Review

Nano Biomed Eng

Emerging Trends in the Biomedical Application of Carbon-based Nanomaterials

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Received: Dec. 6, 2023; **Revised:** Apr. 9, 2024; **Accepted:** Jun. 3, 2024

Citation: S.M. Banihashemi Jozdani, Z. Hashemian, S. Ebrahim Damavandi, et al. Emerging trends in the biomedical application of carbon-based nanomaterials. *Nano Biomedicine and Engineering*, 2024, 16(3): 357−369.

http://doi.org/10.26599/NBE.2024.9290091

Abstract

Nanotechnology, defined as engineering at the nanometer scale, involves developing materials or systems to perform a systematic arrangement for various platforms in biomedical applications. This study presents possible applications of carbon-based nanomaterials in regenerative biomedicine, drug delivery, and cancerous conditions. We highlight significant advancements in carbon nanotubes-based nanotechnology, with an emphasis on carbon nanotubes, which accelerate various regenerative therapies in the liver, nervous system, heart, vascular system, and bone tissue engineering. Using carbon nanomaterials to deliver drugs precisely to their site of action is also one area of interest, attracting the attention of researchers and giving great hope for carbon nanomaterials' widespread use in medicine. Moreover, green nanotechnology was introduced as an innovative and noninvasive discipline in carbon-based nanomaterials for human biomedicine. It can solve the problem of using dangerous and toxic chemical nanoscale materials.

Keywords: nano biomedicine; green nanotechnology; nanomaterial scaffolds; nanocarbon materials; regenerative biomedicine; cancer treatments

Introduction

Several characteristics of the physical, chemical, optical, magnetic, mechanical, electrical, and thermodynamic properties of nanomaterials were improved strongly compared with bulk materials [1, 2]. Additionally, nanotechnology has emerged in various fields, such as environmental science, agriculture, food industry, and medicine, due to nanoparticles' high ratio of surface area/volume atoms, which modify their physicochemical properties and increase their chemical reactivity [3, 4]. Biomedicine is an attractive application field for nanotechnology [5]. This technology may provide targeted therapy by modifying the nanoparticles' surface and developing nanoscale instruments in biomedicine [6]. Nanotechnology recreates the nanoscale features of tissues to improve cellular

adhesion, migration, and differentiation [7]. Tissue regeneration can be achieved by combining living cells and materials to provide biological functionality and stimulate cell proliferation using scaffolds. Nanotechnology covers broad aspects of tissue engineering, producing material structures that mimic the biological structure and provide efficient delivery systems. When mammalian cells receive signals for tissue regeneration, the structured nanoscale components from the surrounding biological environment are directed toward the target site. Nanotechnology-based products enhance the regeneration of damaged, cancerous, or nonfunctional tissues through improved interactions between material surfaces and biological entities [8].

Carbon nanotubes (CNTs) are nanosized, carbon-structured compounds with a regular, hollow graphitic structure. Their characteristics include having a large surface area/volume ratio, high length-to-diameter ratio, and very low weight. Their diameter ranges from 1 to 100 nm. CNTs comprise several layers of graphitic carbon concentric to each other. Each atom in CNTs is bonded to three neighboring atoms, and like graphite, CNTs have sp2 bonds, which confer their unique strength. CNTs are becoming increasingly popular as nanoscale carriers. Discovered in 1991 by Dr. Iijima [9], CNTs are nontoxic, have excellent optical properties, and have a significant ability to bind to other elements or particles for greater functionality [10]. Some CNTs in drug delivery systems share the same advantages as C-dots, in that the tumor's acidic environment provides a mechanism for drug release [11]. The degree of functionalization of carbon nanotubes varies; as a result, the amount of drug released can be accurately controlled [12]. Pharmaceutical CNTs appear more dynamic in their biological applications owing to their unique properties [13]. To overcome limitations, such as limited solubility and maximum biodistribution, scientists have begun to use CNTs for targeted drug delivery to treat cancer cells [14, 15]. CNTs can easily cross various biological boundaries, pass through the plasma membrane, and penetrate the cytoplasm through a "small nanoneedle," facilitating the transport and delivery of narrow molecules or desired treatments to the target tissue [16]. Additionally, the possibility of placing a large group of biochemical substances on CNTs surface paves the way for numerous medical applications [17]. CNTs are promising candidates due to three key features: (1) the utilization of single-walled CNTs containing functional groups as a biocompatible platform to deliver therapeutic or diagnostic drugs, (2) the continuous delivery of anticancer agent prodrug modules organized within tumor cells in a particular form, releasing the drug at the tumor site, and (3) tumor identification modules attached to the nanotube surface [16]. The fast-growing nanotechnology market has increased the demand for nanomaterials in recent years. The global nanomaterial trade in nanomedicine reached 242.6 billion dollars in 2021 and is projected to grow at an annual rate of 15.3% from 2021 to 2026, reaching 493.5 billion dollars by 2026.

This review explains the utilization of carbon-based nanomaterials in regenerative medicine, drug delivery, and cancer treatments, emphasizing CNTs in tissue regeneration, and highlights the main successes of these nanostructures' application in biomedicine.

Emergence of Carbon-based Nanomaterials in Biomedicine

CNTs were first discovered in 1991 in Japan [18]. Gradually, single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs) were developed, with distinct advantages based on their structures [17]. These nanostructures can carry various drugs, proteins, antibodies, DNA, and enzymes owing to their large and stable surface area. Additionally, functionalized CNTs can cross the cell membrane and deliver biological molecules to cells or organs. These advantages of CNTs lead to their application in drug delivery systems, diagnosis, treatment, and targeted therapies [19].

CNTs have emerged as powerful tools in improving biomedical approaches for managing numerous diseases, including cancer, liver disease, and neural disorder. CNTs can penetrate cell membranes and functionalize with almost every biomolecule or compound, allowing them to target cells and deliver drugs under appropriate conditions. Therefore, targeted drug delivery combined with selective treatment directed toward the intended tissues appears to be the most promising approach for CNTs [20].

In recent years, carbon nanomaterials have shown great progress in biomedical applications through

surface functionalization, which can specifically target tumor tissues, increasing the therapeutic potential and significantly reducing the adverse effects of therapy in drug delivery [21]. CNTs-based nanotechnology have catalyzed advancements in treatment of various diseases.

Carbon-based nanomedicine progress in liver regeneration

The liver is the largest organ in the body and plays a role in bile formation, energy production, and drug metabolism [22]. Liver transplantation is the only treatment strategy for patients with end-stage liver failure [23]. Although in more than 100 countries at least one liver transplantation occurred in 2020–2021, worldwide, most patients with life-threatening liver disease do not have access to liver transplantation, making biomedicine approaches a more effective solution [24]. Three-dimensional (3D) printing and cell therapies are promising candidates for treating liver diseases [25]. One nanotechnology-based method is electrospun scaffolds. The correct orientation of the fibers on the collector in the electrospinning method is essential for liver cell growth. The collector's condition greatly influences the type of fibers produced and their correct arrangement. Rotating collectors result in the production of aligned nanofibers, whereas stationary collectors result in randomly patterned nanofibers. Cellular behavior depends on the electrospun scaffold's surface topography. Several studies have confirmed that the rates of proliferation and attachment of primary hepatocyte cells on aligned nanofibers are noteworthy [26].

CNTs have shown promising progress in the interdisciplinary fields of nanotechnology and liver regenerative medicine. CNTs can be incorporated into scaffolds and hepatocytes to help regenerate liver tissues in liver tissue engineering. This approach can improve the treatment results of acute or chronic liver disorders by activating normal liver function [27]. The most recent research on scaffolds used for liver tissue engineering involves culturing cells as 3D spheroids. By modifying traditional electrospinning methods and shortening the fibers, Wei et al. created liver cell spheroids on scaffolds [28]. CNTs have been used in the structure of 3D liver scaffolds and in the hepatic differentiation of stem cells to improve cell affinity and mechanical strength [29]. The arrangement of CNTs in different polymer scaffolds has improved the porosity and mechanical strength [30]. Additionally, CNTs in the form of nanofibers create conductive surfaces and improve the formation of liver cell spheroids [31]. 3D scaffolds with CNTs, generally used for seeding liver cells, comprise microarchitecture porous scaffolds, such as Cryogels®, and scaffolds designed via 3D printing or electrospinning [32]. Despite the interesting physicochemical properties of CNTs, their toxicity and poor dispersion in water have been investigated and noncovalent functionalization has been proposed to increase their biocompatibility [33]. Generally, CNT nanocomposite scaffolds have emerged as promising frameworks for liver tissue engineering by facilitating the regeneration of the injured liver [34].

