Graphene induces formation of pores that kill spherical and rod-shaped bacteria. *ACS Nano*. 2015;9 (8):8458–8467. doi:10.1021/acsnano.5b03368
153. Li R, Guiney LM, Chang CH, et al. Surface oxidation of graphene oxide determines membrane damage, lipid peroxidation, and cytotoxicity in macrophages in a pulmonary toxicity model. *ACS Nano*. 2018;12(2):1390–1402. doi:10.1021/acsnano.7b07737
154. Li Y, Liu Y, Fu Y, et al. The triggering of apoptosis in macrophages by pristine graphene through the *MAPK* and TGF-beta signaling pathways. *Biomaterials*. 2012;33(2):402–411. doi:10.1016/j.biomaterials.2011.09.091
155. Shvedova AA, Castranova V, Kisin ER, et al. Exposure to carbon nanotube material: assessment of nanotube cytotoxicity using human keratinocyte cells. *J Toxicol Environ Health A*. 2003;66(20):1909–1926. doi:10.1080/713853956
156. He B, Shi Y, Liang Y, et al. Single-walled carbon-nanohorns improve biocompatibility over nanotubes by triggering less protein-initiated pyroptosis and apoptosis in macrophages. *Nat Commun*. 2018;9:2393. doi:10.1038/s41467-018-04700-z
157. Wan B, Wang ZX, Lv QY, et al. Single-walled carbon nanotubes and graphene oxides induce autophagosome accumulation and lysosome impairment in primarily cultured murine peritoneal macrophages. *Toxicol Lett*. 2013;221(2):118–127. doi:10.1016/j.toxlet.2013.06.208
158. Park EJ, Zahari NEM, Kang MS, et al. Toxic response of HIPCO single-walled carbon nanotubes in mice and *Raw264.7* macrophage cells. *Toxicol Lett*. 2014;229(1):167–177. doi:10.1016/j.toxlet.2014.06.015
159. Pelin M, Fusco L, Martín C, et al. Graphene and graphene oxide induce *ROS* production in human HaCaT skin keratinocytes: the role of xanthine oxidase and NADH dehydrogenase. *Nanoscale*. 2018;10(25):11820–11830. doi:10.1039/c8nr02933d
160. Zhu J, Shang J, Zhu T. A new understanding of the mic*ROS*tructure of soot particles: the reduced graphene oxide-like skeleton and its visible-light driven formation of reactive oxygen species. *Environ Pollut*. 2021;270:116079. doi:10.1016/j.envpol.2020.116079
161. Xu A, He P, Ye C, et al. Polarizing graphene quantum dots toward long-acting intracellular reactive oxygen species evaluation and tumor detection. *ACS Appl Mater Interfaces*. 2020;12(9):10781–10790. doi:10.1021/acsami.9b20434
162. Liu S, Xu A, Gao Y, et al. Graphene oxide exacerbates dextran sodium sulfate-induced colitis via *ROS*/AMPK/p53 signaling to mediate apoptosis. *J Nanobiotechnol*. 2021;19(1):85. doi:10.1186/s12951-021-00832-5
163. Makhado BP, Oladipo AO, Gumbi NN, et al. Unravelling the toxicity of carbon nanomaterials - from cellular interactions to mechanistic understanding. *Toxicol in vitro*. 2024;100:105898. doi:10.1016/j.tiv.2024.105898
164. Samadian H, Salami MS, Jaymand M, et al. Genotoxicity assessment of carbon-based nanomaterials; Have their unique physicochemical properties made them double-edged swords? *Mutat res Rev mutat res*. 2020;783:108296. doi:10.1016/j.mrrev.2020.108296
165. Zheng S, Tian Y, Ouyang J, Shen Y, Wang X, Luan J. Carbon nanomaterials for drug delivery and tissue engineering. *Front Chem*. 2022;10:990362. doi:10.3389/fchem.2022.990362
166. Saleemi MA, Hosseini Fouladi M, Yong PVC, Chinna K, Palanisamy NK, Wong EH. Toxicity of carbon nanotubes: molecular mechanisms, signaling cascades, and remedies in biomedical applications. *Chem Res Toxicol*. 2021;34(1):24–46. doi:10.1021/acs.chemrestox.0c00172
167. Lin HY, Yen SC, Kang CH, et al. How to evaluate the potential toxicity of therapeutic carbon nanomaterials? A comprehensive study of carbonized nanogels with multiple animal toxicity test models. *J Hazard Mater*. 2022;429:128337. doi:10.1016/j.jhazmat.2022.128337
