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Multifunctional carbon-based nanostructures (CBNs) for advanced biomedical applications – a perspective and review

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Carbon-based nanostructures (CBNs) have attracted immense attention from biomedical researchers due to their unique combination of extraordinary mechanical, thermal, electrical, and optical properties. They can be easily conjugated with several organic and inorganic molecules, enhancing their potential to perform advanced therapeutic actions, which are not possible with existing materials and techniques. As such, the current advances in some of the diagnostic and therapeutic applications of CBNs are discussed in this review. In particular, the applications of carbon nanotubes (CNTs), graphene, and its oxides, as well as diamond-like carbon in tissue engineering, drug delivery, antimicrobial coatings, and medical diagnostics are critically reviewed. Among the several types of CBNs currently in use, it is shown that nanocomposites of functionalized graphene oxide outweigh the mechanical strength of other biomaterials by 110% without compromise to their biocompatibility. Similarly, due to the unique combination of the surface properties of CNTs, such as charge, polarity, and chemistry, these materials are useful for detecting protein molecules at concentrations as low as 5 ng mL⁻¹. Due to its ease of production, robust mechanical strength, and biocompatibility, DLC is effective as an antimicrobial coating for biomedical implants and devices. Further, we provide insight into the biotoxicity and limitations of current CBNs and highlight the need for a novel biomaterial that can outperform the materials that are currently in use. Finally, the future perspective of carbon-based nanostructures in biomedical applications is discussed by introducing Q-carbon, a newly discovered ferromagnetic phase of carbon with interesting structural and functional properties. We describe the structure and multifunctional capabilities of Q-carbon. We envision Q-carbon as an alternative to CBNs for therapeutic applications, diagnostic applications, and as a protective coating for medical devices.

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Introduction

Biomaterials have gained significant focus over the last four decades as a unique means of treating various diseases.¹ The objective of medical treatment is no longer limited to external medical devices but an amalgamation of implant devices functionalized with biomaterials and therapeutic approaches. Approximately 8000 medical devices involve the use of biomaterials to diagnose and/or treat medical conditions.² The efficacy of a biomaterial is regulated by its response to its biological surroundings. A functional biomaterial is characterized by its ability to perform without affecting the functions of the human body and offers excellent mechanical strength and

prolonged resistance to wear and corrosion.³ Along with biocompatibility, it should be non-toxic to the human body.

In that regard, several conventional metals and alloys, such as titanium and its oxides, stainless steel, and Nitinol, have been used for different biomedical applications for a long time.^{4,5} However, metals release ions into their surroundings gradually and can prove to be cytotoxic. Metals corrode and degrade over time and thus fail to offer a sustainable solution to the problem. This issue calls for sustainable design and development of biomaterials with enhanced capabilities. In the case of first-generation implants, the prototypes were primarily designed based on the bulk properties of the chosen material. However, recent advancements in nanomaterial research have led to the evolution of biomedical devices controlled by their surface properties, offering improved performance and efficiency.⁶

Due to their atypical surface structure and number density, nanoscale materials significantly alter their functional properties.⁷ As such, nanoparticles can be engineered to allow

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site-specific and faster distribution in the body.⁸ Among nanoparticles in general, carbon nanomaterials demonstrate a wide range of structures and morphology, including nanodiamonds (0D), carbon nanotubes (CNTs) (1D), and graphene (2D); each of these materials exhibits unique functionalities. Furthermore, carbon-based nanostructures (CBNs) have the highest rate of distribution in the body, making them suitable candidates for biomedical implant devices.⁹ Several functional CBNs have played a crucial role in clinical and biomedical research due to their unique combination of extraordinary mechanical strength, high chemical resistance, biocompatibility, and adsorption properties.^{10,11} For instance, nanodiamonds with superior biocompatibility are explored for bioimaging and

phototherapy applications.¹² A facile technique for uptake and clearance in melanoma cells, exploiting the surface charges in graphene quantum dots (GCD), has also been demonstrated.¹³ As such, carbon dots or carbon quantum dots are being widely explored for theranostic and diagnostic applications due to their excellent biocompatibility, photostability, tunable fluorescence emission, and excitation properties.^{14–16}

Diamond-like carbon (DLC) coatings offer unique properties such as excellent wear resistance, chemical inertness, and biocompatibility, making them suitable for orthopedic and cardiovascular implants.³ In addition, functionalized CNTs are being explored as biomaterial reinforcements due to their unique structure and physicochemical properties.¹⁰ Moreover, chemically modified CNTs are emerging as promising candidates in tissue engineering due to their multifunctional capabilities.^{17–19} Similarly, we have recently shown that reduced graphene oxide (rGO) performed exceptionally well as stent coatings, facilitating the growth of outgrowth endothelial cells on the implants. Fig. 1 shows the quantification and morphology of the proliferation of outgrowth endothelial cells on the bare silicon substrate and those coated with diamond-like carbon and reduced graphene oxide layers. rGO showed about a 150% increase in the proliferation of endothelial cells. This study also showed that rGO is hemocompatible and was effective in controlling the adverse physiological response from the cellular surroundings.²⁰ Q-Carbon, a newly discovered phase of carbon, shows exceptional mechanical properties compared to all other CBNs, making it a promising candidate for biomedical devices.²¹

Carbon-based nanomaterials have demonstrated significant potential for use in biomedicine, including use in diagnosis and therapy.²² The tunable exterior surface function groups in CBNs enable their seamless integration into a wide range of biomaterials, including lipid-based, metal-based, and polymer-based biological structures; these materials may find use for



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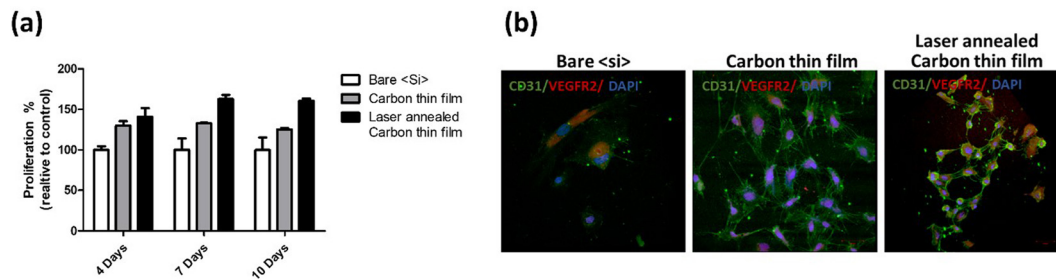


