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Recent advances in targeting cancer stem cells by using nanomaterials

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ABSTRACT

Cancer stem cells (CSCs) are a special group of cells that start, regenerate, and maintain the growth of tumors. Cancer stem cells (CSCs) contribute to the dissemination of tumors, their recurrence following treatment, and the mechanisms by which cancers develop resistance to therapies. CSCs reside in a unique microenvironment influenced by a variety of factors from their immediate surroundings. These factors include low oxygen levels, too much new blood vessel growth, a shift in how cells use energy from breathing oxygen to breaking down glucose, and an increase in certain markers and signals related to stem cells that help remove drugs from the body. Antibodies and special molecules that focus on the unique features keeping the environment stable are used to deliver cancer treatments to CSCs. As a result, nanoparticles are extremely effective in delivering drugs that combat cancer directly to cancer stem cells. Right now, stem cell nanotechnology is a new and interesting area of study. Some experiments on how stem cells interact with tiny structures or materials have shown good results. The importance of tiny structures and materials in creating treatments using stem cells for diseases and injuries has been clearly understood. The way nanomaterials are built and their characteristics influence how stem cells grow and change. This area of study is a new and exciting field where material science meets medicine. This review talks about the biology of CSCs and new ways to create nanoparticles (NPs) that can deliver cancer drugs specifically to these CSCs. This review talks about the creation of different types of tiny particles, including synthetic and natural polymer particles, lipid particles, inorganic particles, protein particles that can assemble themselves, combined antibody-drug particles, and small bubbles called nanovesicles, all aimed at targeting cancer stem cells. This paper talks about recent progress and opinions on using nanotechnology in stem cell research and therapy. It also covers how nanoparticles can help track, control, and improve the retention of stem cells.

1. Introduction

Cancer remains one of the most perilous diseases that poses a significant threat to our health. In patients undergoing conventional treatments such as chemotherapy or radiation therapy (Rahimkhoei et al., 2024). Moreover, cancer has the potential to return and disseminate to different areas of the body. Conventional therapies may be ineffective due to the presence of small populations of unique cancer

Abbreviations: **ABC**, ATP-binding cassette; **ADCs**, Antibody-drug conjugates; **AML**, Acute myeloid leukemia; **AuNPs**, Gold nanoparticles; **BCSCs**, Breast cancer stem cells; **CSC**, Cancer stem cell; **DEX**, Dextran; **DTX**, Docetaxel; **ECM**, Extracellular matrix; **EGFR**, Epidermal growth factor receptor; **EVs**, Extracellular vesicles; **FND**, Fluorescent nanodiamonds; **GF**, Growth factor; **GO**, Graphene oxide; **GOQDs**, Graphene oxide quantum dots; **HA**, Hyaluronic acid; **hMSCs**, human mesenchymal stem cells; **hNSCs**, human neural stem cells; **IGF-1**, Insulin-like growth factor 1; **IONP**, Iron nanoparticles; **LSCs**, leukemia stem cells; **MNP**, Metal nanoparticles; **MPS**, Mononuclear phagocyte system; **mRNA**, messenger RNA; **MWCNTs**, Multi-walled carbon nanotube; **NDs**, Nanodiamonds; **NPs**, Nanoparticles; **OvCSCs**, Ovarian cancer stem cells; **PAA**, Polyacrylic acid; **PDX**, Patient-derived xenografts; **PEG**, Polyethylene glycol; **PEI**, Polyethyleneimine; **PLA**, Polylactic acid; **PLGA**, Polylactic-glycolic acid; **PVDF**, Polyvinylidene fluoride; **RGD**, Arginine-glycine-aspartic acid; **RIPs**, Ribosome-inactivating proteins; **ROS**, Reactive oxygen species; **SAL**, Salinomycin; **SBMA**, Sulfobetaine methacrylate; **SF**, Silk fibroin; **SWCNT**, Single-walled carbon nanotubes; **TGF-b3**, transforming growth factor b3; **Ti**, Titanium; **uPAR**, urokinase plasminogen activator receptor.

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cells within tumors, referred to as cancer stem cells (CSCs) (Ramezanpour et al., 2024).CSC possesses multiple characteristics, including self-renewal, the capacity to differentiate into various cell types, and the presence of unique proteins known as ATP-binding cassette (ABC), which aid in resisting cancer therapies and radiation.

Similar to conventional stem cells, cancer stem cells exhibit diminished quantities of specific reactive species when juxtaposed with the predominant mass of the tumor. The presence of reduced levels of reactive oxygen species (ROS) in cancer stem cells contributes to their maintenance of characteristics akin to those of normal stem cells, thereby enhancing their resistance to modalities such as radiation therapy or chemotherapy (Wang et al., 2024b). This phenomenon can be attributed, in part, to the diminished incidence of DNA damage during therapeutic interventions, a factor that can precipitate the recurrence of cancer following such treatments (Lendeckel and Wolke, 2022; Xiao et al., 2025). Nonetheless, the response of drug-resistant cancer stem cells to oxidative stress remains ambiguous. Elevated concentrations of ROS are associated with various outcomes, including genetic anomalies, which constitute a fundamental characteristic of malignant cells. Furthermore, oxidative stress modifies the metabolic pathways of lipids within the organism by generating entities referred to as lipid peroxidation (LPO) products (Fan et al., 2024). LPO and reactive aldehydes represent significant biochemical entities that serve as biomarkers for various pathological conditions, notably including neoplasia. 4-Hydroxy-2-nonenal (HNE) is a metabolite synthesized by cells in response to oxidative stress induced by elevated oxygen levels. HNE modulates numerous signaling cascades and exerts considerable influence over critical cellular processes such as proliferation, differentiation, and apoptotic mechanisms (Bellezza et al., 2018).

Properly regulating the differentiation of stem cells into specialized cells is crucial for their effective application in various medical treatments. Biochemical signals, like growth factors and chemical substances, are usually used to help grow and manage how stem cells develop. However using growth factors and chemicals to make stem cells change into different types of cells is often unreliable, not very effective, and can be risky (Choe et al., 2019; Halim et al., 2018). It's simple to create various types of nanomaterials, such as carbon materials (including graphene and carbon nanotubes), precious metal particles (like gold and silver), organic compounds, and liposome nanoparticles. These materials vary in size and can undergo modifications on their surfaces (Abdolahinia et al., 2019; Bigham et al., 2022; Shamsian et al., 2020). The use of nanomaterials is contributing to significant breakthroughs in targeted therapy. In the past decade, there has been extensive use of miniaturized technologies and materials in the field of medical research. Their efforts have led to the establishment of novel approaches for cell imaging (Huang et al., 2019), siRNA and drug delivery (Aqil et al., 2019; Bayati-Komitaki et al., 2024; Satpathy et al., 2019), and targeted cancer therapy (Kim et al., 2019; Rezaie et al., 2022; Shafiei-Irannejad et al., 2022).

Nowadays, cancer stands as one of the primary reasons for death. Nanotechnology in medicine involves six key areas: 1) finding changes in molecules that indicate disease; 2) diagnosing and creating images of health issues; 3) delivering medicine effectively; 4) using both treatment and diagnosis together; 5) Providing an evaluation of the effectiveness of the treatment; and 6) Approaches for applying nanotechnology in scientific disciplines and fundamental research (Wang et al., 2024a). A diverse array of nanostructures, engineered from both naturally occurring and artificially synthesized materials, are presently employed in the identification and management of cancer, either by autonomously detecting neoplasms or by navigating designated pathways to access them. An innovative nanoscale delivery system comprising nanovesicles, liposomes, polymeric micelles, dendrimers, and polymeric nanoparticles is capable of infiltrating solid tumors via the interstices found within the tumor's vascular architecture. Upon successful internalization, these nanostructures can precisely administer therapeutic agents aimed at eradicating the tumor (Farahzadi et al., 2023; Yong et al., 2019). Nanomaterials designed with appropriate targeting components can bind to particular proteins or receptors on their intended cells. This powerful technology minimizes damage to non-target cells, allowing nanomaterials to more effectively penetrate the intended cells (Zhang et al., 2022).

Over the course of the last several decades, nanomaterials have garnered considerable scholarly interest and are anticipated to sustain this focus in the foreseeable future owing to their distinctive interactions with light, chemical substances, and electrical phenomena (Rahimkhoei et al., 2021; Rheima et al., 2024). These extraordinary properties have facilitated their application across various domains, including catalysis (Dias and Abou-Hassan, 2024; Rahimkhoei et al., 2020), energy storage systems (Ji et al., 2024; Rahimkhoei et al., 2025), advanced imaging techniques (Hsu et al., 2023; Uniyal et al., 2024; Wang et al., 2024c), biochemical sensors (Song et al., 2023), identification of tumor cells (Vajhadin et al., 2023), and the development of targeted therapeutic strategies (Zhang et al., 2025), among numerous other applications. The exceptional attributes of nanomaterials stem from their substantial surface area relative to their volumetric dimensions. The numerous surface atoms present in nanomaterials confer unique surface characteristics (Teli et al., 2024). These characteristics can be leveraged to enhance the efficacy of anti-cancer pharmaceuticals, active therapeutic agents, and targeting molecules that are routinely employed in oncological treatments (Murali et al., 2021).