Carbon-based nanomaterials for neural disorder treatments

Neural injuries can seriously impair movements and sensory reactions, jeopardizing patients' quality of life, and imposing critical economic burdens [35]. Compared with other tissues, the complexity of the structure and function of the nervous system and its gradual regeneration rate make it more challenging to treat when an injury occurs. Common therapeutic approaches, including autografts, allografts, and pharmacological agents, cannot fully restore nervous system injuries [36], the regeneration of neural tissue at the injury site remains negligible. The major issues of neural injury include nervous degeneration, scar tissue formation, and loss of connections between neurons and surrounding cells [37]. Recent developments in nanotechnology and tissue engineering have attracted many researchers to invent nanomaterials for neural science use [36]. Nanomaterials present promising results in improving cell adhesion, cell proliferation, and neuronal cell differentiation to enhance neuron regeneration [37].

Various nanomaterial-based methods are available to investigate, prevent, or treat neural injuries. Nanomaterials are classified into inorganic materials—such as metals, alloys, silica, magnetic, upconversion nanoparticles, and quantum dots, and organic materials—such as polymeric nanoparticles, nanofibers, carbon-based nanomaterials (CNTs and graphene), liposomes, micelles, and dendrimers [37]. These are promising nanomaterials containing suitable physicochemical properties for neuroengineering applications; the selectivity and specificity of each nanomaterial depend on its surface

properties [38]. Owing to their unique properties, nanomaterials are applied to distinct technological challenges associated with conventional science [39]. CNTs are promising nanomedicine for central nervous system (CNS) diseases. Drug delivery to the nervous system is limited by the presence of two anatomical and biochemical dynamic barriers separating the blood from the cerebral parenchyma: the blood–brain barrier and the blood–cerebrospinal fluid barrier [40]. These barriers restrict drug delivery to the CNS, leading to inefficient diagnosis and therapy of neurological disorders [15]. CNTs are biocompatible and permissive substrates/scaffolds for neural cells, thus revolutionizing neurological disease diagnosis and treatment. CNTs are increasingly being used as scaffolds for neuronal growth and differentiation [41, 42]. Based on their physicochemical properties, CNTs have the potential to be employed as theranostic tools for neurological pathologies, such as Alzheimer's disease and Parkinson's disease, as well as for ischemic stroke diagnosis and treatment [43]. Furthermore, researchers have achieved controlled and targeted delivery of active pharmaceutical ingredients by tuning the CNT surface functionality [44].

Carbon-based nanomaterials progress in heart tissue engineering

Heart valve disease mortality has increased the demand for implantable tissue-engineered heart valves. Despite the significant progress in improving tissue-engineered heart valve constructs, viable and functional human implantable constructs remain ambiguous [45]. Cardiovascular diseases are a leading cause of death in many countries [46]. Cardiac myocytes are differentiated cells with minimal fundamental ability to self-regenerate; therefore, cardiac tissue engineering has emerged as one of the most accurate cardiac repair mechanisms [47]. Nanotechnology has invented new methods for drug delivery to prevent cardiovascular disease (e.g., stroke or high blood pressure) [48]. Owing to the increasing demand for heart tissue replacement and reconstruction, cardiovascular tissue engineering has quickly transitioned to nanotechnology [49]. The microscale and nanoscale technologies include nano/microfiber-based scaffolds, 3D cell-encapsulated hydrogels, microfluidics, micro-bioreactors, and nano/microscale biosensors. Additionally, computational methods for biological tissue simulation have improved the functionality of implantable tissue-engineered constructs [45]. These methods promote the accurate delivery of growth factors or genes to specific cells in certain tissue areas, achieve microstructure synthesis with anisotropic arrangement and layer-by-layer fabrication [50], utilize micromolding for fabricating complex geometries of tissue-engineered heart valves [51], and control microfluidic delivery of chemicals, biomolecules, and nonviral gene carriers [52].

Several studies have proposed advantageous nanomaterials for heart treatment. The CNT scaffolds promote cardiomyocyte proliferation, maturation, and long-term survival. 3D scaffolds of CNT-based composites can also promote cardiomyocyte growth, electrophysiological maturation, and functional syncytium formation. For example, a microporous and self-standing material made of polydimethylsiloxane, containing micrometric cavities, and integrating MWCNTs into a 3D scaffold displayed improved viability and a more defined and mature sarcomeric phenotype compared with the traditional scaffolds. These properties are essential in cardiac tissue engineering and offer novel strategies for developing innovative cardiac repair therapies [47].

Vascular tissue engineering progress using carbon-based nanomaterials

Traditional vascular tissue engineering methods were bioreactor-based, expensive, difficult, and time-consuming. Advances in nanotechnology improved the structure of vascular scaffolds and induced directed stem cell differentiation into the desired cell type [53]. Controlling cell behavior is essential in vascular tissue engineering. Indeed, nanotechnology provides an appropriate environment for directing cells toward cell differentiation and tissue assembly using nanostructured hydrogels and scaffolds [54]. For example, type I collagen nanofibers produced by electrospinning improve mesenchymal stem cell proliferation [55]. Advances in nanotechnology approaches for rapidly fabricating vascular tissue and eliminating bioreactors are state-of-the-art advances in vascular tissue engineering [53].

The vascular grafts used in tissue engineering should be covered with thrombogenic endothelial cells. Tissue assembly includes three methods: cell seeding of porous scaffolds, cell embedding inside

hydrogels, and sheet assembly with rolling single-cell layers [56]. The three main scaffold structures in vascular tissue engineering are hydrogels, solid porous scaffolds, and nanofibers. Nanobased scaffold structures mimic the organization of a natural vascular extracellular matrix (ECM), thus improving cell attachment [57]. Interestingly, CNTs promoted endothelial tubulogenesis, a late step during angiogenesis. Furthermore, mechanistic studies demonstrated that CNTs, but not fullerenes, could induce integrin clustering and activate focal adhesion kinase and downstream phosphoinositide-3-kinase signaling in endothelial cells, thus explaining the distinct angiogenic outcomes [58].

Evidence indicates that vascular nanostructured scaffolds containing a monolayer of stabilized lipids can reduce thrombogenicity [59]. Three nanotechnology-based approaches are available to develop thromboresistant surfaces: stabilization of blood thromboresistant molecules to produce desired nanosurfaces [60], stabilization of molecules confirmed to increase endothelial cells [61], and an increase in the number of endothelial cells through iron nanoparticle or magnetic microbead labeling. Amphiphilic, lipid-like surfaces made of antithrombotic phospholipid polymers can prevent thrombosis after implantation [62]. Polyurethane-thromboresistant nanocomposites were also prepared by adding polyhedral oligomeric silsesquioxane [63]. Nanodrugs can target vascular occlusion sites via the mechanical activation of blood vessels by the high fluid shear strain in the vessel. *In vitro* and *in vivo* studies have confirmed the efficacy of these drugs [64].

In a tumor microenvironment, angiogenesis occurs abnormally to meet the metabolic and nutritional demands of cancer cell growth; therefore, regulating angiogenesis using carbon nanostructures, including CNTs, might treat cancer [65, 66]. Cheng et al. used SWCNTs and three molecules, including arginine, glycine, and aspartic acid, to modify SWCNTs' surface to target angiogenesis sites. The nanotubes were loaded with thalidomide as an anti-angiogenesis drug and rhodamine as a tracking dye. In a zebrafish tumor model, nanoconjugates can bind to newly formed blood vessels and significantly inhibit angiogenesis [67].