Fig. 1 (a) Proliferation of outgrowth endothelial cells on silicon substrates (b) Morphology and phenotypic expression of outgrowth endothelial cells cultured on Si substrates. Si substrates coated with diamond-like carbon and laser annealed (subsequently forming rGO) showed the highest proliferation rate at all time points.²⁰

bioimaging and sensing applications.^{23–25} In addition to their capability for functionalization, nanocarbon-embedded probes may have use in the detection of individual biomolecules such as DNA. Moreover, the structural strength and tunable functional (*e.g.*, electrical, optical, magnetic, and chemical) properties of these nanostructures facilitate their use in developing personalized tools with point-of-care diagnostics.²⁶ The high strength and biocompatibility of carbon nanostructures also make them suitable for therapeutic applications. Specifically, the ability of carbon nanostructures to manipulate individual molecules at a cellular level has made these materials potential candidates for drug delivery and regenerative medicine applications. Furthermore, carbon nanostructures offer the capability for directing cell differentiation toward specific lineages, making these materials valuable tools in tissue engineering.²² For instance, CBNs have been considered for use in neural scaffold engineering due to their unique combination of mechanical strength, biocompatibility, and tunable electrical conductivity, which sets these materials apart from other nanomaterials. The diversity of CBNs in various biomedical applications is largely attributed to their structure and properties, which can be controlled by selecting the appropriate processing technique. Some recent examples of carbon nanostructures and the most common processing techniques employed for biomedical applications are listed in Table 1.

This review provides a comprehensive evaluation of the performance and biomedical applications of three primary classes of CBNs: diamond-like carbon (DLC), carbon nanotubes (CNTs), as well as graphene and its oxides. We present a critical assessment of their applications in diagnostics, including bioimaging and biosensing, therapeutics (*e.g.*, drug delivery), and tissue engineering. Further, we explore the potential of CBNs as antimicrobial and protective coatings for biomedical implants and devices. Table 2 provides a comprehensive list of the biomedical applications of the carbon-based nanostructures that are discussed in this paper. Finally, we present an overview of the biotoxicity and limitations of existing CBNs as well as introduce Q-carbon as an emergent biomaterial with enhanced structural strength and multifunctional capabilities, with the potential to surpass the performance of existing CBNs. Fig. 2 illustrates the various classes of CBNs employed in different areas of biomedical research that are reviewed in this paper.

1. Carbon nano tubes (CNTs)

A carbon nanotube (CNT) is a one-dimensional cylindrical structure formed by rolling up of sp^2 -hybridized graphene sheet.^{28,29} CNTs are categorized into single-walled (SWCNT)

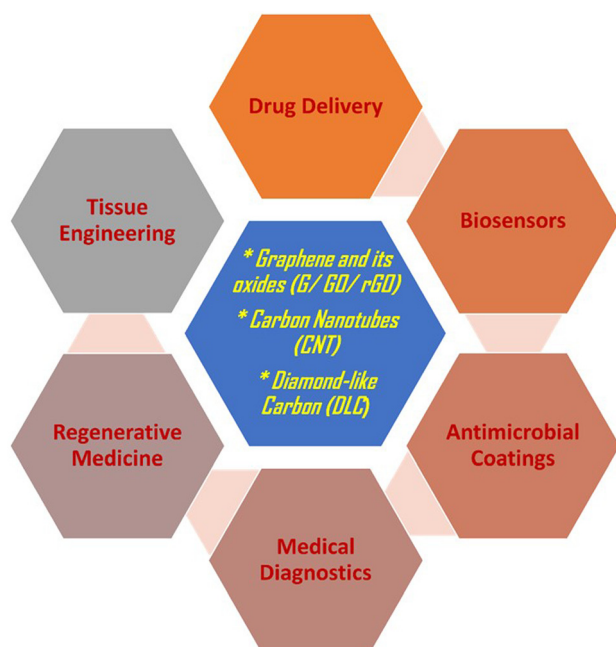
Table 1 Most common types of carbon nanostructures, processing techniques, and their biomedical applications²⁷

Carbon nanostructure	Processing technique	Application
Carbon quantum dots	Hydrothermal	Bioimaging Biosensing Antibacterial
	Microwave Pyrolysis	Bioimaging Biosensing Analgesic
	Sonochemical	Bioimaging
Nano diamonds (NDs)	Laser ablation	Biosensing
	Microplasma jet	Biosensing
Oxidized NDs	Arc discharge	Biosensing
	Laser ablation	Bioimaging
Oxidized carbon nano tubes	Electrochemical	Biosensing
	Photoelectrochemical	Biosensing
Graphene oxide (GO)		Biosensing
Reduced GO	Ascorbic acid reductant	Drug delivery
Diamond-like carbon	Chemical vapor deposition	Drug delivery Protective coatings



Table 2 List of carbon-based nanostructures and their biomedical applications discussed in this review

CBN	Diagnostic application	Therapeutic application	Protective coating
CNT-poly(T) DNA conjugate		DNA separation and gene delivery	
Single-walled CNT (SWCNT)-polyethylene glycol conjugate		Neuronal outgrowth	
CNT-functionalized gold quantum dots	Photoacoustic imaging		
Indium tin oxide (ITO)-treated multi-walled CNTs (MWCNT)	Ultrasensitive detection of urea in blood		
Graphene oxide (GO)-chitosan hydrogel scaffolds		Proliferation of pre-osteoblast MC3T3-E1 cells	
Reduced graphene oxide (rGO) coated stents		Proliferation of outgrowth endothelial cells	
GO	Biosensing of quadruplex-DNA binding ligands		
rGO/iron oxide nanocomposite	Triple-mode sensor for fluorescence, photoacoustic tomography (PAT), and magnetic resonance imaging (MRI)		
Diamond-like carbon (DLC)-coated metal-polyethylene			Hip joint with high wear resistance
DLC-coated stents		Reduction in thrombocyte adhesion	Anticorrosive
Ag-doped DLC			Antibacterial
Si-doped DLC			Antifungal

**Fig. 2** Advanced biomedical applications of various carbon-based nanostructures that are currently in use.

and multi-walled carbon nanotubes (MWCNT) based on the arrangement of the graphene cylinders. CNTs have outstanding mechanical strength, thermal stability, and electrical properties owing to their size and nanostructure.²⁹ Recent studies have shown that CNTs possess superior antioxidant properties against the photodegradation of polymeric materials.³⁰ It is also possible to conjugate a wide range of biomolecules with CNTs, enabling the formation of complex biological structures for target-specific drug delivery in the human body. As such,

CNTs have gained much attention for biomedical applications due to their multifunctional capabilities.³¹

SWCNTs and MWCNTs are synthesized through chemical vapor deposition (CVD), laser ablation, arc discharge techniques, and several other techniques.^{29,32} MWCNTs are highly crystalline, and weaker van der Waals forces hold together the walls of the cylinders. They find numerous applications in optical and electrical systems due to their versatile structure and properties. As such, the arc discharge method is popularly used to grow MWCNTs due to its ease of synthesis.³² Despite its multi-functionality, one of the significant challenges in using CNTs in biomedical devices is their toxicity. The enhanced surface area of CNTs increases their contact area with cellular membranes, resulting in higher absorption and transportation of toxins.³³ Fig. 3 shows various cellular responses leading to toxicity in CNT. Furthermore, external factors like the presence of metal impurities and solubilizing agents in the chains also determine the toxicity of CNTs. Besides toxicity, CNTs are highly susceptible to fragmentation in biological fluids.³⁴ However, functionalized CNT is still emerging as an inevitable source of drug carriers due to its advanced drug action and cell penetration capabilities.³⁵ This section is focused on some of the advanced biomedical applications of functionalized CNTs.