These characteristics can all be attributed to the unique properties of these nanomaterials, such as their high surface area relative to their volume, their adaptability, their distinctive optical traits, and their unusual behaviors at nanoscale sizes (Aghebati-Maleki et al., 2020; Rahimkhoei et al., 2023). In the future, combining and utilizing the exceptional attributes of various nanomaterials will create more effective methods for targeting and eliminating cancer stem cells. This review aims to summarize the recent uses of different nanomaterials in targeting CSC.

2. Cancer stem cell (CSC)

Tumors can often develop from normal stem cells. Both stem cells and cancer cells, including cancer stem cells (which are a small, unique group of cells that can create new tumors), can renew themselves in similar ways (Fig. 1). CSCs represent a limited subset of cancer cells

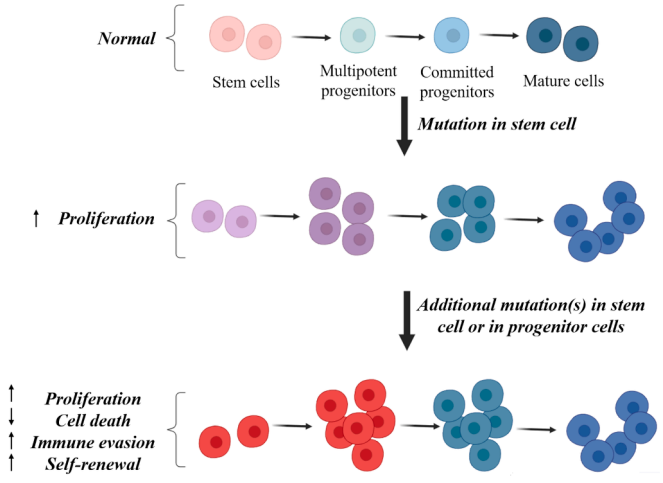

Fig. 1. The role of cancer stem cells in the growth of tumors. Normal stem cells develop into different types of cells, including multipotent progenitor cells, committed progenitor cells, and fully mature cells. Changes in a stem cell can lead to another stem cell that grows too much, causing an early form of cancer. More mutations cause cancer cells to grow faster, live longer, avoid the immune system, and increase the number of stem cells, which is common in cancer. Reprinted from (Qin et al., 2017) with permission from Qin et al. (2017).

commonly referred to as "initiating cells of cancer". These cells, which were identified in the late 1990 s, are largely accountable for the return of cancer because they have the capability to multiply (Smith and Macleod, 2019). The initial discovery of leukemia stem cells (LSCs) in human acute myeloid leukemia (AML), a form of CSC, was made by Bonnet and Dick (Boutzen et al., 2022). A small group of CD34+/CD38- LSC cells in AML has two key features of stem cells: their ability to self-replicate and differentiate into various cell types. Later, scientists found that CSCs are also present in many other solid tumors, which makes them a promising focus for cancer treatment studies (Atashzar et al., 2020). It is well known that CSC exhibits discrete properties of resistance to existing chemotherapy and radiotherapy, as well as its highly invasive and metastatic tumorigenicity (Makena et al., 2020). Therefore, CSC has become a trend in translational cancer research looking for suitable and effective treatment methods, because the existing treatment methods only destroy cancer cells without eliminating CSC because they have a unique drug resistance mechanism. It has also been found that highly invasive and radiation-resistant malignant tumors are resistant to a variety of currently used drugs, which can cause CSCs to cause disease recurrence (Turdo et al., 2019).

2.1. Targeting strategies

To a significant degree, the efficacy of successful tracing is contingent upon the implementation of proficient CSC targeting methodologies. At present, the targeting of CSCs is predominantly executed through the utilization of antibodies, which are specifically directed toward surface markers that are unique to CSCs, components of CSC-specific signaling pathways, and the niches that support CSCs. The approach that focuses on targeting CSCs via specific surface markers is the most frequently employed methodology. The surface marker CD44 has been utilized as a target in the therapeutic management of acute myeloid leukemia (AML) (Mai et al., 2023). In a similar vein, anti-CD44 antibodies, namely H90 and A3D8, have been employed to facilitate the differentiation of AML CSCs, consequently inhibiting their proliferation and expediting apoptosis (Wu et al., 2024). Furthermore, ongoing investigations are being conducted to target proteins associated with drug resistance, as well as other antigens relevant to cancer. Currently, there exists a lack of universally recognized markers that are specific to CSCs across any tumor type. Indeed, a significant number of the established markers are also expressed on the surface of normal cells, thereby presenting a considerable challenge for the clinical application of this promising therapeutic strategy. The implementation of CSC targeting strategies utilizing non-specific markers may inadvertently impact normal tissues, leading to adverse toxicological effects. Consequently, to enhance the feasibility of targeting CSCs through surface markers, future research endeavors must focus on the identification of CSC-specific surface markers. Numerous studies have demonstrated that CSCs do not share identical signaling pathways with normal cells, particularly normal stem cells. Given that abnormalities in signaling pathways can precipitate malignant transformation, the targeting of specific components within CSC signaling pathways constitutes an alternative strategy for CSC-targeted therapy. Cells in vivo must engage in interactions with their surrounding microenvironment. Both cell-intrinsic and cell-extrinsic factors present within the microenvironment govern the physiological activities of cells. Normal stem cells also require these factors to sustain their stem-like characteristics and maintain homeostasis. This indicates that a balance must exist between differentiated and undifferentiated cells within the stem cell population. The microenvironment plays a crucial role in preserving stem properties by providing essential factors such as Notch, Wnt, and bone morphogenetic protein (BMP). For instance, the activation of the Notch pathway results in the effector protein hypoxia-inducible factor-1α (HIF-1α) promoting the retention of glioblastoma stem cell characteristics by sustaining a hypoxic environment.

A multitude of factors present in the microenvironment are components related to signaling pathways. Cancer stem cell niches exhibit similarities to normal stem cell niches; however, certain specific signaling pathways are dysregulated, resulting in a distinctive microenvironment within tumor tissues. Several stem cell signaling pathways have been demonstrated to be dysregulated in CSCs. In each phase of tumor advancement, diverse environmental constituents are requisite to facilitate tumor proliferation. Given the pronounced tumorigenicity of CSCs, the inhibition of CSC invasion emerges as a viable therapeutic approach to mitigate cancer recurrence and metastasis. Leukemic cells, exemplified by acute lymphoblastic leukemia (ALL) cells, exhibit expression of C-X-C chemokine receptor type 4 (CXCR4), which has been documented to promote the migration of tumor cells toward the microenvironments conducive to the preservation of stem cell characteristics. Consequently, the targeted inhibition of CXCR4 presents the opportunity to disrupt the CSC niche (Chu et al., 2024). A substantial number of normal stem cells demonstrate elevated expression levels of ATP-binding cassette (ABC) transporters. Considering that CSCs represent a distinct class of stem cells known for their pronounced resistance to anticancer therapies, ABC transporters, which are integral to the mechanistic basis of drug resistance, are posited to modulate the proliferation of CSCs. Indeed, empirical investigations have revealed that various ABC transporters, including ABCA2, ABCG2, ABCB1/MDR1, and multidrug resistance protein 1 (MRP1), display upregulation within the side population of human lung cancer cell lines. Furthermore, retinoblastoma cells, hepatocellular carcinoma cells, and pancreatic neoplastic cells have been reported to exhibit elevated levels of ABCG2. Therefore, ABC transporters possess significant potential to serve as targets for antitumor interventions (Cho and Kim, 2020; Guo et al., 2022; Mengistu et al., 2024). Consequently, notwithstanding our advancing comprehension of CSCs, considerable progress remains necessary to develop effective and precise targeting strategies.

2.2. Targeted therapies

Traditional oncological therapies, including chemotherapy and radiotherapy, exhibit numerous limitations that culminate in treatment failure and subsequent cancer recurrence. These limitations stem from both systemic and localized toxicity, as the therapeutic agents lack sufficient selectivity and may inadvertently impact healthy tissues. An additional challenge is the phenomenon of drug resistance, which can be attributed to the unique characteristics of CSCs, such as a diminished rate of cellular division, elevated expression of drug-efflux transporters, robust DNA repair capabilities, as well as specific microenvironmental factors like hypoxia and acidosis. Consequently, the strategic targeting of CSCs has emerged as a critical component in the management of cancer and the prevention of tumor relapse. In recent years, a plethora of strategies has been developed with the explicit objective of eradicating CSCs and their associated niches. These strategies encompass the targeting of specific cell surface markers, modulation of intracellular signaling pathways, alteration of microenvironmental signals, inhibition of drug-efflux mechanisms, manipulation of microRNA expression, and the induction of apoptosis and differentiation in CSCs. A comprehensive summary of these therapeutic modalities is illustrated in Fig. 2. Currently, several of these approaches are being effectively implemented in clinical settings, primarily in conjunction with conventional therapies, while others remain subject to ongoing investigation.