168. Chetyrkina MR, Fedorov FS, Nasibulin AG. In vitro toxicity of carbon nanotubes: a systematic review. *RSC Adv*. 2022;12(25):16235–16256. doi:10.1039/d2ra02519a
169. Kumar S, Tripathi A, Chakraborty I, Ghangrekar MM. Engineered nanomaterials for carbon capture and bioenergy production in microbial electrochemical technologies: a review. *Bioresour Technol*. 2023;389:129809. doi:10.1016/j.biortech.2023.129809
170. Parvin N, Kumar V, Joo SW, Mandal TK. Emerging trends in nanomedicine: carbon-based nanomaterials for healthcare. *Nanomaterials*. 2024;14(13):1085. doi:10.3390/nano14131085
171. Chen H, Zheng Y, Li J, et al. AI for nanomaterials development in clean energy and Carbon Capture, Utilization and Storage (CCUS). *ACS Nano*. 2023;17(11):9763–9792. doi:10.1021/acsnano.3c01062
172. He Z, Lin H, Sui J, et al. Seafood waste derived carbon nanomaterials for removal and detection of food safety hazards. *Sci total environ*. 2024;929:172332. doi:10.1016/j.scitotenv.2024.172332
173. Rousseau M, Lacerda Mariano L, Canton T, Ingersoll MA. Tissue-resident memory T cells mediate mucosal immunity to recurrent urinary tract infection. *Sci immunol*. 2023;8(83):eabn4332. doi:10.1126/sciimmunol.abn4332
174. Srivastava K, Carreño JM, Gleason C, et al. SARS-CoV-2-infection- and vaccine-induced antibody responses are long lasting with an initial waning phase followed by a stabilization phase. *Immunity*. 2024;57(3):587–599.e4. doi:10.1016/j.immuni.2024.01.017
175. Licona-Limón P, Arias-Rojas A, Olguín-Martínez E. IL-9 and Th9 in parasite immunity. *Semin Immunopathol*. 2017;39(1):29–38. doi:10.1007/s00281-016-0606-9

176. Daëron M. The immune system as a system of relations. *Front Immunol*. 2022;13:984678. doi:10.3389/fimmu.2022.984678
177. Pieren DKJ, Boer MC, de Wit J. The adaptive immune system in early life: the shift makes it count. *Front Immunol*. 2022;13:1031924. doi:10.3389/fimmu.2022.1031924
178. DeMaio A, Mehrotra S, Sambamurti K, Husain S. The role of the adaptive immune system and T cell dysfunction in neurodegenerative diseases. *J Neuroinflammation*. 2022;19(1):251. doi:10.1186/s12974-022-02605-9
179. González-González RB, Rodríguez-Hernández JA, Araújo RG, et al. P*ROS*pecting carbon-based nanomaterials for the treatment and degradation of endocrine-disrupting pollutants. *Chemosphere*. 2022;297:134172. doi:10.1016/j.chemosphere.2022.134172
180. Keshavan S, Calligari P, Stella L, et al. Nano-bio interactions: a neutrophil-centric view. *Cell Death Dis*. 2019;10(8):569. doi:10.1038/s41419-019-1806-8
181. Dong J, Ma Q. Type 2 immune mechanisms in carbon nanotube-induced lung Fib*ROS*is. *Front Immunol*. 2018;9:1120. doi:10.3389/fimmu.2018.01120
182. Sosnowska M, Wierzbicki M, Nasiłowska B, et al. Fullerenol C60(OH)40 nanoparticles and ectoine protect human nasal epithelial cells against the cytokine storm after addition of the full-length spike protein from SARS-CoV-2. *Int J Nanomed*. 2024;19:12221–12255. doi:10.2147/IJN.S482652
183. Dumortier H, Lacotte S, Pastorin G, et al. Functionalized carbon nanotubes are non-cytotoxic and preserve the functionality of primary immune cells. *Nano Lett*. 2006;6(7):1522–1528. doi:10.1021/nl061160x
184. Elkodous MA, Olojede SO, Sahoo S, Kumar R. Recent advances in modification of novel carbon-based composites: synthesis, properties, and biotechnological/ biomedical applications. *Chem Biol Interact*. 2023;379:110517. doi:10.1016/j.cbi.2023.110517
185. Sager TM, Wolfarth MW, Andrew M, et al. Effect of multi-walled carbon nanotube surface modification on bioactivity in the C57BL/6 mouse model. *Nanotoxicology*. 2014;8(3):317–327. doi:10.3109/17435390.2013.779757