SWCNTs can also be used to treat cancer by inhibiting angiogenesis. Wierzbicki et al. compared the antiangiogenic potential of diamond nanoparticles, graphite nanoparticles, graphene nanoparticles, MWCNTs, and C_{60} fullerene. Diamond nanoparticles and MWCNTs exhibit fewer antiangiogenic properties in the chicken chorioallantoic membrane. C_{60} fullerene can even increase blood vessel formation, suggesting that the effect of carbon nanomolecules on angiogenesis depends on their morphology [68]. The beneficial and adverse effects of CNTs on vascular systems remain largely unknown and require further extensive studies [69].

Bone tissue engineering using carbon nanomaterials

Nanotechnology holds promise for universally improving nanomaterials used in bone regeneration compared with their micron-structured counterparts [70]. Engineered nanoparticles and 3D scaffolds facilitate new bone growth. Natural bone comprises 30% w/v organic collagen fibrils and 70% w/v inorganic calcium phosphate crystals [71]. Advances in nanotherapeutic approaches have led to further manipulation of the extracellular matrix and provided more appropriate surface chemistry and interconnected porosity for cellular proliferation and angiogenesis [72]. Critical bone defects caused by tumor resection, trauma, or surgery have posed challenges to the current standard therapies [73]. Bone repair mainly depends on the wound size [73]. Overall, CNTs have great potential for bone tissue engineering. They have good strength, elasticity, and fatigue resistance, making them good strengthening materials in bone tissue engineering. Additionally, CNTs with strong bonding capacity contribute to effective load transfer and reinforce the strength and toughness of the matrix [74]. Conversely, their porous structure and high surface-to-volume ratio are useful for protein absorption, cell adhesion, and drug loading. Therefore, CNT-based materials can develop and integrate bone healing and drug systems [75]. However, pure CNT scaffolds are unsuitable for regenerative bone tissue culture and should be used with other materials, such as polycaprolactone, poly-lactic acid, or poly (lactic-co-glycolic) acid [76, 77].

The rate of bone deficiency repair exceeds the healing capacity of osteogenic tissues, as fibrous connective tissue tends to dominate the free space more rapidly than normal bone tissue [78]. Biodegradable polymers offer adjustable degradation

rates and ease of processing and increase the overall mechanical strength of the composite owing to their high compressive modulus and hardness [79]. Artificial nanomaterial development to repair the bone's nanoscale features can lead to promising results in biomaterials [80].

Figure 1 represents the carbon-based nanomedicine and tissue engineering contributing to different systems and organs in the human body.

Carbon-based nanomaterials for drug delivery

The emerging discipline of nanomedicine has brought nanotechnology and medicine together over the past decade to develop novel therapies and improve current treatments. Nanomedicine directs internalization and penetration, facilitating targeted drug delivery and combination therapy [81]. Two factors play crucial roles in successful drug delivery: targeting and triggering. Nanotechnology-based drug delivery methods decrease the therapeutic dose for cancer treatment and other diseases and minimize their side effects. To attain this goal, drug delivery should have the ability to specifically target tumor cells [82]. Doxorubicin (DOX) is a common therapy for various cancers, inducing apoptosis in cancer and normal cells, including those in the heart and liver. However, nanotechnology-based compounds such as liposomes and magnetic nanoparticles direct DOX to the tumor area without affecting healthy cells [83]. They target tumor cells via the interaction between ligands and receptors. Cancer cells overexpress some molecules on their surface, distinguishing them from normal cells. Such molecules include the epidermal growth factor receptor, the folate receptor, glycoproteins, and the transferrin receptor. The nanoparticle surface ligands interact with cancer cell receptors and trigger receptor-mediated endocytosis [84]. Nanoparticles can also be modified by specific biological and chemical groups, including amino acids, carbohydrate monoclonal antibodies, peptides, and vitamins, which are used to target tumor sites and increase drug uptake [85].

Moreover, the triggered release or modulation of drug release is another aspect that enhances drug delivery systems. Tumor sites have acidic extracellular pH values [86], and pH-sensitive nanomaterials are designed to release drugs in the acidic cancer microenvironment. For example, cationic liposomes modified with sorafenib and siRNA, along with carboxymethyl chitosan, have gained pH-sensitive properties. Nanomaterials can also be designed with light-, enzyme-, and redox-responsive characteristics [87]. Endogenous and

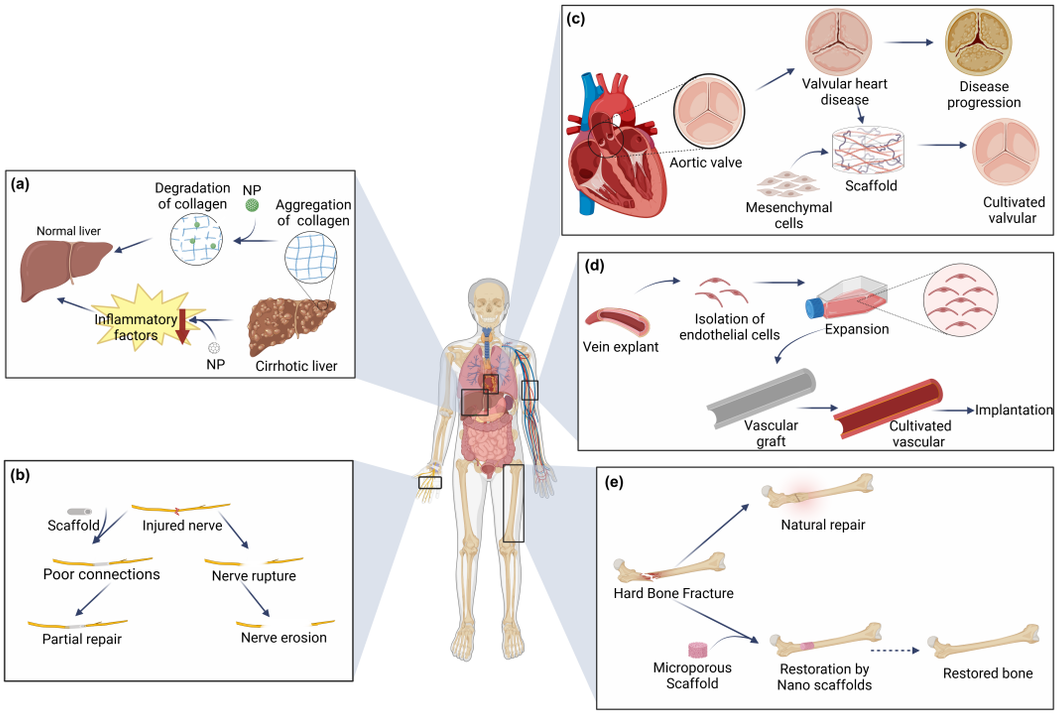

Fig. 1 CNTs-based nanotechnology using nanoscaffolds contributes to **(a)** reducing liver cirrhosis symptoms, **(b)** assisting nerve repair, **(c)** treating heart valve diseases, **(d)** creating artificial vessels, and **(e)** helping restore severe bone trauma.

exogenous stimuli-responsive drug delivery systems are developed and release drugs at the specific tumor sites (Fig. 2). Endogenous stimulus nanoplatforms are designed considering the tumor's microenvironment, and the nanoparticle determines the tumor's location and the drug release depending on the characteristics of the microenvironment around the tumor. For example, the tumor microenvironment is acidic, and existing hypoxia leads to high concentrations of GSH, ROS, and some specific enzymes. Nanoparticles responsive to exogenous stimuli, such as magnetic field, laser, ultrasonic waves, and temperature, are developed, thereby enhancing their applicability in more complex versatile scenarios [88].

Compared to other nanomaterials, CNTs appear more dynamic in drug delivery. For example, the main application of quantum dots is exclusively in cancer cell imaging, whereas CNTs can be used for imaging, drug delivery, and thermal ablation. The shape of CNTs allows different drugs to be transported by various methods, such as active radiation, active lipid permeation, or endocytosis. CNTs are easily attached to the cell surface and taken up by the cell membrane. Their hollow structure and unique properties, including high drug-loading capacity, large surface area, high mechanical strength, and good chemical stability, make them attractive candidates as nanoscale carriers for drug delivery [89, 90].