3. Nanotechnology in cancer stem cell therapy

The application of nanotechnology in cancer management may overcome the onerous challenges encountered by traditional methods so that smart nanocarriers can be accurately orientated in the body (Chen et al., 2019). NP carriers function as vehicles for transporting a wide array of unstable pharmaceutical agents targeting cancer. These nanoparticles play a crucial role in shielding the drugs from deterioration in difficult environments within the body. Utilizing stem cells for the

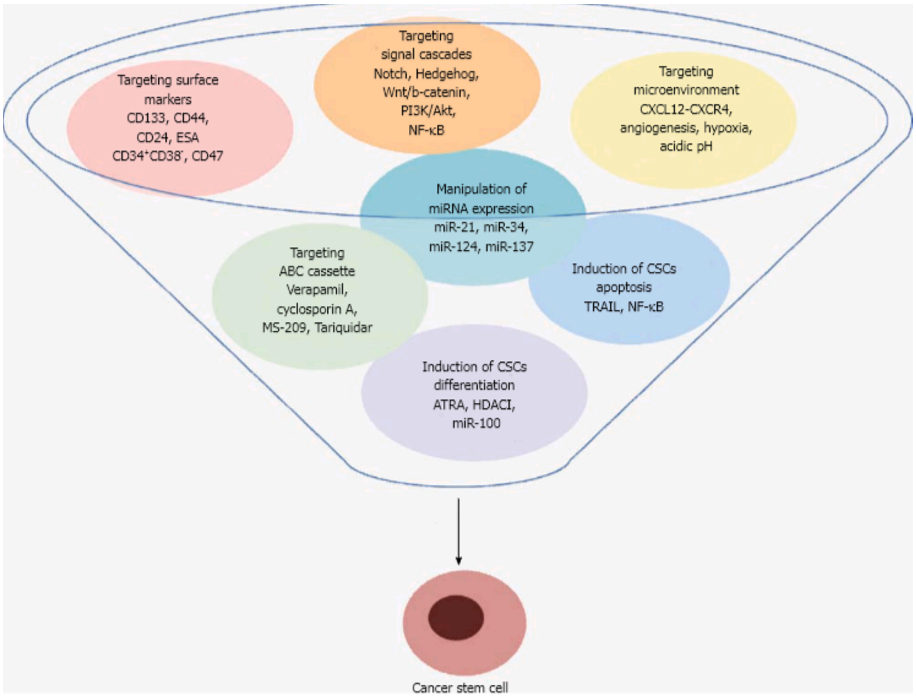

Fig. 2. Therapies targeting cancer stem cells. Reprinted from (Dragu et al., 2015) with permission from Dragu et al. (2015).

delivery of nanoparticles may address challenges such as the inability to effectively target micrometastasis, poor distribution within solid tumors, and other related concerns (Mollania et al., 2020). Compared with a free drug or drug delivery system using only nanoparticles, this method increases and expands the distribution of drugs in tumors and promotes tumor cell apoptosis. Therefore, stem cell-mediated NP-based drug delivery has shown broad prospects in cancer treatment and is worthy of further study.

3.1. Carbon-based nanoparticles

3.1.1. Graphene oxide

Graphene oxide (GO) is a variant of graphene characterized by carbon atoms that are bonded to oxygen functional groups, which can be used in many different ways because it has special chemical properties. GO is an excellent substance with various applications, including medicine, electronics, photochemical reactions, sensors, and energy storage in batteries and supercapacitors. Substances derived from graphene, such as graphene oxide and reduced graphene oxide, hold substantial promise for medical applications (Kim et al., 2017). Pure GO and its enhanced variants, which encompass complex formation, nanoparticle immobilization, and surface functionalization, have proven to be valuable assets in the field of medical biotechnology (Wang et al., 2019). Previous investigations have indicated that GO can be utilized for focused disease treatments, forestall tumor development, and hinder tumor cell relocation (Campbell et al., 2019; Liu et al., 2020b; Mariadoss et al., 2020). Graphene, along with its related forms like GO and graphene oxide quantum dots (GOQD), has recently gained a lot of interest, due to their role in guiding the differentiation of stem cells into bone cells. In 2018, the effects of GO and GOQDs on the osteogenic differentiation of human deciduous teeth stem cells were discussed (Yang et al., 2019).

Targeting and eliminating CSCs with GO represents a distinct approach compared to traditional chemotherapy. For instance, Yang et al. (Yang et al., 2018b) changed the state of GO and showed that it helps improve the growth and development of stem cells while keeping the oxygen levels safe. This change causes oxygen atoms to build up on the surface of GO, making it stick better to other materials. This also helps human mesenchymal stem cells (hMSCs) develop into bone cells more effectively. Additionally, the adhesion of modified GO was enhanced by facilitating a stronger attachment of the osteogenic growth peptide (Yang et al., 2018b). A novel approach to medicine delivery involves coating mesenchymal stem cells (MSC) with GO. This combination allows GO to hold various treatments, while MSC can successfully transport these medicines to the tumor location (Suryaprakash et al., 2018). The application of protein nanofibril clusters made from graphene oxide sheets successfully facilitates the differentiation of human stem cells into bone cells. A fascinating study found that when GO nanosheets are added to a water solution with SF molecules, they help the SF molecules come together to form organized strands called nanofibrils. This process creates SF/GO films with special nanomorphology and makes them stronger after the water is removed. The special structure of the SF/GO membrane helps cells stick to it faster and encourages human stem cells to grow into bone cells, even without adding other substances to the growth solution. It shows a better ability to help hMSCs stick to surfaces early on (Fig. 3) (Shuai et al., 2018).

Recently, graphene-based two-dimensional nanomaterials have garnered significant interest due to their potential applications in medicine. Their ability to accommodate a wide range of biomolecules makes them excellent for the delivery of drugs and other materials. The capacity of GO to emit distinct biological signals is also an exciting area that requires more research in tissue engineering, particularly for steering the growth of mesenchymal stem cells. For example, research by Zhou and colleagues (Zhou et al., 2019) showed that GO-adsorbed transforming growth factor b3 (TGF-b3) can be dispersed in a 3D gel together with hMSC, thereby effectively inducing cartilage formation. The results show that GO sheets can efficiently deliver growth factor (GF) in 3D, thereby guiding cells and inducing tissue formation in the same scaffold. The development of tissue engineering technology has led to remarkable changes in the treatment of nerve injuries, particularly with the application of neural stem cells. However, the low biological activity greatly restricts the use of biodegradable implants in nerve growth. Insulin-like growth factor 1 (IGF-1) is a growth factor for neuroprotection and neurogenesis. In this regard, IGF-1 was successfully immobilized on GO doped with polylactic-glycolic acid (PLGA) biodegradable electrospun nanofibers. After fixing IGF-1, PLGA/GO

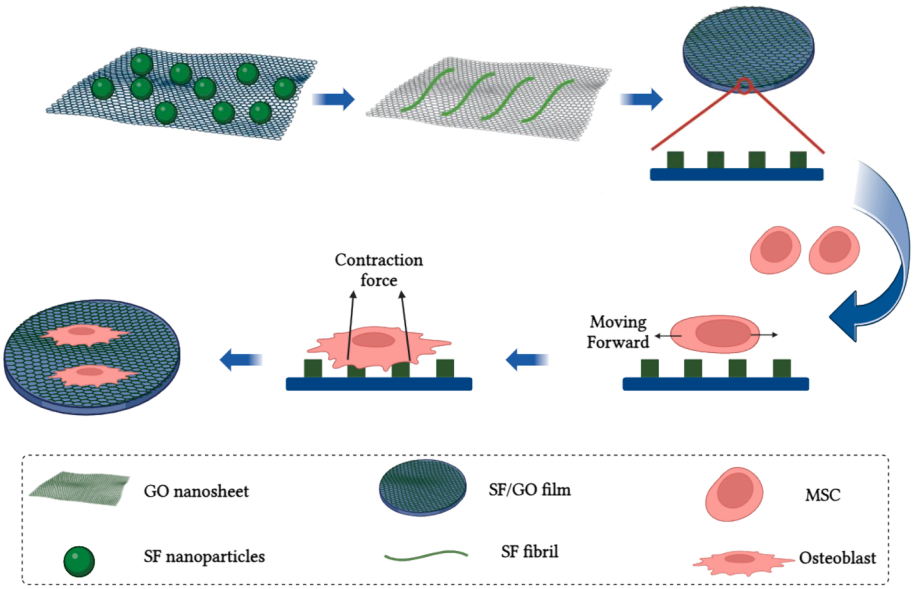

Fig. 3. Diagram of the Fabrication of small protein fibers (SF nanofibrils) using a GO template and how this fiber structure helps MSCs grow into bone cells. (A) Small round protein particles and GO sheets were mixed together in a single step. (B-C) After mixing, the round protein particles formed fibers (nanofibrils) that covered the GO sheets, creating a film made of both materials. (D) Human stem cells were grown on this SF/GO film and stuck to it. (E) The cells were stretched while on the film, which helped their internal structure change. (F) Without special factors to promote bone growth, the stem cells showed better attachment and started changing into bone cells. Reprinted from (Shuai et al., 2018) with permission from Shuai et al. (2018).

nanofibers have excellent biological activity and can support the survival, proliferation, and differentiation of neural stem cells (Qi et al., 2019).