1.1. CNTs in regenerative medicine

The use of CNTs in tissue engineering and regenerative medicine has been explored recently. The superior conducting property and its ability to stimulate cells have enabled the use of CNTs as scaffolds in the human body.³⁷ Furthermore, the functionalization of CNTs has made it possible to stimulate cells for differentiation and proliferation. This approach has enabled the use of CNTs to engineer the growth of new tissue through a cell encapsulation approach.^{37,38} In one of the studies, Johnson *et al.* presented a model demonstrating the binding of CNTs to DNA, allowing the effective dispersion of



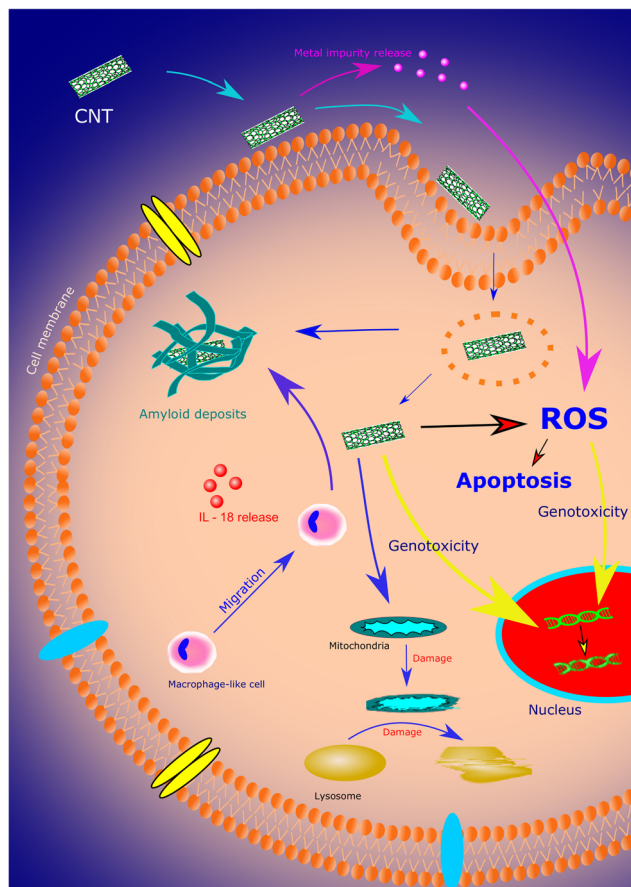


Fig. 3 A schematic representing various cellular responses to CNT leading to toxicity. Reproduced from ref. 36 with permission from Elsevier, copyright 2019.

the molecule in aqueous solutions. This work emphasizes applications in CNT solubilization, CNT sorting, biological sensing, ultrafast DNA sequencing, and chemical sensing.³⁹ Fig. 4 shows a binding model of a carbon nanotube with DNA in an aqueous and non-aqueous environment. In another study, neurons were incorporated with SWCNTs and polyethylene glycol (PEG) to enable the faster growth of neurites.⁴⁰ As CNTs can be easily functionalized with biomolecules, conjugation of CNT with endogenous ligands in the central nervous system (CNS) has enabled the reduction in nerve growth factor and consequent extension of neuronal outgrowth.^{40,41} CNTs have also been explored as promising neuroprosthetic implants.⁴² Surface-modified CNTs have been considered for use as electrode materials in a neuroprosthetic cochlear implant for spiral ganglion neurons.⁴³ Similarly, Eleftheriou *et al.* have demonstrated the use of CNTs as electrode materials in retinal implants due to their improved biocompatibility and electrical properties.⁴⁴ Ostrovsky *et al.* suggest that the unique combination of surface properties of CNTs, such as charge, polarity, and chemistry, can revolutionize the production of advanced neuroprosthetic implants with advanced neuron electrode coupling.⁴⁵

1.2. Diagnostic and therapeutic applications of CNT

The ease of functionalization of CNTs has transformed biomedical imaging and sensing techniques to image and quantify the constituents of cells, tissues, and organs. Moreover, CNTs are stimulated by applying an external magnetic field, advancing their applications in magnetic resonance imaging (MRI).⁴⁶ Chen *et al.* reported that using CNT electrodes in MRI tests resulted in low-distortion images as compared to other electrodes.⁴⁷ Gong *et al.* imply that tumor cell imaging can be significantly improved by using CNTs functionalized with gold quantum dots in fluorescent bioimaging probes.^{46,48} They also suggest that CNTs are an excellent choice for photoacoustic imaging due to their higher absorption capabilities in the NIR regions. In a similar study, it was reported that CNTs functionalized with metal oxide nanoparticles enhanced functionality for bioimaging techniques.⁴⁹ Minati and others suggest that modified carbon nanotubes are promising materials for both diagnostic and therapeutic applications.⁵⁰ A study conducted by a team of researchers from the University of Genova reported that biosensors made from CNTs have enhanced sensitivity, faster action, and greater shelf life.⁵¹ The bioelectrode formed

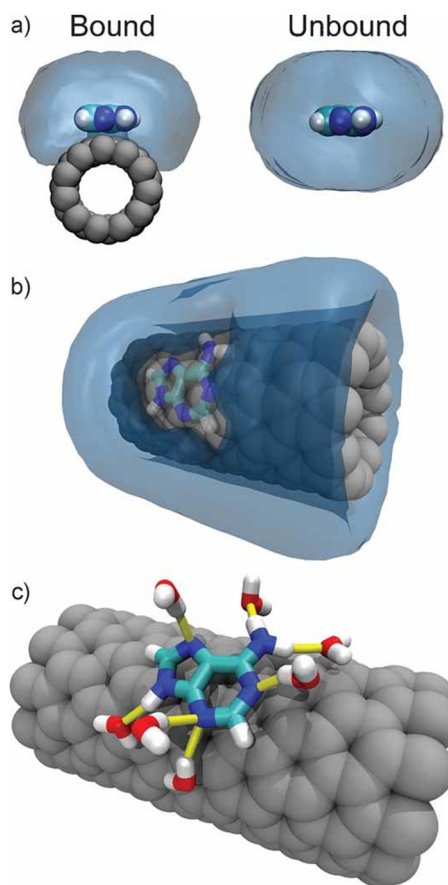


Fig. 4 (a) Water density around bound and unbound DNA (b) water density around CNT showing water excluded from the CNT surface due to the presence of the bound DNA (c) water remains capable of forming hydrogen bonds (yellow) with bound DNA. Reproduced from ref. 39 with permission from John Wiley and Sons, copyright 2009.