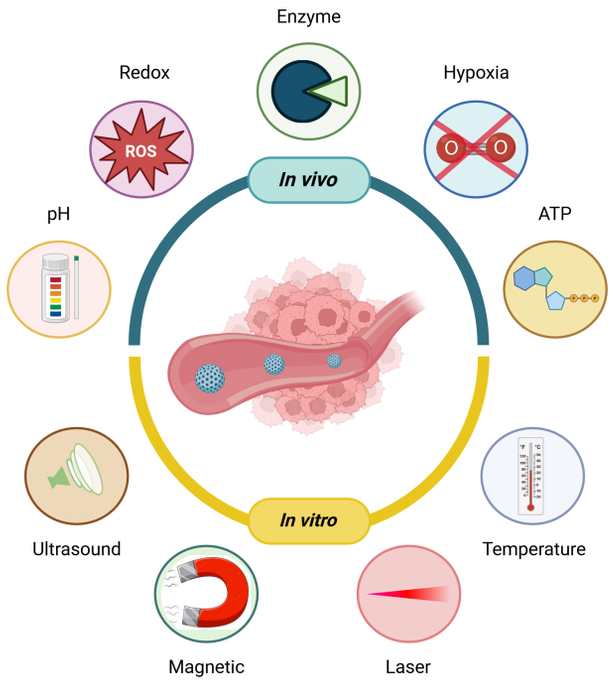

Fig. 2 Schematic representation of exogenous and endogenous stimulus-responsive nanoplatforms for tumor therapy.

CNT-based drug delivery systems are widely used for cancer treatment, given their targeting function. CNTs can be designed to be sensitive to the tumor microenvironment, thereby reducing multidrug resistance and inhibiting cell proliferation and the cell cycle in infected cancer cells [91]. Peptide-modified SWCNTs have high antitumor effects and enhanced targeting. CNTs also serve as carriers for immunization against antigens. Some substances that are not easily delivered to the brain, such as acetylcholine, can be easily delivered using SWCNTs. However, chemical modification of SWCNTs with amide and ester bonds allows the drug to have a sufficient delay in drug release from water and organic media, increasing its solubility in water and organic media [91].

Green Nanotechnology in Carbon-based Biomedicine

The use of various nanoparticles across science and technology has sparked increasing interest in integrating natural and biological particles into nanotechnology. The presence of many toxic chemicals and the extreme environmental concerns associated with the physicochemical production of nanoparticles have prompted the employment of green methods using biological sources [92]. Given the current materials and processes involved in nanotechnology techniques, there is a need to limit nonrenewable resources that generate hazardous waste. Therefore, the combination of green chemistry with nanotechnology is highly favorable due to their biodegradability, renewability, and low cost as biological sources [93]. Scientists, engineers, and entrepreneurs face challenges ranging from technical issues in science to regulatory issues in industry. Just as nanoscale inventions require new insights from scientists, they also drive the development of policies aimed at designing novel products that prioritize human and environmental health. This recognition has led to the development of "green nanoscience" [94]. Green nanotechnology refers to the use of biological sources to employ biological activities and specificities to develop modern technology at the nanoscale [94]. Therefore, by integrating green nanotechnology principles, the subsequent products

can establish safe and ecofriendly nanoparticles lacking toxicity in their synthesis, reducing environmental impacts, improving conservation, and protecting resources, and human health [94]. Many microorganisms can produce nanostructured mineral crystals and metallic nanoparticles with properties similar to those of chemically synthesized materials while focusing on the strict control of particle size, shape, and composition. Some examples include the formation of magnetic nanoparticles by magnetotactic bacteria, the production of silver nanoparticles inside the periplasmic space of *Pseudomonas stutzeri*, and the formation of palladium nanoparticles using sulfate-reducing bacteria [95]. Furthermore, actinomycetes are prokaryotes and have the exceptional ability to produce secondary metabolites, including antibiotics. A novel actinomycete genus, *Thermomonospora* sp., can synthesize extracellular gold nanoparticles when exposed to gold ions under alkaline conditions [96]. Fungi have been widely used for the biosynthesis of nanoparticles with well-defined dimensions. Compared to bacteria, fungi are preferred as a source for producing large quantities of nanoparticles because they secrete higher amounts of proteins, which contributes to the higher productivity of nanoparticle formation [97]. Moreover, plants are even better candidates than bacteria and fungi for nanoparticle synthesis. They were introduced for nanoparticle synthesis owing to advantages such as being easily available, being safe to handle, and possessing a broad variability of metabolites [98]. Some plants are specifically used to investigate their role in nanoparticle synthesis. Gold nanoparticles could be synthesized using live alfalfa plants [99]. Furthermore, silver, nickel, cobalt, zinc, and copper nanoparticles have been synthesized from live *Brassica juncea* (Indian mustard), *Medicago sativa* (alfalfa), and *Helianthus annus* (sunflower). Certain plants, such as *B. juncea,* accumulate higher concentrations of metals than others and are termed hyperaccumulators [100]. Carbon is one of the most abundant elements on Earth. In recent years, various carbon-based nanoparticles, such as carbon quantum dots, carbon dots, and CNTs with diverse applications, have been introduced as one of the most valuable groups of nanomaterials [101]. Carbon nanomaterials possess unique characteristics such as remarkable electrical conductivity, a large surface area, and excellent mechanical strength, making them highly promising for applications across various fields [93]. Green synthesis of carbon materials has several advantages such as the low-cost, non-toxic raw materials, simple operations, expeditious reactions, renewable resources [102]. Table 1 presents some examples of applications of green synthesized carbon nanomaterials, including drug delivery, regenerative medicine, tissue engineering, and cancer treatment. The novel outcomes of green synthesis in nanotechnology can be further explored through *in silico* and *in vitro* research, where carbon nanoparticle synthesis and design have displayed potential outcomes across diverse fields [103−110]. Green nanotechnology improves the biocompatibility of carbon nanoparticles in different biomedicine fields.

Conclusions

Carbon-based nanomaterials have drawn much interest in biomedical engineering due to their distinctive physical chemical, and optical properties. CNTs, as integral components of cutting-edge nanotechnology have shown promising results in drug delivery, regenerative medicine and cancer treatments. By modifying the surface chemistry of CNTs, scientists can attach specific molecules that can bind to receptors on the surface of particular cells or tissues. This allows for the selective delivery of therapeutic agents to the desired location within the body, minimizing the impact on healthy cells and reducing side effects. Innovations in controlled release mechanisms, responsive to external stimuli or medical conditions, will help to fabricate carbon-based nanomaterials for effective drug delivery. Moreover, the green synthesis of carbon-based nanomaterials not only substantially cut the costs of producing nanomaterials, enabling their usage on an industrial scale, but also minimize the quantity of trash produced, making the process more environmentally friendly.

This work reviews current important branches of biomedicine through the effective and efficient use of nanotechnology, emphasizing CNTs to facilitate the discovery of solutions for human degenerative problems and remarkable advances in regenerative medicine. Therefore, conducting additional studies on carbon-based nanotechnology will help generate new

Table 1 A summary of the application of green nanochemistry principles for carbon materials-based drug delivery, regenerative medicine, tissue engineering, and cancer treatment

Green carbon nanoparticles	Use	Advantages	Ref.
Naked carbon nanoparticles driven from commercial food-grade honey	Imaging sentinel lymph nodes	Real-time high-resolution intraoperative photoacoustic imaging in conjunction with a near-infrared probe	[103]
Carbon nanoparticles using an edible yogurt drink (lassi) by microwave irradiation	Potential utilization in bioimaging and drug delivery	Successful delivery of drugs into the nuclei and its subsequent pH-dependent activity for releasing CNPs as promising drug delivery vehicles in nanomedicine	[104]
Bioactive polysaccharides based on graphene oxide nanoparticle	Promising carrier for anticancer drug delivery	Major advantages of the developed approach include demonstrating its capability as a promising nanocarrier for biomedical applications	[105]
Native bacterial cellulose combined with functionalized multi-walled carbon nanotubes	3D scaffold for osteoblastic cell culture	Bacterial cellulose-multi-walled carbon nanotube scaffolds support osteoblast viability, adhesion, and proliferation at higher levels compared to traditional culture substrates	[106]
Cross-linked hollow fluorescent carbon nanoparticles with green emission	Cell-imaging applications	Hollow fluorescent carbon nanoparticles are a superior fluorescent bioimaging agent based on their low toxicity, stability, and resistance to photobleaching, compared with traditional dyes and CdTe quantum dots	[107]
Green carbon dots synthesized from renewable biomass such as agro-waste, plants or medicinal plants, and other organic biomaterials	Bioimaging, biosensing, and nanomedicine	Excellent luminescence effect, strong stability, and good biocompatibility	[108]
Renewable and ecofriendly carbon-based nanomaterials	Dental tissue engineering	Ideal for dental tissue engineering, due to various functional groups	[109]
Aqueous fluorescent C-dots synthesized from cinnamon, red chili, turmeric, and black pepper	Human glioblastoma cancer cell treatment	Tumor cell growth inhibition properties observed in the spice-derived C-dots	[110]

concepts for the ongoing fight against cancer, heart valve diseases, severe bone trauma, and other diseases.