The combination of graphene oxide with metal nanoparticles enhances the biomedical properties of nanoparticles. Choi et al. formulated a blend of graphene oxide with silver nanoparticles, named GO-Ag, and conducted tests on human ovarian cancer cells in addition to ovarian cancer stem cells (OvCSCs). The combination of rGO-Ag and salinomycin results in a fivefold increase in cell death compared to using either treatment alone. It also effectively targets and kills ovarian cancer stem cells while making tumor cells more sensitive to treatment (Choi et al., 2018). Due to several limitations faced by surgeons in the process of bone tissue implantation, the daily demand for new cell-copolymer composites for bone tissue engineering methods is increasing. Furthermore, Saburi and coworkers tried to develop a suitable nanostructured bio-composite material to enhance the osteogenic differentiation of human induced pluripotent stem cells (iPSC). Prepared polyvinylidene fluoride-graphene oxide (PVDF-GO) nanofibers (Saburi et al., 2019).

The fact that titanium (Ti) materials do not react with the body is the main barrier to their use in medicine. In a compelling investigation, scientists formulated a specialized coating comprised of GO, polydopamine, and strontium ions (GO/PDA/Sr^{2+}) applied to a titanium surface as shown in Fig. 4. This coating helps increase the biological activity of strontium ions. In vitro experiments demonstrated that the interaction between GO and the release of Sr^{2+} significantly enhanced the adhesion, spreading, and proliferation of stem cells (MSCs) on surfaces coated with

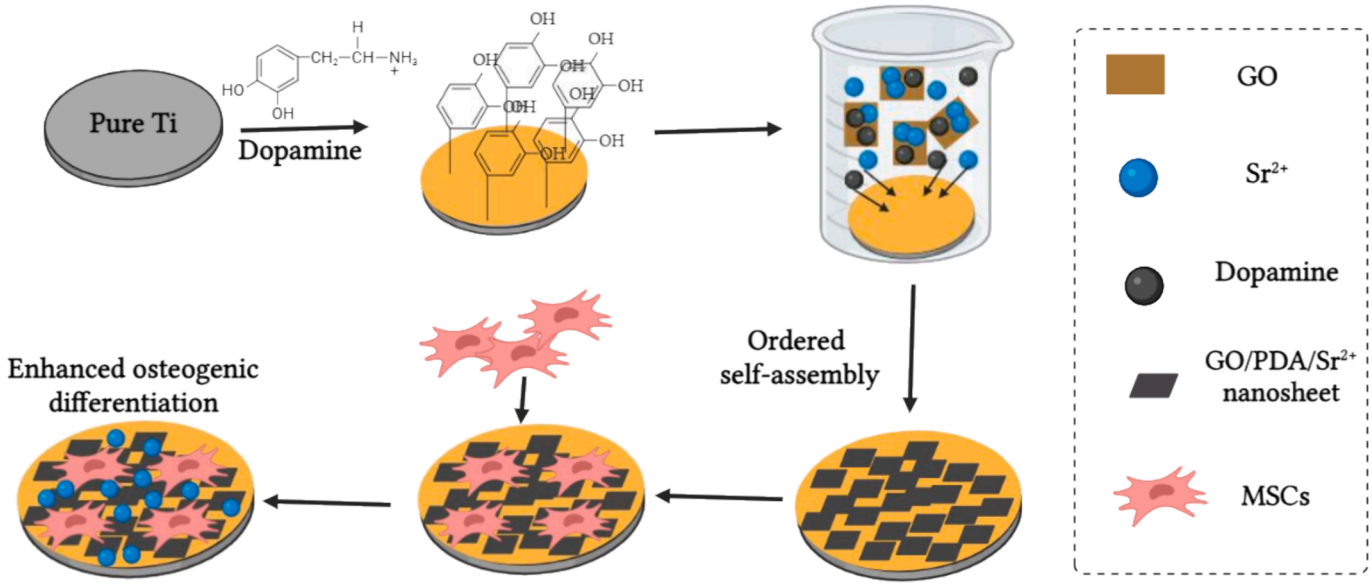

Fig. 4. A simplified schematic of GO/PDA or GO/PDA/Sr^{2+} deposition on PDA modified Ti substrates. Reprinted from (Xu et al., 2019) with permission from Xu et al. (2019).

GO/PDA/Sr^{2+}. This advancement increased the production of bone-related proteins and genes, facilitating the quicker formation of the extracellular matrix (ECM) that envelops cells (Xu et al., 2019).

3.1.2. Carbon nanotubes

Carbon nanotubes are minuscule cylindrical structures formed by rolling a single layer of graphene (Negri et al., 2020). These nanoparticles are called single-walled carbon nanotubes (SWCNT) because they have one layer in their structure. They are made of carbon and usually have a diameter between 0.4 and 40 nm. They may consist of various layers that assemble into tubular formations, maintaining a distance of 35 nm between them, which resembles the layer spacing in graphite. These tubes can have diameters from 2 to 100 nm (Fig. 5a). Nanotubes typically feature ends resembling half of a fullerene molecule and exhibit five-sided defects at their tips. CNTs can also be divided into three categories, depending on whether the rolled sheet is an armchair, zigzag, or chiral nanotube (Fig. 5b). Because carbon nanotubes have many biocompatibilities, fast electron transfer kinetics, lightweight, chemical inertness, high tensile strength, lightness, and antimicrobial properties, they have a wide range of application prospects, because carbon nanotubes have many advantages the characteristics that make them a leader in biomedical applications. Functional groups are easy to couple and can be mass-produced (Simon et al., 2019).

Multi-walled carbon nanotubes (MWCNTs) effectively infiltrated the tumor and damaged cancer cells under light exposure, leading to a pronounced effect on tumor spheroids. By combining antibody-based cancer targeting and local tumor ablation with photothermal therapy, carbon nanotubes targeting P-glycoprotein have been developed to achieve highly cancer-specific treatments. When exposed to light, the specialized MWCNTs negatively affected drug-resistant cancer cells, but normal cells lacking Pgp were unaffected in the absence of light (Suo et al., 2018). In one interesting study, single-walled CNTs induced Fibroblast-associated stem cell acquisition and fibrogenic responses in primary human lung fibroblasts (Kiratipaiboon et al., 2020). Furthermore, the most common of these involves acid treatment, which generates carboxyl groups on the walls of CNTs (Cao et al., 2018; De Menezes et al., 2018), thereby generating functionalized CNTs. However, it has been found that this treatment is responsible for the cytotoxic effect in specific cell lines. Another way to generate functional groups on CNTs is to modify hyperbranched biocompatible polymers (Huang et al., 2018), such as attaching extracellular matrix molecular chains to the CNT wall to achieve biocompatibility and make the polymerized CNTs interact more easily with cells. Song research team examined the impact of various treated multi-walled carbon nanotubes (MWCNT) on the health of stem cells isolated from rat bone marrow. Experiments conducted on cells indicate that both acid-treated MWCNTs and raw MWCNTs are highly toxic to BMSCs, whereas polyethylene glycol (PEG)-MWCNTs and hydroxyapatite (HA)-MWCNTs are less harmful and more compatible with these cells (Song et al., 2019).

In a study by Garnica-Gutiérrez and coworkers (Garnica-Gutiérrez et al., 2018), different cell parameters were used to evaluate the influence of acid functionalization and poly-citric acid-(PCA-) polymerized carbon nanotubes (CNTs) in contact with the outer cell membrane of mesenchymal stem cells (MSC). A basic diagram in Fig. 6a-c outlines the method for producing functionalized carbon nanotubes and their polymerization with citric acid. According to Fig. 6d, the polymerized nanotubes are internalized by the cell in lesser quantities compared to the functionalized nanotubes, primarily remaining on the surface. This is significant as it enhances the adhesion of MSCs to their intended target tissues following treatment with poly-citric acid-MWNTs. Moreover, Khoobi and his colleagues investigated the effectiveness of silymarin in addressing significant issues related to the calvarial bones in rats. They used stem cells taken from rat Wharton jelly (HWJMSC) and grew them on a special material made from polylactic acid and carbon nanotubes (PLA/CNT) using an electrospinning technique. Their investigation focused on the tissue structure and size in different groups after an 8-week duration. New bone or early bone tissue was also seen in the old bone. In the bone tissue formed, several small spaces had bone cells in them. Many blood vessels grew in those areas, and new bone started to form from the edge toward the middle of the gap. At this stage, loose connective tissue was not as common. The new bone growth was about 44 %, which was much higher than in the control group and Groups 2 and 3. So, using both the scaffold and silymarin together worked well for repair (Fig. 6e). The study found that the electrospun PLA/CNT scaffold is safe for use with HWJMSC cells, allowing them to attach and grow in large numbers. This scaffold is an effective choice for supporting the healing of bones (Khoobi et al., 2020).