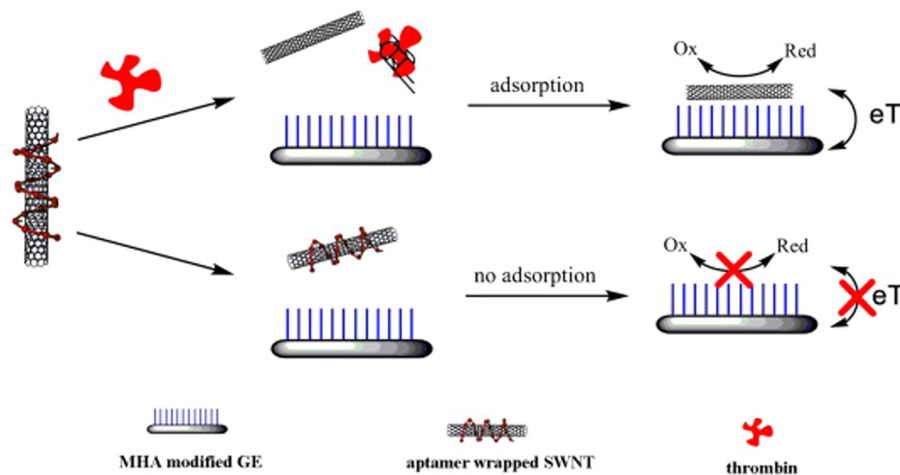


Fig. 5 Electrochemical biosensor strategy for thrombin using aptamer-wrapped SWNT as electrochemical labels. Reproduced from ref. 53 with permission from Elsevier, copyright 2011.

by treating MWCNTs with indium tin oxide (ITO) was found to be highly sensitive in detecting urea in the bloodstream.⁵² Guo *et al.* have developed a DNA-coated CNT-based biosensor as a unique means of detecting proteins with high sensitivity.⁵³ Fig. 5 describes the electrochemical activity of the aptamer (DNA)-CNT-based biosensor for detecting target proteins. This approach improved the capabilities of biosensors in medical diagnostics as well as forensic sciences. Recently, Arancibia and the team have shown that CNT-based sensors can be potential tools for sensing therapeutic molecules from different pharmaceutical combinations.⁵⁴ As such, CNT is emerging as a promising biomaterial due to its unique properties and capabilities.

2. Graphene and its oxides:

Due to their outstanding mechanical strength and biocompatibility, graphene- and graphene-based carbon materials (referred to as graphene-materials hereafter) are of great interest in the biomedical industry.³ Graphene-coated intravascular implants are known to facilitate the growth of outgrowth endothelial cells, improve the hemocompatibility of biomedical implant material, and control the adverse physiological response from the surroundings.²⁰ However, this approach is not commercially viable for preparing large-scale graphene layers as the current methods of synthesis of graphene are associated with low production rates,⁵⁵ high thermal budget values,^{56–59} and contamination.⁵⁷ Graphene oxide (GO), on the other hand, is straightforward to grow at a large scale without contamination.⁶⁰ However, GO is insulating, and the oxygen component in the material disturbs its conjugate structure;⁶¹ this phenomenon poses complications⁶² in the biological environment if used as a coating on biomedical implants. Reduced graphene oxide (rGO) overcomes these problems and shows potential for use in biosensors,⁶³ corrosion inhibitors,⁶⁴ and biomedical implants.⁶⁵ Moreover, the method of reduction controls the functional properties of rGO, influencing the potential biological applications of these

materials.^{66,67} This section reviews some of the advanced biomedical applications of graphene, GO, and rGO, as represented in Fig. 6.

2.1. Graphene materials in tissue engineering

Composites of graphene are being explored for applications in regenerative medicine, wound healing, and tissue engineering because of their superior mechanical properties and specific biological response.⁶⁹ Graphene materials are one of the most researched systems for potential reinforcements in tissue engineering scaffolds.⁷⁰ Recently, it was shown that the tensile strength of polylactide (PLA)/graphene oxide/parathyroid hormone nanofiber membranes was increased up to 110% compared to that of a pure PLA sample, without compromising with the biocompatibility of the system.⁷¹ In addition, Zhang *et al.* reported a significant increase in tensile strength of 132% in GO-incorporated polyvinyl acetate (PVA)-based hydrogels without affecting the cytotoxicity towards osteoblast cells.⁷² In one of the studies conducted on murine fibrosarcoma cell culture, Depan *et al.* obtained similar results in graphene-reinforced chitosan films.⁷³ Similarly, dopamine-functionalized graphene oxide nanoplates (GOPD) and gelatin methacrylate (GelMA) were used to develop a printable shear-thinning nanocomposite hydrogel for soft tissue engineering and 3D bioprinting applications. The high mechanical strength of GO imparted an enhancement to the compressive modulus and degradability of the hydrogel.⁷⁴ Another research reported a substantial development in the adhesion, differentiation, and proliferation of pre-osteoblast MC3T3-E1 cells reinforced with GO-chitosan hydrogel scaffolds.^{73,75} In a similar study, Nagarajan *et al.* incorporated antioxidant GO in polycaprolactone scaffolds which were coated with Schwann cell-derived acellular matrix. These scaffolds exhibited antioxidant and remyelination properties; Schwann RSC96 cells seeded on the scaffold showed an increase in cell proliferation as well as significant remyelination.⁷⁶ The ability to tailor various functionalities on the surface of graphene-based materials has



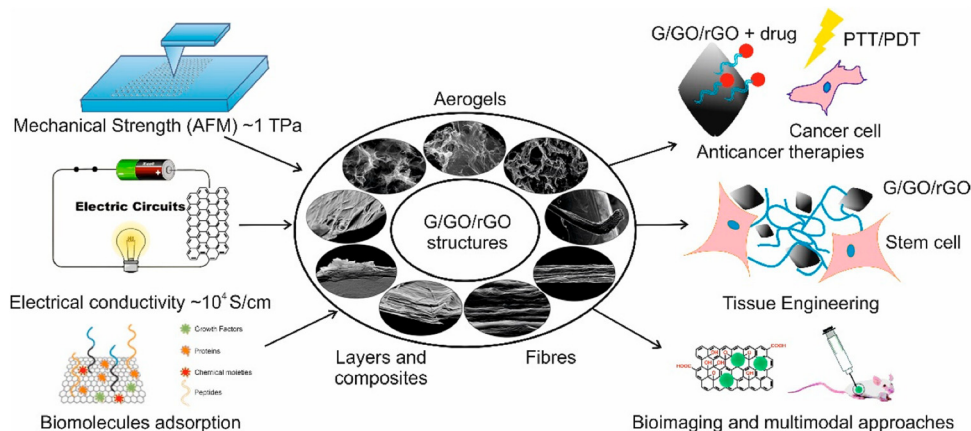


Fig. 6 Schematic showing versatile functionalities of graphene (G), graphene oxide (GO), and reduced graphene oxide (rGO) structures and their typical uses in biomedical devices and systems.⁶⁸