CRediT Author Statement

Sayed Mustafa Banihashemi Jozdani and **Zohreh Hashemian** wrote the initial format of the manuscript and prepared the figures, **Sajedeh Ebrahim Damavandi** contributed to manuscript writing and table arrangement, **Zahra Elyasigorji** designed the manuscript sections and organized the finalized manuscript, **Massoud Vosough** supervised, directed and managed the study, **Zahra Elyasigorji** and **Massoud Vosough** approved and revised the last version to be submitted and published.

Acknowledgements

The authors would thank to the Iranian Biological Resource Center (IBRC) and Royan institute for their scientific supports.

Conflict of Interests

The authors of this study confirm that there are no known conflicts of interest associated with this publication.

References

[1] J. Jeevanandam, A. Barhoum, Y.S. Chan, et al. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. *Beilstein Journal of Nanotechnology*, 2018, 9: 1050−1074. https://doi.org/10.3762/bjnano.9.98

[2] J.W. Qin, X.H. Chen, Y.L. Wang, et al. Fabrication techniques and the formation mechanism of nanoparticles and nanoclusters in metal materials. *Metals*, 2022, 12(9): 1420. https://doi.org/10.3390/met12091420

[3] M. Thiruvengadam, G. Rajakumar, I.M. Chung. Nanotechnology: Current uses and future applications in the food industry. *3 Biotech*, 2018, 8(1): 74. https://doi.org/10.1007/s13205-018-1104-7

[4] C. Fabbro, H. Ali-Boucetta, T. Da Ros, et al. Targeting carbon nanotubes against cancer. *Chemical Communications*, 2012, 48(33): 3911. https://doi.org/10.1039/c2cc17995d

[5] D.Y. Li, Y.X. Liu, N. Wu. Application progress of nanotechnology in regenerative medicine of diabetes mellitus. *Diabetes Research and Clinical Practice*, 2022, 190: 109966. https://doi.org/10.1016/j.diabres.2022.109966

[6] J.K. Patra, G. Das, L.F. Fraceto, et al. Nano based drug delivery systems: Recent developments and future prospects. *Journal of Nanobiotechnology*, 2018, 16: 71. https://doi.org/10.1186/s12951-018-0392-8

[7] Y.F. Yang, A. Chawla, J. Zhang, et al. Applications of nanotechnology for regenerative medicine; healing

tissues at the nanoscale. In: Principles of Regenerative Medicine. Amsterdam: Elsevier, 2019: 485–504. https://doi.org/10.1016/b978-0-12-809880-6.00029-1

[8] Q. Ali, S. Malik, A. Malik, et al. Role of modern technologies in tissue engineering. *Archives of Neuroscience*, 2020, 7(1): e90394. https://doi.org/10.5812/ans.90394

[9] S. Iijima. Helical microtubules of graphitic carbon. *Nature*, 1991, 354(6348): 56−58. https://doi.org/10.1038/354056a0

[10] D. Yang, F. Yang, J.H. Hu, et al. Hydrophilic multi-walled carbon nanotubes decorated with magnetite nanoparticles as lymphatic targeted drug delivery vehicles. *Chemical Communications*, 2009, 7(29): 4447−4449. https://doi.org/10.1039/b908012k

[11] L.Y. Niu, L. J. Meng, Q.H. Lu. Folate-conjugated PEG on single walled carbon nanotubes for targeting delivery of doxorubicin to cancer cells. *Macromolecular Bioscience*, 2013, 13(6): 735−744. https://doi.org/10.1002/mabi.201200475

[12] A. Pistone, D. Iannazzo, S. Ansari, et al. Tunable doxorubicin release from polymer-gated multiwalled carbon nanotubes. *International Journal of Pharmaceutics*, 2016, 515(1−2): 30−36. https://doi.org/10.1016/j.ijpharm.2016.10.010

[13] J.Y. He, Y.Y. Hou, Z.X. Zhang, et al. Carbon-based nanozymes: How structure affects performance. *Nano Biomedicine and Engineering*, 2024, 16(1): 28−47. https://doi.org/10.26599/nbe.2024.9290053

[14] W.X. Zhang, Z.Z. Zhang, Y.G. Zhang. The application of carbon nanotubes in target drug delivery systems for cancer therapies. *Nanoscale Research Letters*, 2011, 6(1): 555. https://doi.org/10.1186/1556-276X-6-555

[15] J. Kaur, G.S. Gill, K. Jeet. Applications of carbon nanotubes in drug delivery. In: Characterization and Biology of Nanomaterials for Drug Delivery. Amsterdam: Elsevier, 2019: 113–135. https://doi.org/10.1016/b978-0-12-814031-4.00005-2

[16] M. Chakrabarti, R. Kiseleva, A. Vertegel, et al. Carbon nanomaterials for drug delivery and cancer therapy. *Journal of Nanoscience and Nanotechnology*, 2015, 15(8): 5501−5511. https://doi.org/10.1166/jnn.2015.10614

[17] S. Marchesan, K. Kostarelos, A. Bianco, et al. The winding road for carbon nanotubes in nanomedicine. *Materials Today*, 2015, 18(1): 12−19. https://doi.org/10.1016/j.mattod.2014.07.009

[18] B.O. Murjani, P.S. Kadu, M. Bansod, et al. Carbon nanotubes in biomedical applications: Current status, promises, and challenges. *Carbon Letters*, 2022, 32(5): 1207−1226. https://doi.org/10.1007/s42823-022-00364-4

[19] J.H. Ma, G.F. Wang, X.Y. Ding, et al. Carbon-based nanomaterials as drug delivery agents for colorectal cancer: Clinical preface to colorectal cancer citing their markers and existing theranostic approaches. *ACS Omega*, 2023, 8(12): 10656−10668. https://doi.org/10.1021/acsomega.2c06242

[20] V. Negri, J. Pacheco-Torres, D. Calle, et al. Carbon Nanotubes in Biomedicine. In: Surface-modified Nanobiomaterials for Electrochemical and Biomedicine Applications. A.R. Puente-Santiago, D. Rodríguez-Padrón, Eds. Springer International Publishing: Cham., 2020: 177–217. https://doi.org/10.1007/978-3-030-55502-3_6

[21] B. Hosnedlova, M. Kepinska, C. Fernandez, et al. Carbon nanomaterials for targeted cancer therapy drugs: A critical review. *The Chemical Record*, 2019, 19(2−3): 502−522. https://doi.org/10.1002/tcr.201800038

[22] S.K. Asrani, H. Devarbhavi, J. Eaton, et al. Burden of liver diseases in the world. *Journal of Hepatology*, 2019, 70(1): 151−171. https://doi.org/10.1016/j.jhep.2018.09.014

[23] L.H. Gu, F. Zhang, J.H. Wu, et al. Nanotechnology in drug delivery for liver fibrosis. *Frontiers in Molecular Biosciences*, 2022, 8: 804396. https://doi.org/10.3389/fmolb.2021.804396

[24] E.S. Mirdamadi, D. Kalhori, N. Zakeri, et al. Liver tissue engineering as an emerging alternative for liver disease treatment. *Tissue Engineering Part B: Reviews*, 2020, 26(2): 145−163. https://doi.org/10.1089/ten.teb.2019.0233