3.1.3. Nanodiamonds

Nanodiamonds (NDs) are small materials designed for their numerous beneficial properties. These characteristics encompass substantial size, excellent heat conductivity, high hardness, durability against wear, non-toxicity, a small and adaptable surface, an extensive surface area, and valuable chemical properties (Tinwala and Wairkar, 2019). These special properties can be used in many areas, such as in quantum optics, coatings that prevent friction or germs, improving polymers, tools for bioimaging, medical implants, polishes, lubricants, fuel, delivering drugs, carrying catalysts, cleaning water, measuring magnetism at the nano level, and measuring electrostatic charges at the nano level (Adel et al., 2023; Laube et al., 2024; Lazovic et al., 2024;

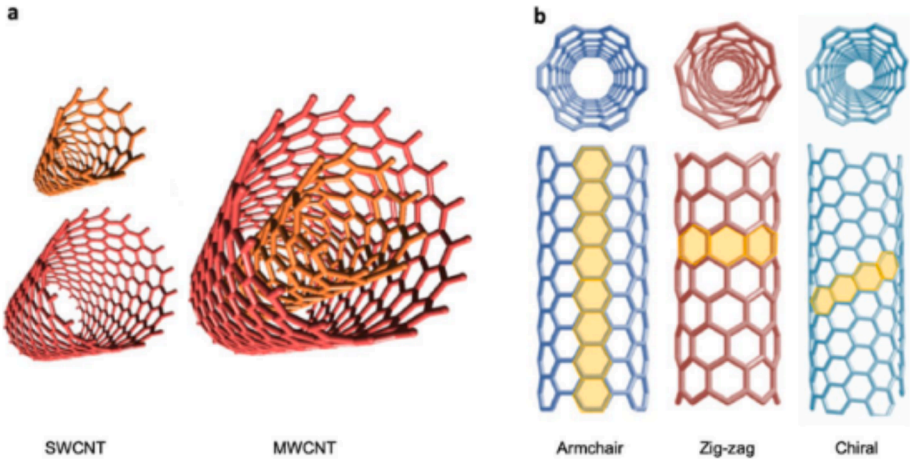

Fig. 5. Carbon nanotube classifications. a) According to the number of sheets, there are single- (SWCNTs) and multi-wall carbon nanotubes (MWCNTs); b) depending on the rolling up of the sheets, they can be armchair, zig-zag, or chiral. Reprinted from (Negri et al., 2020) with permission from Negri et al. (2020).

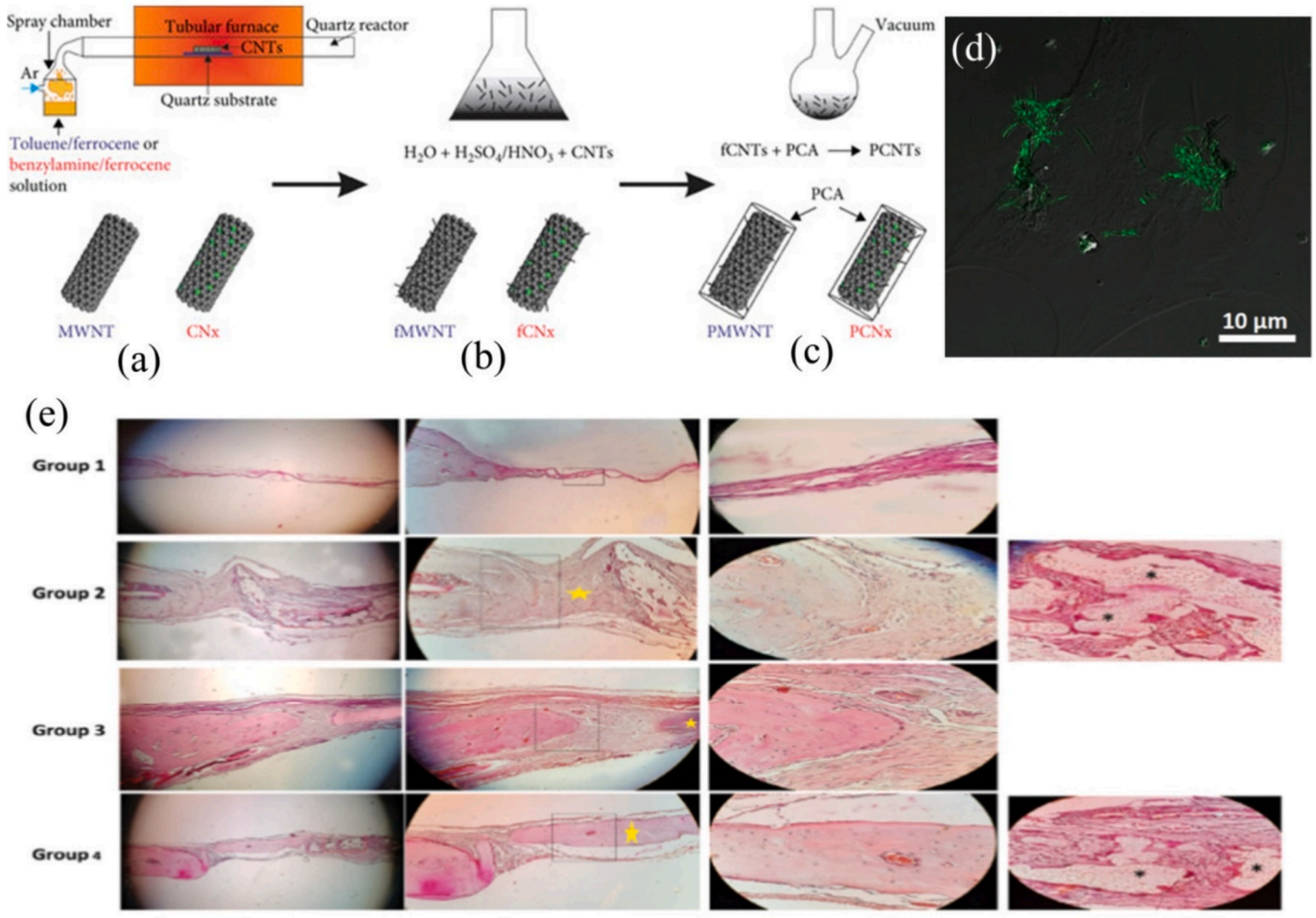

Fig. 6. Schematic representation of the three steps for the (a) nanotube synthesis, (b) acid functionalization, (c) PCA polymerization, (d) PMWNTs in contact with a MSC. Unlike the rest of the CNTs analyzed in cell cultures, the PMWNTs are in contact with the cells and mostly remain outside the cell, and (e) Hematoxylin–eosin staining. Group 1: control group, Group 2: scaffold group alone, Group 3: scaffold group plus cells, Group 4: scaffold group plus cells and silymarin orally with different magnification. Black rectangles: A selected area for further magnification. Red rectangles: Scaffolding location shown with more magnification in, *Scaffold; yellow stars: new bone; red crescent: location of the lesion where the healing begin. Reprinted from (Garnica-Gutiérrez et al., 2018) and (Khoobi et al., 2020) with permission of Garnica-Gutiérrez et al. and Khoobi et al. (2018, 2020). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Leung et al., 2023; Pan et al., 2023; Zhao et al., 2024). They are allotropes of carbon, just like jewel diamonds (Kumar et al., 2019). The only difference is that their size happens to be in the nanometer range. NDs have attracted much attention due to their unique biocompatibility and safety, because of their unique structure and optical properties (Wang and Cui, 2019).

The best way to track cells should be safe for living things and not harmful, without changing their genes. For this purpose, Hu et al. (Hu et al., 2017) introduced a novel approach to protein delivery that utilizes tiny diamond particles (nanodiamonds) in engineered cells and Drosophila. This system was very good at sticking to proteins, high efficiency, and releasing proteins that function properly inside cells. The research indicates that consumption of NDs-RNase can result in the death of certain intestinal cells while also stimulating the proliferation and division of intestinal stem cells, ultimately increasing the number of stem cells and their immature forms within the intestines of fruit flies. For tracking cells, the utilized systems must have the capability to identify single cells and tally their numbers in any region of the body. For example, Su and his team suggested a new system that uses albumin-bound fluorescent nanodiamonds (FND). These diamonds pose no harm to the body and continue to shine brightly. They can be used to accurately track the human placenta and choroid in small pigs by using magnetic signals from stem cells taken from the placenta. (Su et al., 2017).