enabled their applications in stem cell engineering. A study conducted by Chen *et al.* showed that GO-coated scaffolds allow for the direct differentiation of induced pluripotent stem cells into insulin-producing β -cells while maintaining their pluripotency.⁷⁷ Another research reported improved cell adhesion, differentiation, and proliferation of human mesenchymal stem cells (hMSCs) on graphene- and GO-coated surfaces as compared to glass, silicon, and polydimethylsiloxane substrates.⁷⁸ Furthermore, graphene foams have shown enhanced differentiation of neural stem cells towards astrocytes.⁷⁹ McManus *et al.* envisage that 3D printing of graphene-based inks may replace the complex 3D structures of tissues with enhanced functionalities in the future.⁸⁰

2.2. Graphene materials as advanced biosensors

Graphene and its oxides are emerging as potential biosensors and platforms for imaging biological entities. Graphene materials are being considered as a potential replacement for existing contrast agents for bioimaging.^{81,82} Yoo *et al.* reported the use of graphene/graphene oxide sensors in fluorescent imaging with high quantum yield. They suggest that the biocompatibility of these structures can be easily tuned by functionalizing the surface of graphene materials with various biopolymers.⁸³ Moreover, the properties of the biopolymer/graphene oxide composites can be improved dramatically if the miscibility and compatibility of the components can be controlled.⁸⁴ For instance, the surface-modified graphene/biopolymer composite showed up to a 95% reduction in the activity of *E. coli* without affecting the biocompatibility of the composite.^{85,86} Similarly, graphene oxides are widely studied for their capabilities of sensing several inorganic and organic biomolecules. Fig. 7 shows some of the biosensing and gas sensing applications of graphene materials achieved by hybridizing graphene with different types of nanomaterials (*e.g.*, metallic, polymeric, and carbon materials).⁸⁷ Gao *et al.* suggest that graphene oxide can be a simple yet superior replacement for biosensing quadruplex-DNA binding ligands because of its fluorescence-quenching capabilities.⁸⁸ As such, GO was

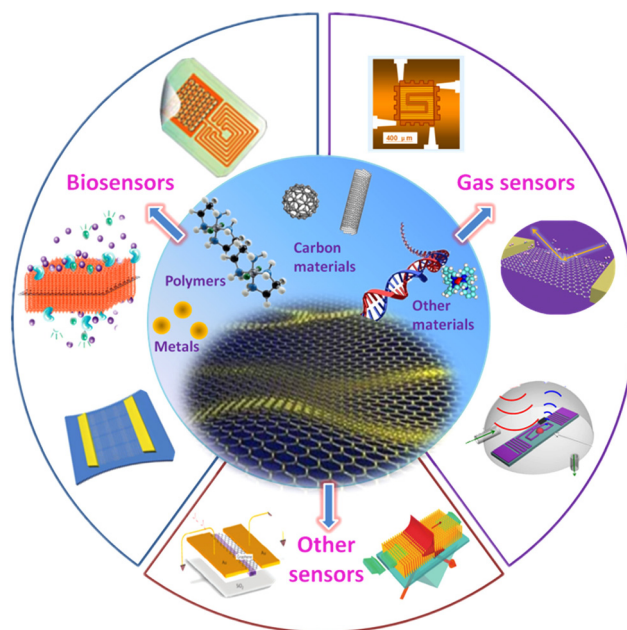


Fig. 7 A schematic showing different kinds of graphene-based composite materials and sensing applications of graphene-materials-based detection devices. Reproduced from ref. 87 with permission from Elsevier, copyright 2017.

employed in the fast and sensitive detection of multiple single-stranded DNA molecules.⁸⁹ Recently, Joshi *et al.* reported a nonenzymatic electrochemical sensing activity of holey graphene oxide films fabricated *via* laser processing.⁹⁰ They show that the sensing capabilities of GO can be controlled by controlling the hole size through laser annealing.^{90,91} Furthermore, graphene and its oxides are being explored in the fabrication of next-generation multimodal materials for bioimaging that can simultaneously perform more than one function. For instance, a study reported the use of rGO/iron oxide nanocomposite in protodermal therapy and as a triple-mode sensor for



photoacoustic tomography (PAT), fluorescence, and magnetic resonance imaging (MRI).⁹² Similarly, Aburto *et al.* have discussed the possibility of employing fluorinated graphene oxide in PAT and MRI while performing as a magnetically driven drug carrier.⁹³ Graphene materials can be an excellent replacement for conventional biosensors as they have enabled rapid and sensitive detection of biomolecules at low cost.

3. Diamond-like carbon (DLC)

Diamond-like carbon is one of the oldest and most popular forms of CBN materials to be explored for biomedical applications.⁹⁴ Thomson *et al.* reported the biocompatibility of DLC coatings in laboratory animals in the early 90s.⁹⁵ Since then, it has been widely studied for various biomedical applications due to its versatile properties. DLC offers high resistance to corrosion, enhanced surface functionalities, improved tribological properties, antimicrobial activity, and anti-inflammatory action, deeming it suitable for biomedical implants and devices.^{3,96,97} Furthermore, DLC coatings can be deposited on various types of substrates at relatively low deposition temperatures. The ease of production and unique characteristics of this class of CBN materials make these materials technologically and commercially important.^{96,98,99} Thus, it has been a popular choice of coating for orthopedic, cardiovascular, and dental implants.