[25] A. Vasudevan, D.M. Tripathi, S. Sundarrajan, et al. Evolution of electrospinning in liver tissue engineering. *Biomimetics*, 2022, 7(4): 149. https://doi.org/10.3390/biomimetics7040149

[26] T.S.R. Bate, V.L. Gadd, S.J. Forbes, et al. Response differences of HepG2 and Primary Mouse Hepatocytes to morphological changes in electrospun PCL scaffolds. *Scientific Reports*, 2021, 11: 3059. https://doi.org/10.1038/s41598-021-81761-z

[27] D.G. Nair, R. Weiskirchen. Recent advances in liver tissue engineering as an alternative and complementary approach for liver transplantation. *Current Issues in Molecular Biology*, 2023, 46(1): 262−278. https://doi.org/10.3390/cimb46010018

[28] J.J. Wei, J.F. Lu, Y.W. Liu, et ak. Spheroid culture of primary hepatocytes with short fibers as a predictable *in vitro* model for drug screening. *Journal of Materials Chemistry B*, 2016, 4(44): 7155−7167. https://doi.org/10.1039/c6tb02014c

[29] G. Lekshmi, S.S. Sana, V.H. Nguyen, et al. Recent progress in carbon nanotube polymer composites in tissue engineering and regeneration. *International Journal of Molecular Sciences*, 2020, 21(17): 6440. https://doi.org/10.3390/ijms21176440

[30] B. Gorain, H. Choudhury, M. Pandey, et al. Carbon nanotube scaffolds as emerging nanoplatform for myocardial tissue regeneration: A review of recent developments and therapeutic implications. *Biomedicine & Pharmacotherapy*, 2018, 104: 496−508. https://doi.org/10.1016/j.biopha.2018.05.066

[31] C.A. Che Abdullah, E.L. Albert. Carbon nanotubes as biological transporters and tissue-engineering scaffolds. In: Synthesis, Technology and Applications of Carbon Nanomaterials. Amsterdam: Elsevier, 2019: 135–156. https://doi.org/10.1016/b978-0-12-815757-2.00006-1

[32] U. Jammalamadaka, K. Tappa. Recent advances in biomaterials for 3D printing and tissue engineering. *Journal of Functional Biomaterials*, 2018, 9(1): 22. https://doi.org/10.3390/jfb9010022

[33] M. Assali, N. Kittana, S. Alhaj-Qasem, et al. Noncovalent functionalization of carbon nanotubes as a scaffold for tissue engineering. *Scientific Reports*, 2022, 12: 12062. https://doi.org/10.1038/s41598-022-16247-7

[34] A. Shar, A. Shar, D. Joung. Carbon nanotube nanocomposite scaffolds: Advances in fabrication and applications for tissue regeneration and cancer therapy. *Frontiers in Bioengineering and Biotechnology*, 2023, 11: 1299166. https://doi.org/10.3389/fbioe.2023.1299166

[35] W.F. Dai, Y.T. Yang, Y.M. Yang, et al. Material advancement in tissue-engineered nerve conduit. *Nanotechnology Reviews*, 2021, 10(1): 488−503. https://doi.org/10.1515/ntrev-2021-0028

[36] A. Halim, K.Y. Qu, X.F. Zhang, et al. Recent advances in the application of two-dimensional nanomaterials for neural tissue engineering and regeneration. *ACS Biomaterials Science & Engineering*, 2021, 7(8): 3503−3529. https://doi.org/10.1021/acsbiomaterials.1c00490

[37] R. Kumar, K.R. Aadil, S. Ranjan, et al. Advances in nanotechnology and nanomaterials based strategies for neural tissue engineering. *Journal of Drug Delivery Science and Technology*, 2020, 57: 101617. https://doi.org/10.1016/j.jddst.2020.101617

[38] F. Wang, H. Wu, V. Venkataraman, et al. Silk fibroin-poly(lactic acid) biocomposites: Effect of protein-synthetic polymer interactions and miscibility on material properties and biological responses. *Materials Science & Engineering C, Materials for Biological Applications*, 2019, 104: 109890. https://doi.org/10.1016/j.msec.2019.109890

[39] M. Chawla, R. Kumar, P.F. Siril, High catalytic activities of palladium nanowires synthesized using liquid crystal templating approach. *Journal of Molecular Catalysis A: Chemical*, 2016, 423: 126–134. https://doi.org/10.1016/j.molcata.2016.06.014

[40] F. Re, M. Gregori, M. Masserini. Nanotechnology for neurodegenerative disorders. *Maturitas*, 2012, 73(1): 45−51. https://doi.org/10.1016/j.maturitas.2011.12.015

[41] K.K. Bokara, J.Y. Kim, Y.I. Lee, et al. Biocompatability of carbon nanotubes with stem cells to treat CNS injuries. *Anatomy & Cell Biology*, 2013, 46(2): 85. https://doi.org/10.5115/acb.2013.46.2.85

[42] J.L. Gilmore, X. Yi, L.D. Quan, et al. Novel nanomaterials for clinical neuroscience. *Journal of Neuroimmune Pharmacology*, 2008, 3(2): 83−94. https://doi.org/10.1007/s11481-007-9099-6

[43] P.P. Komane, Y.E. Choonara, L.C.mdu Toit, et al. Diagnosis and treatment of neurological and ischemic disorders employing carbon nanotube technology. *Journal of Nanomaterials*, 2016, 2016: 9417874. https://doi.org/10.1155/2016/9417874

[44] R. Kumar, A. Singh, K. Sharma, et al. Preparation, characterization and *in vitro* cytotoxicity of Fenofibrate and Nabumetone loaded solid lipid nanoparticles. *Materials Science & Engineering C, Materials for Biological Applications*, 2020, 106: 110184. https://doi.org/10.1016/j.msec.2019.110184

[45] A. Hasan, J. Saliba, H. Pezeshgi Modarres, et al. Micro and nanotechnologies in heart valve tissue engineering. *Biomaterials*, 2016, 103: 278−292. https://doi.org/10.1016/j.biomaterials.2016.07.001

[46] K. Mc Namara, H. Alzubaidi, J.K. Jackson. Cardiovascular disease as a leading cause of death: How are pharmacists getting involved. *Integrated Pharmacy Research and Practice*, 2019, 8: 1−11. https://doi.org/10.2147/iprp.s133088

[47] V. Martinelli, S. Bosi, B. Peña, et al. 3D carbon-nanotube-based composites for cardiac tissue engineering. *ACS Applied Bio Materials*, 2018, 1(5): 1530–1537. https://doi.org/10.1021/acsabm.8b00440

[48] S. Sim, N. Wong. Nanotechnology and its use in imaging and drug delivery (Review). *Biomedical Reports*, 2021, 14(5): 42. https://doi.org/10.3892/br.2021.1418

[49] A. Benko, L.B. Truong, D. Medina-Cruz, et al. Green nanotechnology in cardiovascular tissue engineering. In: Tissue Engineering. Amsterdam: Elsevier, 2022: 237–281. https://doi.org/10.1016/b978-0-12-824064-9.00012-5

[50] A.P. Durko, M.H. Yacoub, J. Kluin. Tissue engineered materials in cardiovascular surgery: The surgeon's perspective. *Frontiers in Cardiovascular Medicine*, 2020, 7: 55. https://doi.org/10.3389/fcvm.2020.00055

[51] S. Jana, B.J. Tefft, D.B. Spoon, et al. Scaffolds for tissue engineering of cardiac valves. *Acta Biomaterialia*, 2014, 10(7): 2877−2893. https://doi.org/10.1016/j.actbio.2014.03.014

[52] Onoe, H., Okitsu, T., Itou, A., Kato-Negishi, M., Gojo, R., Kiriya, D., Sato, K., Miura, S., Iwanaga, S., Kuribayashi-Shigetomi, K. et al. Metre-long cell-laden microfibres exhibit tissue morphologies and functions. *Nature Materials*, 2013, 12(6): 584−590. https://doi.org/10.1038/nmat3606