Organisms operate with extremely small materials that are less than the size of cells. These interactions have the potential to affect cellular behavior, and by skillfully tweaking the shape and chemical traits of nanomaterials, we can enhance their functionality in various advantageous ways. In pursuit of this goal, researchers examined the interactions between nanodiamond layers and human neural stem cells (hNSC). Modifying the surface coating of nanodiamonds influences the adhesion and proliferation of human neural stem cells. Amine Reactive 2nd Generation (AR2G) biosensors help attach LN to the tip of an optical fiber. The immobilization is done by making a standard amide bond using EDC, which creates a strong connection between the carboxylic acid part of the biosensor and a reactive amine on the LN. A diagram illustrating the immobilization process can be found in Fig. 7a. The research shows that these cells can attach well to nanodiamonds with oxygen coating (O-NDs), but not to those with hydrogen coating (H-NDs) (Taylor et al., 2017). The images displayed in Fig. 7b, depict the hNSC culture after 4 days in vitro (DIV). After 7 days of growing, the human neural stem cells (hNSCs) completely covered the surfaces of both the control (TCPS) and O-NDs. Moreover, Fig. 7c illustrates a fluorescence emanating from the distinctive dye that was used on

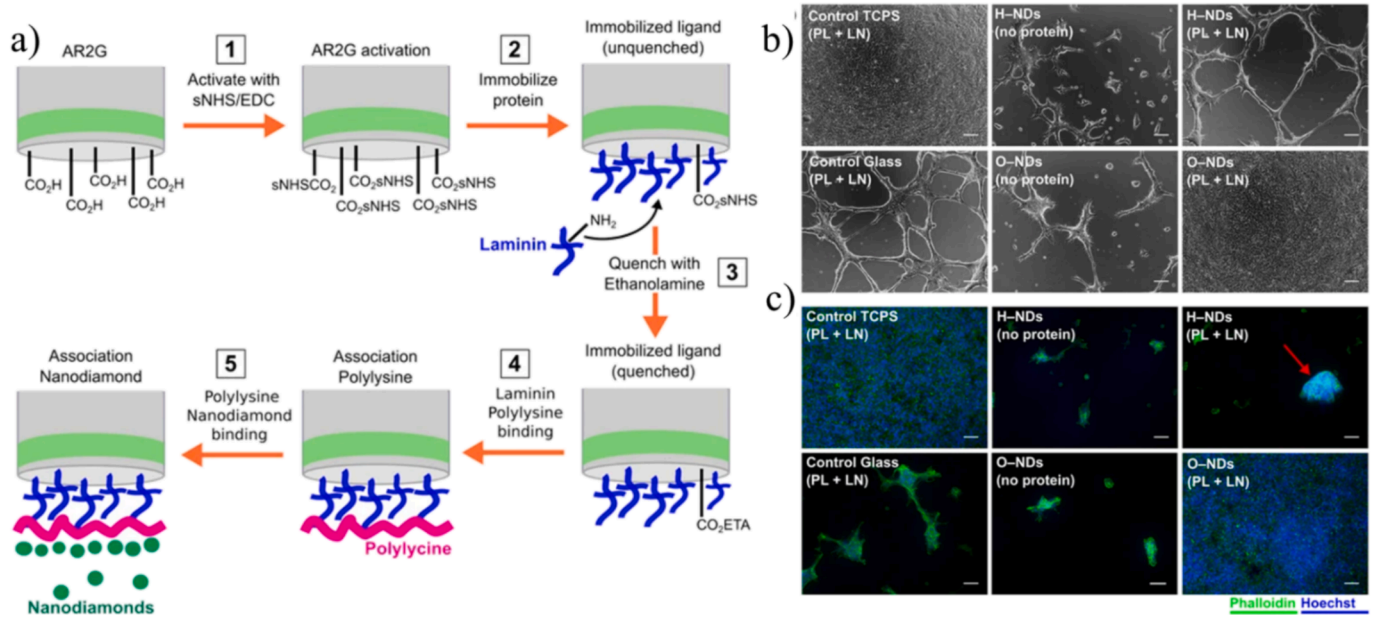

Fig. 7. A) a straightforward illustration depicts the adhesion of laminin to ar2g-coated biosensors, which is subsequently followed by the binding of poly-l-lysine and nanodiamonds. step 1: edc helps a sensor, which has carboxylic acid on it, react with snhs, making the carboxylic acid more reactive. step 2: ln is strongly attached to the sensor. a covalent bond is made between a reactive amine group on laminin and the carboxyl group on the surface of the biosensor. step 3: ethanolamine is used to stop any leftover active carboxylic groups on the sensor head. this helps prevent unwanted binding. step 4: poly-l-lysine sticks to the sensor that has a layer of laminin on it, and we measure how thick this layer is using bio-layer interferometry. step 5: nanodiamonds are attached to poly-l-lysine, and the thickness of the binding is measured using bio-layer interferometry. b and c) visual representations of living human neural stem cells (hnscs) along with actin staining are presented, grown on various materials: b) the images illustrate hnscs after four days of laboratory growth on regular plastic, conventional glass, and two other surfaces, both with and without the special coatings of poly-l-lysine and laminin. c) human neural stem cells (hnscs) were marked with a green dye (alexa fluor® 488 phalloidin) to see actin and a blue dye (hoechst) to see the nuclei after 7 days in culture on regular plastic, regular glass, H-NDs, and O-NDs, both with and without PL + LN coating. The red arrow shows a possible neurosphere on the H–NDs. Reprinted from (Taylor et al., 2017) with permission of Taylor et al. (2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

human neural stem cells developed on TCPS, glass, and H- and O-NDs. The observations indicate that both TCPS control and O-NDs provide excellent surfaces for hNSC cells to adhere, as evidenced by the dense layer of cells depicted in the images. In comparison, there are uneven areas of sticking on both the glass control and H–NDs. The presence of clusters of human neural stem cells (hNSCs) shows that the cells stick together better than they stick to the surface, which often results in the formation of neurospheres. This shows that these surfaces are great for the cells to attach and grow. The findings indicated that the coating applied to nanodiamonds influences both their adhesion properties and overall effectiveness. According to these techniques, nanodiamonds are a more reliable option than hazardous radioisotope marking strategies for cell tracking and targeting cancer stem cells.

3.2. Polymeric-based nanoparticles

Attaching ligands to the surfaces of nanoparticles enables drugs to target CSC effectively and regulate different genes or proteins, potentially resulting in the elimination of CSCs. CD133 is seen as a sign of the starting cells in osteosarcoma, a type of bone cancer. All-trans retinoic acid (ATRA) is an important form of vitamin A that belongs to a group called retinoids. It is a new medicine that can help treat different types of cancer cells. A captivating research project examined the efficacy of ATRA and ATRA-loaded nanoparticles linked to CD133 aptamers, referred to as ATRA-PLNP-CD133, in targeting osteosarcoma stem cells, a form of bone cancer (Gui et al., 2019). In order to facilitate the absorption of materials by cells, it is important to evaluate aspects such as the number of attachment points, surface charge characteristics, and the effectiveness of the materials' adhesion during their design. In 2015, Ni and colleagues developed nanoparticles designed to deliver neomycin specifically to CD133 + cancer stem cells in osteosarcoma for targeted elimination. Next, the nanoparticles made from a special type of plastic called PEGylated poly (lactic-glycolic acid copolymer) were created. These nanoparticles were filled with a drug called salinomycin using a method that involves mixing and evaporating a solvent. Subsequently, they were bonded with the CD133 aptamer, which culminated in the formation of the entity known as Ap-SAL-NP. The results show that CD133 is a well-known marker found on CSC. It could be a good target for delivering drugs to treat osteosarcoma, and it's possible to greatly reduce the growth of osteosarcoma by destroying the CD133 + cancer stem cells (Mi et al., 2018).

The conjugate significantly improves the solubility and biological activity of poorly soluble drugs (such as etoposide, salinomycin, and curcumin) to CSC. Although salinomycin is a promising therapeutic agent, it has been proven to kill CSC in various types of cancer, but its poor water solubility hinders its clinical application. In comparison to salinomycin and salinomycin nanoparticles (SAL-NPs), CD133-SAL-NPs were more effective in reducing the population of CD133 + ovarian cancer stem cells in ovarian cell cultures. This shows that CD133-SAL-NPs specifically target CD133 + ovarian cancer stem cells. Mi and colleagues used salinomycin-loaded polylactic acid-glycolic acid-polyethylene glycol nanoparticles combined with CD133 antibody (CD133-SAL-NP) to eliminate CD133 + ovarian CSC (Mi et al., 2018). To address the issue of drug resistance in cancer therapy, Wang and his team formulated advanced miniature particles by combining PLGA with the substances HA and PF127. These small particles are manufactured through a specialized process that results in a dual-layer structure. They are capable of releasing medication in acidic conditions while also reacting to heat simultaneously (Wang et al., 2015).