186. Yamaguchi SI, Takemura M, Miwa K, Morimoto N, Nakayama M. Siglec-14-mediated inflammatory responses to carbon nanomaterials. *ACS Appl Bio Mater*. 2025;8(4):2927–2937. doi:10.1021/acsabm.4c01736
187. Seke M, Jovanović I, Mačak N, Živković M, Stanković A. Physico-chemically different carbon nanomaterials may elicit similar inflammatory molecular pathways within the lungs of mice. *Toxicol Res*. 2025;14(4):tfaf082. doi:10.1093/toxres/tfaf082
188. Meindl C, Absenger-Novak M, Jeitler R, Roblegg E, Fröhlich E. Assessment of carbon nanotubes on barrier function, ciliary beating frequency and cytokine release in in vitro models of the respiratory tract. *Nanomaterials*. 2023;13(4):682. doi:10.3390/nano13040682
189. Zhang XL, Li B, Zhang X, et al. 18β-Glycyrrhetinic acid monoglucuronide (GAMG) alleviates single-walled carbon nanotubes (SWCNT)-induced lung inflammation and fib*ROS*is in mice through PI3K/AKT/*NF-κB* signaling pathway. *Ecotoxicol Environ Saf*. 2022;242:113858. doi:10.1016/j.ecoenv.2022.113858
190. de Godoy KF, de Almeida Rodolpho JM, de Lima Fragelli BD, et al. Cytotoxic effects caused by functionalized carbon nanotube in murine macrophages. *Cell Physiol Biochem*. 2022;56:514–529. doi:10.33594/000000573
191. Sasidharan A, Panchakarla LS, Sadanandan AR, et al. Hemocompatibility and macrophage response of pristine and functionalized graphene. *Small*. 2012;8(8):1251–1263. doi:10.1002/smll.201102393
192. Wils RS, Jacobsen NR, Vogel U, Roursgaard M, Møller P. Inflammatory response, reactive oxygen species production and DNA damage in mice after intrapleural exposure to carbon nanotubes. *Toxicol Sci*. 2021;183(1):184–194. doi:10.1093/toxsci/kfab070
193. Kinaret PAS, Scala G, Federico A, Sund J, Greco D. Carbon nanomaterials promote M1/M2 macrophage activation. *Small*. 2020;16(21):e1907609. doi:10.1002/smll.201907609
194. Petersen E, Barrios AC, Bjorkland R, et al. Evaluation of bioaccumulation of nanoplastics, carbon nanotubes, fullerenes, and graphene family materials. *Environ Int*. 2023;173:107650. doi:10.1016/j.envint.2022.107650
195. Karimi-Maleh H, Orooji Y, Yola ML. Pharmaceutical and personal care products (PPCPs) treatment and sensing by 2D carbon nanomaterials; challenges and perspectives. *Chemosphere*. 2023;311(Pt 1):136967. doi:10.1016/j.chemosphere.2022.136967
196. Qian S, Li L, Wu K, Wang Y, Wei G, Zheng J. Emerging and versatile platforms of metal-ion-doped carbon dots for biosensing, bioimaging, and disease therapy. *ChemMedChem*. 2023;18(1):e202200479. doi:10.1002/cmdc.202200479
197. Lai C, Li L, Luo B, Shen J, Shao J. Current advances and P*ROS*pects in carbon nanomaterials-based drug deliver systems for cancer therapy. *Curr Med Chem*. 2023;30(24):2710–2733. doi:10.2174/0929867329666220821195353
198. Luo X, Xie D, Su J, Hu J. Inflammatory genes associated with pristine multi-walled carbon nanotubes-induced toxicity in ocular cells. *Int J Nanomed*. 2023;18:2465–2484. doi:10.2147/IJN.S394694
199. Fukushima S, Kasai T, Senoh H, et al. Contribution of toxicological pathology to occupational health: lung carcinogenicity of fibrous and particulate substances in rats. *J Toxicol Pathol*. 2023;36(2):69–83. doi:10.1293/tox.2022-0086
200. Kordzadeh A, Zarif M, Amjad-Iranagh S. Molecular dynamics insight of interaction between the functionalized-carbon nanotube and cancerous cell membrane in doxorubicin delivery. *Comput Methods Program Biomed*. 2023;230(107332):107332. doi:10.1016/j.cmpb.2022.107332
201. Raja IS, Molkenova A, Kang MS, et al. Differential toxicity of graphene family nanomaterials concerning morphology. *Adv Exp Med Biol*. 2022;1351:23–39. doi:10.1007/978-981-16-4923-3_2