[53] A. Weekes, N. Bartnikowski, N. Pinto, et al. Biofabrication of small diameter tissue-engineered vascular grafts. *Acta Biomaterialia*, 2022, 138: 92−111. https://doi.org/10.1016/j.actbio.2021.11.012

[54] C.D. Devillard, C.A. Marquette. Vascular tissue engineering: Challenges and requirements for an ideal large scale blood vessel. *Frontiers in Bioengineering and Biotechnology*, 2021, 9: 721843. https://doi.org/10.3389/fbioe.2021.721843

[55] A.C. Bean, R.S. Tuan. Fiber diameter and seeding density influence chondrogenic differentiation of mesenchymal stem cells seeded on electrospun poly(ε-caprolactone) scaffolds. *Biomedical Materials*, **2015**, 10(1): 015018. https://doi.org/10.1088/1748-6041/10/1/015018

[56] L. Song, D. Sengupta, C.E. Shu. Vascular tissue engineering: From *in vitro* to *in situ*. *WIREs Systems Biology and Medicine*, 2014, 6(1): 61–76. https://doi.org/10.1002/wsbm.1246

[57] S. Pradhan, O.A. Banda, C.J. Farino, et al. Biofabrication strategies and engineered *in vitro* systems for vascular mechanobiology. *Advanced Healthcare Materials*, 2020, 9(8): e1901255. https://doi.org/10.1002/adhm.201901255

[58] P. Chaudhuri, R. Harfouche, S. Soni, et al. Shape effect of carbon nanovectors on angiogenesis. *ACS Nano*, 2010, 4(1): 574−582. https://doi.org/10.1021/nn901465h

[59] A. Laganowsky, E. Reading, T.M. Allison, et al. Membrane proteins bind lipids selectively to modulate their structure and function. *Nature*, 2014, 510(7503): 172−175. https://doi.org/10.1038/nature13419

[60] M. Ashcraft, M. Douglass, Y.J. Chen, et al. Combination strategies for antithrombotic biomaterials: An emerging trend towards hemocompatibility. *Biomaterials Science*, 2021, 9(7): 2413−2423. https://doi.org/10.1039/d0bm02154g

[61] A. Assmann, C. Delfs, H. Munakata, et al. Acceleration of autologous in vivo recellularization of decellularized aortic conduits by fibronectin surface coating. *Biomaterials*, 2013, 34(25): 6015−6026. https://doi.org/10.1016/j.biomaterials.2013.04.037

[62] Y. Iwasaki, K. Ishihara. Cell membrane-inspired phospholipid polymers for developing medical devices with excellent biointerfaces. *Science and Technology of Advanced Materials*, 2012, 13(6): 064101. https://doi.org/10.1088/1468-6996/13/6/064101

[63] S.K. Jaganathan, M.P. Mani, M. Ayyar, et al. Blood compatibility and physicochemical assessment of novel nanocomposite comprising polyurethane and dietary carotino oil for cardiac tissue engineering applications. *Journal of Applied Polymer Science*, 2018, 135(3): e45691. https://doi.org/10.1002/app.45691

[64] C.R. Lankala, M. Yasir, A. Ishak, et al. Application of nanotechnology for diagnosis and drug delivery in atherosclerosis: A new horizon of treatment. *Current Problems in Cardiology*, 2023, 48(6): 101671. https://doi.org/10.1016/j.cpcardiol.2023.101671

[65] J. Saleem, L.M. Wang, C.Y. Chen. Carbon-based nanomaterials for cancer therapy via targeting tumor microenvironment. *Advanced Healthcare Materials*, 2018, 7(20): 1800525. https://doi.org/10.1002/adhm.201800525

[66] X.F. Ding, Y.J. Su, C. Wang, et al. Synergistic suppression of tumor angiogenesis by the co-delivering of vascular endothelial growth factor targeted siRNA

and candesartan mediated by functionalized carbon nanovectors. *ACS Applied Materials & Interfaces*, 2017, 9(28): 23353−23369. https://doi.org/10.1021/acsami.7b04971

[67] J.P. Cheng, Y.J. Gu, Y.J. Wang, et al. Nanotherapeutics in angiogenesis: Synthesis and *in vivo* assessment of drug efficacy and biocompatibility in zebrafish embryos. *International Journal of Nanomedicine*, 2011, 6: 2007−2021. https://doi.org/10.2147/IJN.S20145

[68] M. Wierzbicki, E. Sawosz, M. Grodzik, et al. Comparison of anti-angiogenic properties of pristine carbon nanoparticles. *Nanoscale Research Letters*, 2013, 8(1): 195. https://doi.org/10.1186/1556-276X-8-195

[69] Y. Cao, Y.M. Luo. Pharmacological and toxicological aspects of carbon nanotubes (CNTs) to vascular system: A review. *Toxicology and Applied Pharmacology*, 2019, 385: 114801. https://doi.org/10.1016/j.taap.2019.114801

[70] C.J. Deng, C. Xu, Q. Zhou, et al. Advances of nanotechnology in osteochondral regeneration. *WIREs Nanomedicine and Nanobiotechnology*, 2019, 11(6): e1576. https://doi.org/10.1002/wnan.1576

[71] C. Zietz, P. Bergschmidt, R. Lange, et al. Third-body abrasive wear of tibial polyethylene inserts combined with metallic and ceramic femoral components in a knee simulator study. *The International Journal of Artificial Organs*, 2013, 36(1): 47−55. https://doi.org/10.5301/ijao.5000189

[72] G.G. Walmsley, A. McArdle, R. Tevlin, et al. Nanotechnology in bone tissue engineering. *Nanomedicine: Nanotechnology, Biology and Medicine*, 2015, 11(5): 1253−1263. https://doi.org/10.1016/j.nano.2015.02.013

[73] G.M. Cooper, M.P. Mooney, A.K. Gosain, et al. Testing the critical size in calvarial bone defects: Revisiting the concept of a critical-size defect. *Plastic and Reconstructive Surgery*, 2010, 125(6): 1685−1692. https://doi.org/10.1097/prs.0b013e3181cb63a3

[74] B.Q. Pei, W. Wang, N. Dunne, et al. Applications of carbon nanotubes in bone tissue regeneration and engineering: Superiority, concerns, current advancements, and prospects. *Nanomaterials*, 2019, 9(10): 1501. https://doi.org/10.3390/nano9101501

[75] R. Eivazzadeh-Keihan, A. Maleki, M. de la Guardia, et al. Carbon based nanomaterials for tissue engineering of bone: Building new bone on small black scaffolds: A review. *Journal of Advanced Research*, 2019, 18: 185−201. https://doi.org/10.1016/j.jare.2019.03.011

[76] K. Brindhadevi, H.A. Garalleh, A. Alalawi, et al. Carbon nanomaterials: Types, synthesis strategies and their application as drug delivery system for cancer therapy. *Biochemical Engineering Journal*, 2023, 192: 108828. https://doi.org/10.1016/j.bej.2023.108828

[77] K.S.K. Krishna Rao, T.J. Sudha Vani, B. Adi Lakshmi, et al. Surface modified carbon nanotubes for bone tissue engineering. In: Surface Modified Carbon Nanotubes Volume 2: Industrial Applications. J. Aslam, C.M. Hussain, R. Aslam, Eds. Washington, DC: American Chemical Society, 2022: 117.