Tiny lipopolymer particles, designed to deliver salinomycin and featuring specific molecules for targeting CD20, referred to as CD20-SA-NPs, were developed by Zeng and colleagues (Fig. 8a). The size of the

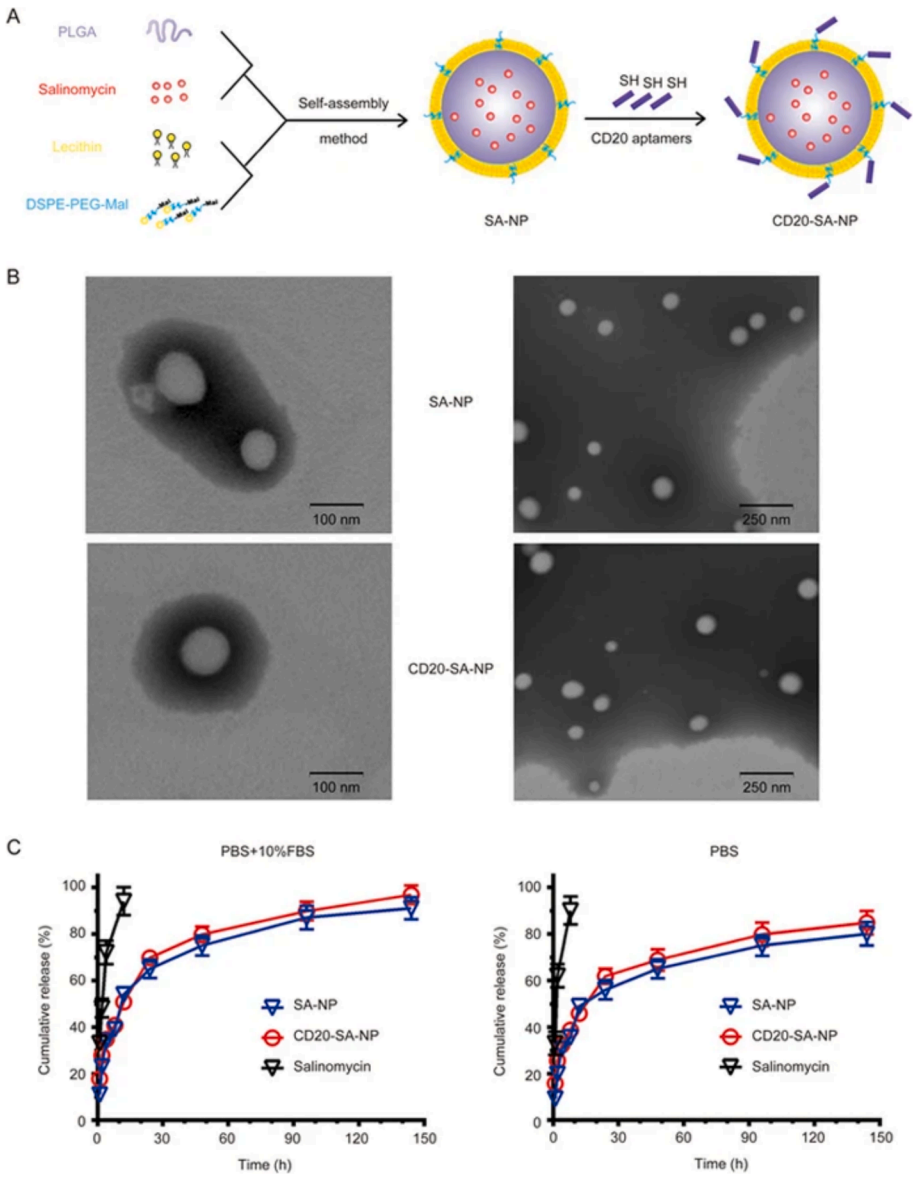

Fig. 8. The making, shape, and release of medicine from tiny particles. a) Making small particles using a method called nanoprecipitation. b) Picture taken with a transmission electron microscope (TEM). The bars show measurements of 100 nm and 250 nm. c) The total amount of salinomycin released from regular salinomycin or the nanoparticles in a solution of PBS or PBS mixed with 10 % FBS. The results are shown as the average ± standard deviation (n = 3). Reprinted from (Zeng et al., 2018) with permission of Zeng et al. (2018).

nanoparticles is small, 96.3 nm. By employing an easy approach, they synthesized small particles referred to as salinomycin-loaded lipopolymer nanoparticles (SA-NPs). Then, they attached a thiolated anti-CD20 aptamer to these particles using a maleimide-thiol reaction. This created a new particle called CD20-SA-NP. The nanoparticles were able to hold more than 60 % of the drug, and they contained over 7 % of salinomycin. This means that using nanoprecipitation is a good method for packing salinomycin into nanoparticles. The nanoparticles were round and all about the same size, as seen in the TEM images (Fig. 8B). The release of the drug in a lab setting was studied, and the results can be seen in Fig. 8C. Free salinomycin quickly released a lot of its content, with over 80 % being released in just 10 h. About 70 % of the drug was released from both nanoparticles within 48 h, and after 96 h, the total amount released was around 80 % (Zeng et al., 2018). The main purpose of combination therapy is to completely eradicate tumors by killing cancer cells and cancer stem cells. Using cationic stabilizers, drug-loaded poly(lactic-glycolic acid) nanoparticles were prepared by emulsion solvent diffusion method (Muntimadugu et al., 2016). In another study, the decyltriphenylphosphonium decylTPP group is conjugated with the primary amino group of polyethyleneimine (PEI) to target breast cancer stem cell-like cells (De Francesco et al., 2019). Compared with CSC only targeting CD133 + osteosarcoma, eradication of CSC and cancer cells in osteosarcoma can achieve higher therapeutic effects. Chen et al. (Chen et al., 2018a) constructed lipopolymer nanoparticles with salinomycin and labeled them with CD133 and Epidermal growth factor receptor (EGFR) aptamer (CESP), which can simultaneously target osteosarcoma cells and osteosarcoma cancer stem cells.

Combination therapy by delivering two or more drugs and nanoparticles at the same time has proven to be an elegant and effective method for cancer treatment. For instance, Sun and his colleagues used combination therapy to eliminate a large number of tumor cells and rare CSC that have high self-renewal capabilities and play a key role in cancer treatment failure (Sun et al., 2015). The co-delivery system has been very effective at delivering two treatments to the same CSCs. It helps the CSCs change into regular cells and stops all tumor cells from growing without increasing the number of CSCs after treatment. This shows that

it can effectively reduce tumors. Gao et al. (Gao et al., 2019a) developed docetaxel (DTX) (a first-line chemotherapeutic drug for breast cancer) and salinomycin (SAL) (anti-breast cancer stem cell BCSCs drug) in a combination of polylactide-glycolide/D-lactide the co-delivery system in rigid nanoparticles composed of esters is α-tocopherol polyethylene glycol 1000 succinate (PLGA/TPGS). The low ability of MSCs to carry things makes it hard for them to be used in delivering small-molecule drugs. To increase the amount of medicine in MSC, researchers looked into using tiny plastic particles that are attached to special TAT proteins. Utilizing a method called emulsion-solvent evaporation, they developed nanoparticles designed to transport the medication paclitaxel. Next, they utilized a specific chemical reaction to bind a molecule known as TAT to the surfaces of these nanoparticles (Moku et al., 2019).

Recently, there has been significant interest in nanoparticles composed of hydrogel and nanogel due to their great potential for drug delivery. Nanogels are tiny, soft structures made of connected polymer chains that can hold water. They are very small, measuring in nanometers, and have properties of both gels and tiny particles. In the last few years, a lot of work has been done to use nanogels in treating cancer (Si et al., 2020). In connection with this, a stimulus-responsive covalent crosslinked nanogel based on biopolymer-dextrin and polylactide was synthesized by free radical polymerization using a homo bi-functional crosslinking agent (MBA). These Nanogel can effectively load and encapsulate the doxorubicin hydrochloride (Dox) in the matrix, with a loading efficiency of 28 % and an encapsulation efficiency of 91 %. In addition, natural nanogels are non-toxic to MG 63 cancer cells, while Dox-loaded nanogels are highly toxic to cancer cells (Das et al., 2016). Pioneering research in this field has proven that covering nanoparticles with cell membranes can prolong the blood circulation time of the resulting "nano vehicle" and increase its accumulation around the tumor. Gao and his associates designed an innovative gel referred to as SCMG, layered with components sourced from bone marrow stem cells. This gel is good at delivering medicine directly to tumors because it is inspired by how well tiny particles with cell membranes work. Stem cell membranes are good for targeting tumors because they are easy to separate and have many parts that can recognize other molecules (Gao et al., 2016). The effects of water-repelling properties on the movement of small particles within tumor tissue, and the potential for these particles to shift between water-attracting and water-repelling states depending on their environment, could play a role in facilitating tumor invasion into surrounding healthy tissues and engaging cancer stem cells. In 2018, a poly(N-isopropyl acrylamide) (PNIPAM)-based nanogel with rapid adaptability and hydrophobicity to effectively coordinate long-term circulation and effectively internalize the contradictory needs of entering a large number of tumor cells and CSC was reported. More importantly, it enhances tumor permeability (Yang et al., 2018a). The nanogels are made using an easy method called precipitation polymerization. They use NIPAM, a type of chemical that reacts to pH, called N-methylallylamine (MAA), and another chemical called sulfobetaine methacrylate (SBMA) as partners. To hold everything together, they include a cross-linker called N, N'-bis(acryloyl) cystamine (BAC), which has special disulfide bonds (Fig. 9a). By varying the quantities of these components, we can design nanogels with tailored temperature properties and surface charge characteristics. The made nanogels are water-loving when in blood (pH 7. 4), allowing them to stay in the bloodstream for a long time. However, they change to water-resistant when they