DLC is a form of amorphous carbon with a mixture of sp^2 - and sp^3 -hybridized carbon bonds, which is deposited utilizing high-energy carbon species as precursors.¹⁰⁰ DLC films can be grown through a number of chemical vapor deposition (CVD) and physical vapor deposition (PVD) techniques such as radio-frequency plasma-enhanced CVD (rf-PECVD), filtered cathodic vacuum arc (FCVA), magnetron sputtering, ion beam sputtering, and pulsed laser deposition (PLD).¹⁰¹ Moreover, Gotzmann *et al.* have shown that the DLC coatings deposited through these techniques all exhibited biocompatible properties.¹⁰² In addition, the properties of DLC can be controlled by alloying it with various metals and non-metals, as the amorphous structure of carbon facilitates straightforward doping of elements.¹⁰³ DLC films have been doped and alloyed with various elements (*e.g.*, P, Ti, N, Si, F, Cu, and Ag¹⁰⁴) as well as various compounds (*e.g.*, ZnO¹⁰⁵ and CaO¹⁰⁶). The properties of the doped-DLC structures can be modulated by controlling the sp^2/sp^3 ratio and hydrogen content in the film.^{100,107}

Among them, Si is widely explored as a popular choice of dopants for DLC as it is known to increase the adhesion of the film to the substrate, improve thermal stability, and reduce the internal stresses in the film.¹⁰⁸ Consequently, it is possible to grow thicker layers of DLC with better adherence to the substrate.¹⁰⁹ Furthermore, Si-doped DLC (Si-DLC) of thickness <100 nm shows a low coefficient of friction and better wear resistance even in a humid environment, as compared to undoped DLC coatings.¹¹⁰ Linder *et al.* observed that the biocompatibility of DLC films is influenced by dopant atoms.¹¹¹ Kheradmandfard and others noted that Si/DLC

multilayer nanocomposite coatings exhibited no toxicity and showed enhanced cell adhesion in comparison to Ti-29Nb-13Ta-4.6Zr alloy.¹¹² Wang *et al.* also showed that plasma-treated Si-DLC exhibits improved corrosion resistance, higher interfacial toughness, and biocompatibility in body fluids.¹¹³ Similarly, Ag-incorporated DLC has been reported to reduce the internal stresses in the coating while providing antimicrobial activity.¹¹⁴ Titanium-containing diamond-like carbon films that grown on silicon substrates at room temperature with the filtered cathodic vacuum arc technique were also noted to reduce the internal stress and enhance the adhesion characteristics of the coatings.¹¹⁵ All these findings indicate that DLC coatings have a strong potential for applications in the biomedical industry. Some of the applications are reviewed in this section.

3.1. Orthopedic applications

The life of prosthetic joints is severely shortened due to their tendency to wear and corrosion over time. So, DLC coatings have attracted interest in orthopedic applications due to their inertness, improved resistance to wear, low friction coefficient, and biocompatibility.³ In one of the studies, it was demonstrated that the DLC-coated femoral head Ti-6Al-4V alloy showed enhanced wear resistance as compared to the wear rate of uncoated titanium, stainless steel, alumina, and zirconia implants.¹¹⁶ In another study, Tiainen *et al.* showed that the wear rate of DLC-coated metal–polyethylene hip joints was reduced by 10^6 times smaller than for metal–metal and metal–polyethylene joints.¹¹⁷ The Dowling group reported improved biocompatibility in DLC-coated hip joints with high sp^3 content,¹¹⁸ achieved by doping DLC with silicon. Similarly, Sheeja *et al.* showed that the corrosion resistance and hardness of Co–Cr–Mo alloy (orthopedic implant material) was significantly increased by coating it with Si-DLC.¹¹⁹ In another study performed by Mitura and others, DLC-coated orthopedic screws showed no signs of corrosion or inflammation even after 52 weeks.¹²⁰ On the other hand, there are reports on the failure of DLC-coated orthopedic implants. DLC-coated knee joint implants showed excessive wear and spallation against ultra-high molecular weight polyethylene (UHMWPE).¹²¹ In a similar study, Taeger *et al.* found that the DLC-coated Ti-6Al-V femoral head failed faster than the alumina femoral head,¹²² indicating a need for the development of a biomaterial with enhanced functionalities.

3.2. Cardiovascular applications

One of the primary requirements of a cardiovascular implant is that it should not activate plasma enzymes in order to prevent thrombosis. As such, early studies on DLC-coated heart implants showed a tendency to prevent platelet activation and coagulation of blood.¹²³ Cheng *et al.* have reported improved hemocompatibility in Ti-doped DLC due to its hydrophobicity and smooth surface.¹²⁴ In another study, researchers have shown that incorporating Si into DLC improves endothelial cell attachment while reducing the adhesion of platelets at the same time.¹²⁵ They saw that the results were even better when



Si-DLC films were treated with fluorine. All these findings indicated that functionalized DLC coatings could be used for cardiovascular devices like stents and heart valves. In addition, Gutensohn *et al.* showed that DLC-coated stents were resistant to corrosion, while non-coated stents released metal ions into the human plasma within four days of implantation.¹²⁶ In another study, Choi and others have shown that catheters coated with silver-doped DLC were highly effective in preventing bacterial infection while preventing the adhesion of platelets.¹²⁷ They indicated that a greater focus should be made on utilizing DLC coatings in cardiovascular devices owing to their multifunctional capabilities.

3.3. Antimicrobial coatings

Microbial biofilms are ubiquitously increasing the risk of medical device infection.¹²⁸ As such, treatment related to medical device infections often requires the removal and replacement of devices, increasing healthcare costs and mortality.^{128,129} Since microbes adhere to the surfaces of medical devices and cause infection, infections can be prevented by coating medical devices with a suitable antimicrobial layer. DLC is widely used as an antibacterial and antifungal coating because of its potential to inhibit the adhesion and growth of microorganisms. Kai-Hung *et al.* demonstrated that oxygen plasma-treated silicon-incorporated DLC is hydrophilic, has lower negative zeta potential, and showed antifungal activity against *Candida albicans* (Fig. 8).¹³⁰ In another study, Robertson and others reported that Ge-doped DLC significantly reduced the formation of *P. aeruginosa* biofilms on SS316 substrates.¹³¹ Bociaga *et al.* opine that the antimicrobial response of Si-DLC is promising but needs further investigation.¹³² A recent report on the anti-biofilm properties of prosthetic meshes coated with several metal-containing DLC thin films indicated that all of the materials showed significant antimicrobial activity against five microbial species.¹³³ They propose that modified DLC coatings are suitable for use as biomedical coatings because of their biocompatibility, mechanical strength, and antimicrobial activity.

4. Biototoxicity of carbon nanostructures

Despite the extraordinary strength and multifunctional capabilities, biototoxicity limits the performance of many current CBNs for biomedical applications.¹³⁴ The toxicity and side effects of these materials are attributed to the size, shape, structure, composition, and surface area of the nanostructures.^{135–138} Srikanth *et al.* noted that graphene was found to be the most toxic among the carbon nanostructures, with an average toxicity of 52.24%, followed by carbon nanotubes, fullerene, and carbon nanowires.¹³⁹ The morphology, concentration, and contact duration of these nanostructures with the fibroblast cells were considered to analyze the extent of toxicity in these materials. In another study, it was shown that functionalized CNTs translocated into brain cells, inducing neuroinflammation