202. Muhammad AN, Ijaz A, Khalid A, et al. Renal effects of graphite oxide sheets in albino rats (rattus norvegicus): a preliminary study. *BIO Integration*. 2024;5(1):966. doi:10.15212/bioi-2024-0052
203. Wu J, Liu Q, Wang S, Sun J, Zhang T. Trends and p*ROS*pects in graphene and its derivatives toxicity research: a bibliometric analysis. *J appl toxicol*. 2023;43(1):146–166. doi:10.1002/jat.4373
204. Ma Y, Wang J, Wu J, Tong C, Zhang T. Meta-analysis of cellular toxicity for graphene via data-mining the literature and machine learning. *Sci total environ*. 2021;793:148532. doi:10.1016/j.scitotenv.2021.148532
205. Torres LK, Pickkers P, van der Poll T. Sepsis-induced immunosuppression. *Ann Rev Physiol*. 2022;84:157–181. doi:10.1146/annurev-physiol-061121-040214
206. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013;13(12):862–874. doi:10.1038/nri3552
207. Rahman M, Ahmad MZ, Ahmad J, et al. Role of graphene nano-composites in cancer therapy: theranostic applications, metabolic fate and toxicity issues. *Curr Drug Metab*. 2015;16(5):397–409. doi:10.2174/1389200215666141125120633

208. Ahmad SZN, Wan Salleh WN, Ismail AF, Yusof N, Mohd Yusop MZ, Aziz F. Adsorptive removal of heavy metal ions using graphene-based nanomaterials: toxicity, roles of functional groups and mechanisms. *Chemosphere*. 2020;248:126008. doi:10.1016/j.chemosphere.2020.126008
209. Pi J, Chen D, Wang J, et al. Macrophage targeted graphene oxide nanosystem synergize antibiotic killing and host immune defense for tuberculosis therapy. *Pharmacol Res*. 2024;208:107379. doi:10.1016/j.phrs.2024.107379
210. Santos CIM, Almeida AC, Martins ALF, et al. Carbon dot-phthalocyanine hybrids: synergistic effects that boost their multifaceted applications. *Nanoscale*. 2025;17(20):12554–12579. doi:10.1039/d5nr00466g
211. Miao Y, Wang S, Zhang B, Liu L. Carbon dot-based nanomaterials: a promising future nano-platform for targeting tumor-associated macrophages. *Front Immunol*. 2023;14:1133238. doi:10.3389/fimmu.2023.1133238
212. Zhang X, Qiu G, Chen Y, et al. Near-infrared-triggered copper-doped carbon nitride nanocomposite inducing domino effect for synergistic tumor therapy and immune microenvironment reprogramming. *Mater Today Bio*. 2025;34:102132. doi:10.1016/j.mtbio.2025.102132
213. Ren C, Zhang H, Yang M, et al. Membrane-coated hollow manganese nitrogen carbon nanocomposites synergize phototherapy and STING activation for immunogenic tumor microenvironment remodeling. *ACS Appl Mater Interfaces*. 2025;17(25):37053–37067. doi:10.1021/acsami.5c05076
214. Othman KA, Ali LIA, Qader AF, Omer RA, Amin AA. Synthesis, characterization, and applications of carbon dots for determination of pharmacological and biological samples: a review. *J Fluoresc*. 2025;35(5):2511–2525. doi:10.1007/s10895-024-03736-3
215. Vallejo FA, Sigdel G, Veliz EA, Leblanc RM, Vanni S, Graham RM. Carbon dots in treatment of pediatric brain tumors: past, present, and future directions. *Int J Mol Sci*. 2023;24(11):9562. doi:10.3390/ijms24119562
216. Quyen Chau ND, Ménard-Moyon C, Kostarelos K, Bianco A. Multifunctional carbon nanomaterial hybrids for magnetic manipulation and targeting. *Biochem Biophys Res Commun*. 2015;468(3):454–462. doi:10.1016/j.bbrc.2015.06.131
217. Xu LL, Zhang W, Shang L, et al. Perylenetetracarboxylic acid and carbon quantum dots assembled synergistic electrochemiluminescence nanomaterial for ultra-sensitive carcinoembryonic antigen detection. *Biosens Bioelectron*. 2018;103:6–11. doi:10.1016/j.bios.2017.10.035
218. Mehra NK, Jain AK, Nahar M. Carbon nanomaterials in oncology: an expanding horizon. *Drug Discovery Today*. 2018;23(5):1016–1025. doi:10.1016/j.drudis.2017.09.013