[78] Y.L. Liu, G. Wu, K. de Groot. Biomimetic coatings for bone tissue engineering of critical-sized defects. *Journal of the Royal Society Interface*, 2010, 7(suppl_5): S631−S647. https://doi.org/10.1098/rsif.2010.0115.focus

[79] H. Stamm. Nanomaterials should be defined. *Nature*, 2011, 476(7361): 399. https://doi.org/10.1038/476399c

[80] R.E. McMahon, L.N. Wang, R. Skoracki, et al. Development of nanomaterials for bone repair and regeneration. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 2013, 101B(2): 387−397. https://doi.org/10.1002/jbm.b.32823

[81] J. Ro, C. Park, J.T. Kim, et al. Enhancing lysozyme loading in powderized liposomes by controlling encapsulation processes. *Bulletin of the Korean Chemical Society*, 2017, 38(7): 744−750. https://doi.org/10.1002/bkcs.11164

[82] V.P. Chavda. Nanobased nano drug delivery. In: Applications of Targeted Nano Drugs and Delivery Systems. Amsterdam: Elsevier, 2019: 69–92. https://doi.org/10.1016/b978-0-12-814029-1.00004-1

[83] Y. Franco, T. Vaidya, S. Ait-Oudhia. Anticancer and cardio-protective effects of liposomal doxorubicin in the treatment of breast cancer. *Breast Cancer: Targets and Therapy*, 2018, 10: 131−141. https://doi.org/10.2147/bctt.s170239

[84] F. Danhier, O. Feron, V. Préat. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release*, 2010, 148(2): 135−146. https://doi.org/10.1016/j.jconrel.2010.08.027

[85] Y.H. Yao, Y.X. Zhou, L.H. Liu, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. *Frontiers in Molecular Biosciences*, 2020, 7: 193. https://doi.org/10.3389/fmolb.2020.00193

[86] H. Zhang, R.Y. Li, X. Lu, et al. Docetaxel-loaded liposomes: Preparation, pH sensitivity, Pharmacokinetics, and tissue distribution. *Journal of Zhejiang University SCIENCE B*, 2012, 13(12): 981−989. https://doi.org/10.1631/jzus.b1200098

[87] Y. Yao, Z.H. Su, Y.C. Liang, et al. pH-Sensitive carboxymethyl chitosan-modified cationic liposomes for sorafenib and siRNA co-delivery. *International Journal of Nanomedicine*, 2015, 10: 6185–6197. https://doi.org/10.2147/IJN.S90524. eCollection 2015

[88] J.A. de Lemos, A.M. Navar. A life-course approach to cardiovascular disease prevention. *Nature Medicine*, 2022, 28(6): 1133−1134. https://doi.org/10.1038/s41591-022-01870-8

[89] A. Seifalian. A new era of cancer treatment: Carbon nanotubes as drug delivery tools. *International Journal of Nanomedicine*, 2011: 2963. https://doi.org/10.2147/ijn.s16923

[90] S. Beg, M. Rizwan, A.M. Sheikh, et al. Advancement in carbon nanotubes: Basics, biomedical applications and toxicity. *Journal of Pharmacy and Pharmacology*, 2011, 63(2): 141−163. https://doi.org/10.1111/j.2042-7158.2010.01167.x

[91] S. Hampel, D. Kunze, D. Haase, et al. Carbon nanotubes filled with a chemotherapeutic agent: A nanocarrier mediates inhibition of tumor cell growth. *Nanomedicine*, 2008, 3(2): 175−182. https://pubmed.ncbi.nlm.nih.gov/18373424/

[92] R.A. Soni, M.A. Rizwan, S. Singh. Opportunities and potential of green chemistry in nanotechnology. *Nanotechnology for Environmental Engineering*, 2022, 7(3): 661−673. https://doi.org/10.1007/s41204-022-00233-5

[93] Ambika, P.P. Singh. Advances in carbon nanomaterial-based green nanocomposites. In: Emerging Carbon - Based Nanocomposites for Environmental Applications. A.K. Mishra, C.M. Hussain, S.B. Mishra, Eds. Scrivener Publishing LLC, 2020: 175–201.

[94] M. Nasrollahzadeh, S.M. Sajadi, Z. Issaabadi, et al. Biological sources used in green nanotechnology. In: Interface Science and Technology. Amsterdam: Elsevier, 2019: 81–111. https://doi.org/10.1016/b978-0-12-813586-0.00003-1

[95] T.N.V.K.V. Prasad, V. Subba Rao Kambala, R. Naidu. A critical review on biogenic silver nanoparticles and their antimicrobial activity. *Current Nanoscience*, 2011,

7(4): 531−544. https://doi.org/10.2174/1573413117961967 36
[96] N. Pantidos. Biological synthesis of metallic nanoparticles by bacteria, fungi and plants. *Journal of Nanomedicine & Nanotechnology*, 2014, 5: 5. https://doi.org/10.4172/2157-7439.1000233
[97] P. Singh, Y.J. Kim, D.B. Zhang, et al. Biological synthesis of nanoparticles from plants and microorganisms. *Trends in Biotechnology*, 2016, 34(7): 588−599. https://doi.org/10.1016/j.tibtech.2016.02.006
[98] D. Nath, P. Banerjee. Green nanotechnology–A new hope for medical biology. *Environmental Toxicology and Pharmacology*, 2013, 36(3): 997−1014. https://doi.org/10.1016/j.etap.2013.09.002
[99] A.N. Geraldes, A.A. da Silva, J. Leal, et al. Green nanotechnology from plant extracts: Synthesis and characterization of gold nanoparticles. *Advances in Nanoparticles*, 2016, 5(3): 176−185. https://doi.org/10.4236/anp.2016.53019
[100] F. Khan, M. Shariq, M. Asif, et al. Green nanotechnology: Plant-mediated nanoparticle synthesis and application. *Nanomaterials*, 2022, 12(4): 673. https://doi.org/10.3390/nano12040673
[101] S. Ahmad, S. Munir, N. Zeb, et al. Green nanotechnology: A review on green synthesis of silver nanoparticles - an ecofriendly approach. *International Journal of Nanomedicine*, 2019, 14: 5087−5107. https://doi.org/10.2147/IJN.S200254
[102] R. Mondal, M.D. Yilmaz, A.K. Mandal. Green synthesis of carbon nanoparticles: Characterization and their biocidal properties. In: Handbook of Greener Synthesis of Nanomaterials and Compounds. Amsterdam: Elsevier, 2021: 277–306. https://doi.org/10.1016/b978-0-12-822446-5.00013-7
[103] L.N. Wu, X. Cai, K. Nelson, et al. A green synthesis of carbon nanoparticles from honey and their use in real-time photoacoustic imaging. *Nano Research*, 2013, 6(5): 312−325. https://doi.org/10.1007/s12274-013-0308-8
[104] J.P. Kumar, R. Konwarh, M. Kumar, et al. Potential nanomedicine applications of multifunctional carbon nanoparticles developed using green technology. *ACS Sustainable Chemistry & Engineering*, 2018, 6(1): 1235−1245. https://doi.org/10.1021/acssuschemeng.7b03557
[105] S. Kesavan, K.S. Meena, R. Dhakshinamoorthy. Bioactive polysaccharides based graphene oxide nanoparticle as a promising carrier for anticancer drug delivery. *Biointerface Research Applied Chemistry*, 2022, 12(3): 3429−3445. https://doi.org/10.33263/briac123.34293445
[106] J.M. Gutiérrez-Hernández, D.M. Escobar-García, A. Escalante, et al. *In vitro* evaluation of osteoblastic cells on bacterial cellulose modified with multi-walled carbon nanotubes as scaffold for bone regeneration. *Materials Science & Engineering C, Materials for Biological Applications*, 2017, 75: 445–453. https://doi.org/10.1016/j.msec.2017.02.074
[107] Y.X. Fang, S.J. Guo, D. Li, et al. Easy synthesis and imaging applications of cross-linked green fluorescent hollow carbon nanoparticles. *ACS Nano*, 2012, 6(1): 400−409. https://doi.org/10.1021/nn2046373
[108] F.Y. Du, M.M. Zhang, X.F. Li, et al. Economical and green synthesis of bagasse-derived fluorescent carbon dots for biomedical applications. *Nanotechnology*, 2014, 25(31): 315702. https://doi.org/10.1088/0957-4484/25/31/315702
[109] S.M. Mousavi, K. Yousefi, S.A. Hashemi, et al. Renewable carbon nanomaterials: Novel resources for dental tissue engineering. *Nanomaterials*, 2021, 11(11): 2800. https://doi.org/10.3390/nano11112800
[110] N. Vasimalai, V. Vilas-Boas, J. Gallo, et al. Green synthesis of fluorescent carbon dots from spices for *in vitro* imaging and tumour cell growth inhibition. *Beilstein Journal of Nanotechnology*, 2018, 9: 530−544. https://doi.org/10.3762/bjnano.9.51