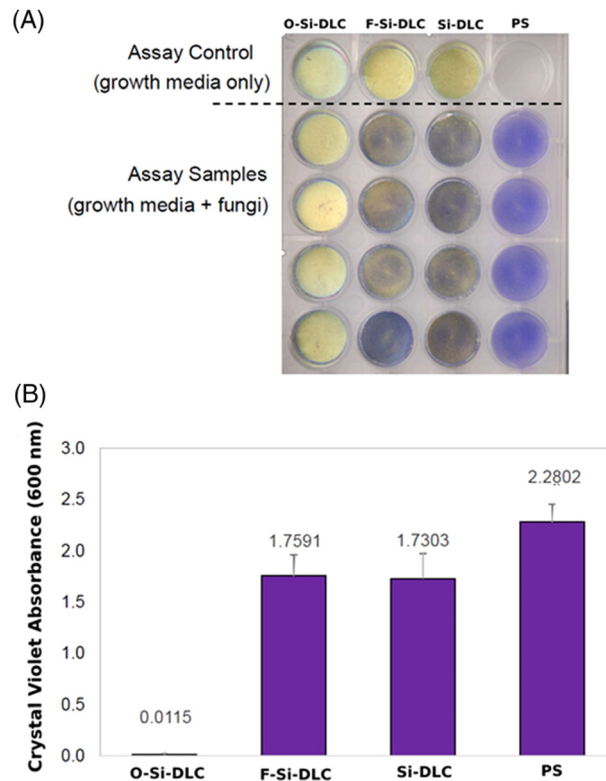


Fig. 8 (A) Images of O-Si-DLC, F-Si-DLC, Si-DLC, and PS with fungal pathogen *Candida albicans* after crystal violet staining. (B) Crystal violet quantification of *C. albicans* on O-Si-DLC, F-Si-DLC, Si-DLC, and PS samples using absorbance measured at 600 nm. (O – oxygen, F – fluorine, PS – polystyrene).¹³⁰

and cognitive impairment.¹⁴⁰ Similarly, Visalli *et al.* found that MWCNTs caused DNA damage as well as overproduction of reactive oxygen species in neurons, leading to cell inflammation.¹⁴¹ Moreover, GO and fullerenes were shown to alter the gene and protein expression in the liver, leading to increased toxicity in the hepatic cells.¹⁴² Several reports described exposure to carbon nanostructures causing nephrotoxicity in both humans and animals. Due to the reduced dispersion of CNTs in biological fluids, human embryonic kidney cells were shown to degrade when exposed to polyethylene-modified CNTs at concentrations above $200 \mu\text{g ml}^{-1}$.¹⁴³ A study on the toxic effects of graphene on kidney cells indicated that GO altered the architecture of the chromatin network, leading to inflammation.¹⁴⁴ Carbon nanostructures have also been shown to induce cardiotoxicity, leading to thrombotic events in humans. A recent study on the inhalation exposure to nanodiamonds in mice revealed the disruption of the mitochondrial membrane potential and high levels of glutathione disulfide (GSSG) in the heart tissue.¹⁴⁵ Moreover, nanodiamonds and graphene have been shown to reduce vascularization and blood vessel density in chicken embryos.¹⁴⁶ Penetration of CBNs into the skin has been reported to have caused contact urticaria, irritation, allergic contact dermatitis, and other cutaneous reactions.¹⁴⁷ One of the most controversial issues of CNT structures is their



tendency to induce various forms of cancer. Recently, Kasai *et al.* reported the carcinogenicity of MWCNTs, causing bronchioloalveolar carcinoma.¹⁴⁸ Another case study reported recently demonstrated the carcinogenicity of different types of CNTs administered *via* intraperitoneal injection in rats.¹⁴⁹ It was shown that MWCNTs induced higher rates of mesothelioma in comparison to other forms of carbon nanotubes. As such, the extent of toxicity of CBNs, as well as their potential effects on human and animal health, are not currently predictable; comprehensive assessment and documentation of the toxicity of these materials are required. As such, it is essential to develop systematic approaches to analyze the toxicity of carbon nanostructures and their impact on the biological environment.

5. Q-Carbon as an emergent biomaterial

The introduction of carbon-based nanostructures has virtually revolutionized the field of biomaterial research. They exhibit superior functional properties, which enables their potential use in biomedical devices. However, carbon nanostructures are often fabricated *via* equilibrium growth techniques that are difficult to reproduce with the same precision.⁵⁵ These techniques employ metal ions as reducing agents, rendering untreated carbon nanostructures toxic to the human body. Moreover, the chemical transfer of carbon nanostructures onto biomedical devices is associated with defects, uneven thickness, and poor adhesion to the substrate.^{55,150} In addition, equilibrium-based processing techniques are often employed with high-temperature annealing processes, limiting their practical applications in medical devices.¹⁵¹ Although it is widely utilized in biomedical devices, diamond-like carbon (DLC) exhibits several strain-localized regions during tensile loading, reducing the stress-bearing functionality of the film.¹⁵² The ultimate tensile strength of Si-incorporated DLC is also known to diminish with increasing temperature, which reduces the utility of DLC-coated implant devices. Moreover, the biotoxicity of some of the CBNs discussed above may require the functionalization of the CBN surface, which may add to the complexity of biomedical device fabrication.¹³⁴ Thus, even though carbon materials have shown promising features for their applications in biomedical devices, they require continual replacement as the materials degrade over time. However, replacement procedures increase operating costs and put the patient at risk for infection. As such, there is a pressing need for a novel biomaterial that offers a unique combination of mechanical strength, biocompatibility, antimicrobial capabilities, and resistance to corrosion; moreover, it should be straightforward to produce at a reasonable cost.

Quenched-in-carbon or Q-carbon is a newly discovered allotrope of carbon, chemically analogous to diamond-like carbon; this material exhibits extraordinary structural and functional properties. Q-Carbon is comprised of randomly packed tetrahedra with a very high sp^3/sp^2 ratio at its interface, making it the hardest known material to date.^{21,153} The Raman spectra

and the microstructure of Q-carbon nanostructures are shown in Fig. 9.¹⁵⁴ Due to its unique structure, Q-carbon has a higher number density of covalently bonded carbon atoms, making it up to 70% harder than diamond. Thus, it can be used in ultrahard coatings as it is harder, tougher, and more adherent than diamond and DLC structures.¹⁵⁵ The Narayan Research Group at NC State University, Raleigh, USA, has developed a process for growing Q-carbon/diamond composite protective coatings for use as a next-generation super-hard coating on practical substrates like sapphire, silicon, glass, steels, and WC-Co.^{155–158} In addition to its high hardness and toughness, Joshi *et al.* have demonstrated that Q-carbon is biocompatible, with superior antimicrobial properties.¹⁵⁷ They showed that silicon-incorporated Q-carbon inhibited the formation of biofilms up to 80%, making it a promising material for several types of biomedical applications. Q-Carbon is conventionally grown by the pulsed laser deposition and subsequent pulsed laser annealing of DLC thin film using a nanosecond pulsed excimer laser source.¹⁵⁵ Recently, Q-carbon growth with wafer-scale integration on substrates as large as 6" in diameter was demonstrated; this approach may enable the industrial-scale production of Q-carbon with controlled thickness and other material properties.¹⁵⁸

In addition to its fascinating structural properties, Q-carbon exhibits robust room-temperature ferromagnetism, with magnetization as high as 20 emu g^{-1} and T_c of ~ 757 K; these characteristics make Q-carbon an excellent candidate for targeted drug delivery applications.^{160,160} Compared to DLC coatings, Q-carbon shows superior field-emission potential due to its unique sp^2/sp^3 mixture in the emitter and the presence of a semimetallic alpha-carbon matrix in the film.¹⁶¹ Q-Carbon-based field emitters display exceptional performance, featuring hysteresis-free emission, high-emission stability, high current density operation without defect generation, and long-term reliability over successive emission measurements.¹⁶² Unlike DLC, Q-carbon is highly resistant to radiation damage, withstanding ion radiations that induce extreme atomic displacements as well as electronic excitations.¹⁶³ Moreover, the large-scale production of Si-incorporated Q-carbon has enabled the wafer-scale growth of epitaxial diamond films, providing a platform to integrate Si-vacancy nanodiamonds for advanced sensing applications.¹⁵⁸ The unique electronic structure of Q-carbon is responsible for its fascinating characteristics, making it an ideal substitute for DLC coatings. Thus, Q-carbon is a truly versatile material with extraordinary properties, finding potential applications in diagnostics and therapeutics. With its ability to overcome the limitations of existing biomaterials, we envision Q-carbon as a superior alternative to the CBNs that are currently in use for a wide range of applications.

Conclusions and future perspective of carbon-based biomaterials

Carbon-based nanostructures have been widely explored in biomedical research due to their outstanding mechanical,



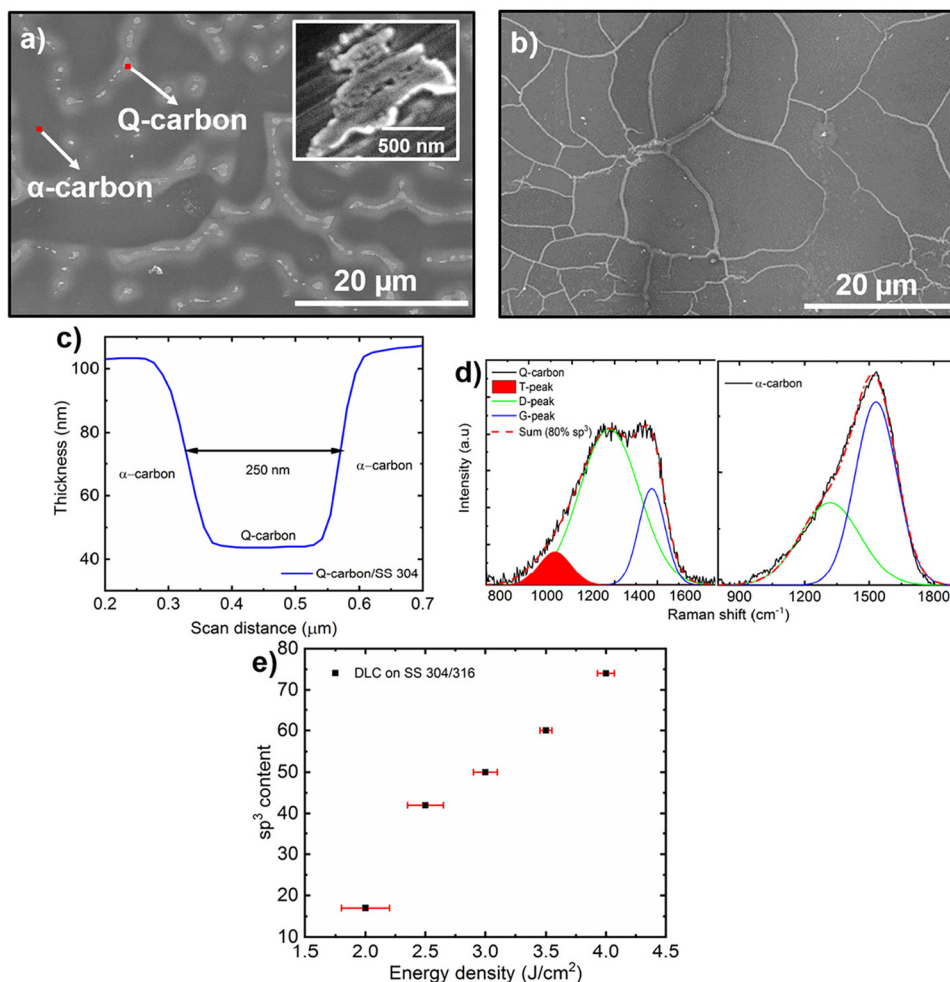


Fig. 9 (a) SEM image demonstrating the formation of Q-carbon on 304 SS, inset shows high-resolution image of Q-carbon in alpha-matrix, (b) SEM image of Q-carbon, (c) surface roughness measurement of Q-carbon, (d) Raman spectra of Q- and alpha-carbon, and (e) correlation between sp³ content of the DLC as a function of laser energy density used during deposition.¹⁵⁹ Reproduced from ref. 154 with permission from Elsevier, copyright 2020.

thermal, electrical, and optical properties. The unique combination of high aspect ratio and chemical reactivity provided by carbon nanostructures make them suitable candidates for applications in drug delivery and regenerative medicine. Furthermore, CBNs may serve as a useful coating material for biomedical devices owing to their antimicrobial capabilities, outstanding mechanical strength, biocompatibility, and corrosion resistance. Thus, the conjugation of CBNs with biomolecules has led to the development of sophisticated biomedical devices for diagnostic applications. The current review has introduced some of the advanced therapeutic and diagnostic applications of diamond-like carbon, carbon nanotubes, and graphene and its oxides in antimicrobial coatings, regenerative medicine, drug delivery, bioimaging, and biosensing. We critically evaluated the use of various carbon materials and their potential biomedical applications. The toxicology and limitations of existing carbon-based nanostructures were also considered. Finally, we have introduced Q-carbon as a novel CBN and assessed its capabilities as a potential biomaterial.

Future perspectives

Despite advancements in the functionalization of CBNs to improve their biocompatibility and reduce toxicity, concerns regarding biosafety of these materials persist. However, CBNs remain indispensable in the biomedical industry due to their unique combination of robust mechanical strength, chemical inertness, and multifunctional capabilities. We envision that Q-carbon may offer an alternative to conventional CBNs.

Data availability

This review article does not contain new data that have been generated or analyzed by the author. All of the data referenced in this paper are available in the original publications that are cited in the reference list.

Conflicts of interest

There are no conflicts of interest to declare.



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