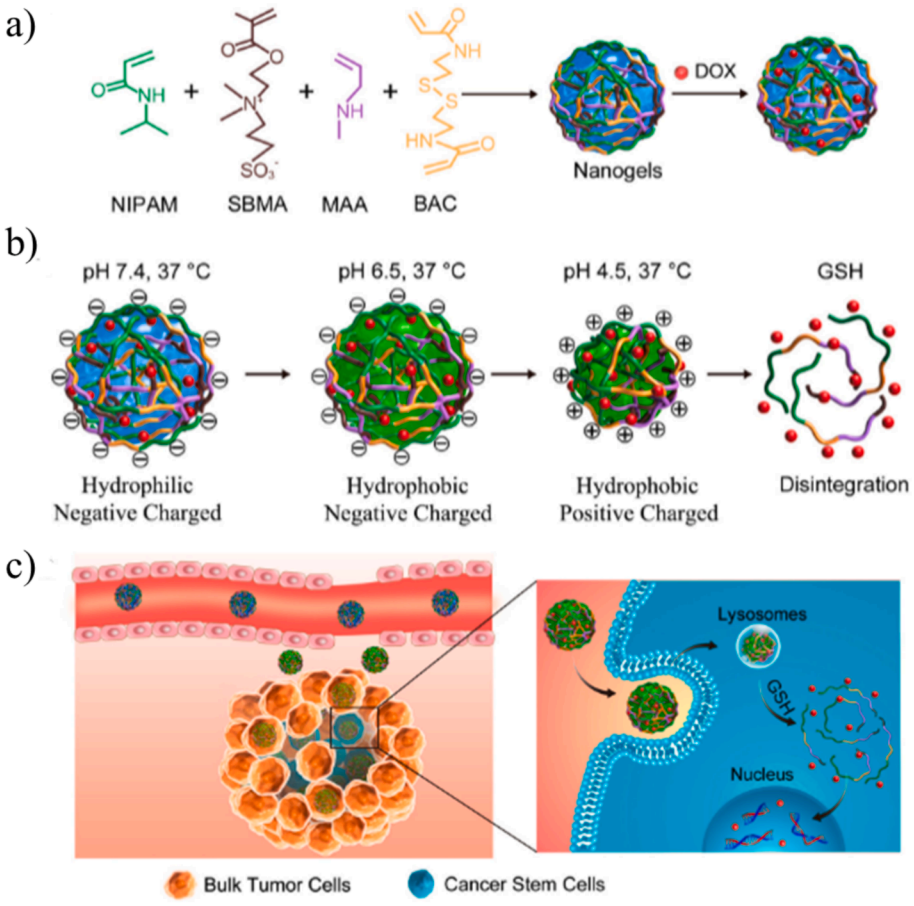

Fig. 9. Schematic illustration of hydrophobicity-adaptive nanogels for programmed anticancer drug delivery. a) Construction of the nanogels. b) Characterization of the nanogels in response to the tumor microenvironment. c) Schematic outline of the in vivo transport prepares of the nanogels during anticancer drug delivery. Reprinted from (Yang et al., 2018a) with permission of Yang et al. (2018).

enter the acidic environment of a tumor (around pH 6. 5) within minutes while keeping their size and surface charge mostly the same. The quick-change ability of the nanogels helps them gather in tumors, move deep into the tumor, and be taken in effectively by both normal tumor cells and CSCs. This leads to a higher concentration of these nanogels in regular tumor cells and the group of cells with CSC traits (Fig. 9b).

In another interesting study, the cationic polymer of PEI is protected by the anionic polymer of hyaluronic acid (HA), which can safely and effectively deliver genes to human mesenchymal stem cells (hMSCs) (Park et al., 2016b). These protected nano gels can be easily taken up by HeLa cells, but this can be decreased if the cells are treated first with anti-CD44 monoclonal antibodies (Park et al., 2016a), sunflower-type nanogels were successfully made to deliver genes into hMSCs and image transplanted cells. Both heparinized nanogels with quantum dots can be used for bioimaging, but their gene delivery capabilities are different. Although QD-encapsulated nanogels have excellent bio-imaging capabilities, they are not suitable for gene delivery due to their structure. On the other hand, sunflower-type nanogels can be used not just for taking pictures of biological materials, but also for delivering genes.

3.3. Metal-based nanoparticles

Through active and passive targeting for tumor imaging, metal nanoparticles (MNP) have gained widespread popularity in targeted drug delivery systems. Appropriate functional groups give these particles specificity (Abdal Dayem et al., 2018). In addition, these particles can be flexibly synthesized and modified according to requirements, so that they can bind to ligands, such as any specific antibodies or drugs (Crous and Abrahamse, 2020; Pedrosa et al., 2018; Rejinold et al., 2018). Combining MNP and plant chemicals can stop the outside surroundings of cells from damaging important active substances. It helps make phytochemicals last longer and makes it easier for substances to move through biofilms (Pallares et al., 2019). This combination offers many new possibilities for cancer treatment, but it also has some limitations. After the medicine is given, some metal from the carrier often stays in the body, which can cause problems because these particles might be toxic (Cho et al., 2017).

The function and behavior of cells are greatly affected by the extracellular matrix (ECM). Building a bionic model is crucial for comprehending the ways in which the ECM assists stem cells in their change and development. In 2017, scientists created gold nanoparticles (Au NP) that were changed with arginine-glycine-aspartic acid (RGD) and could have different amounts of surface coating. This was implemented to simulate the environment of the ECM (Li et al., 2018). Utilizing specialized materials to precisely direct stem cells to transform into bone-building cells (osteoblasts) offers a hopeful approach to accelerating bone healing and regeneration. In a study by Liang and colleagues (Liang et al., 2019), the hydroxyapatite (HA-Au) nanocomposite material loaded with gold nanoparticles (AuNPs) was created to help human bone marrow stem cells change into bone cells. This was done by using the combined effects of the gold nanoparticles and hydroxyapatite.

Considering the need for effective anti-cancer drugs, while still reducing potential damage to surrounding healthy tissues, salinomycin is combined with polyethylene glycol-coated biocompatible gold nanoparticles (AuNPs) to increase its specificity for targeting breast cancer stem cells (BCSCs). BCSC derived from the $CD24^{low}/CD44^{high}$ subgroup is highly sensitive to Sal-AuNP treatment (Zhao et al., 2019). Gold nanoparticles (AuNPs) are small particles that can help deliver and hold onto drugs better. Due to their size and shape, they are effective in targeting particular antibodies. This means that photodynamic therapy (PDT) can be made better to treat lung cancer by focusing on CSC in the lungs. In 2020, using photosensitizer (PS) (AlPcS4Cl), AuNPs, and Abs to construct nano-bioconjugates (NBC) (Crous and Abrahamse, 2020). Due to the existence of CSC, the complete eradication of invasive oral cancer remains a challenge. They have self-renewal, drug efflux, and effective DNA repair capabilities, so they can resist conventional chemotherapeutics. Nanoparticles (QAuNP) were formulated with quinacrine and gold and characterized. The anti-angiogenesis and anti-metastasis effects of OSCC-CSCs were studied (Satapathy et al., 2018). Nanosystems can cause effective targeting of cancer cells and lead to their killing, especially under laser ablation. In addition, thanks to the contrast of gold nanorods (GNR), in vitro photoacoustic imaging can identify the tumor area. In this regard, binary nano structural agents containing Adriamycin drugs and GNRs are further implanted into biocompatible nanocarriers and modified with targeted anti-EpCAM antibodies (Fig. 10), so that CSC can be effectively identified and killed (Locatelli et al., 2019).

It has been proposed that employing microscopic particles for the delivery of medication directly into cells is an effective approach to cancer treatment. Nonetheless, there are restrictions on the number of nanoparticles that can be introduced into cells, as the tiny particles present within them can be dangerous and may leak out upon release. For instance, Kang et al. (Kang et al., 2017) introduced a hybrid plate made of AuNPs and GO. This plate sticks well to cell surfaces and shows strong heat effects when exposed to light. There is considerable focus on RNA interference (RNAi) technology as a promising approach for tackling cancer. It uses small pieces of RNA called siRNA to specifically turn off messenger RNA (mRNA) that makes proteins related to cancer in animal cells. Researchers claim that selecting a particular glucose molecule that adheres to glucose transporter 1 (GLUT1), which is highly present in CSCs, allows for a tiny carrier under 50 nm to transport small interfering RNA (siRNA) directly to these cells (Yi et al., 2019). In order to find new therapies for chemotherapy-resistant breast cancer cells characterized by high levels of Wnt receptors and active Wnt signaling, Miller-Kleinhenz and their collaborators created a small magnetic iron oxide nanoparticle (IONP) drug. The carrier, the drug with dual targeting Wnt/LRP5/6 and urokinase plasminogen activator receptor (uPAR) polypeptide (Miller-Kleinhenz et al., 2018). Nano-drug delivery systems work well with the body and can aim at specific areas, making them a hopeful option for combining hyperthermia (heat treatment) and chemotherapy (cancer treatment) in medical use. A unique silica-based system, consisting of nanoparticles, transports a cancer medication and features a magnetic core. It is also covered with a specific antibody that targets lung cancer stem cells (Liu et al., 2020a). This work proved the feasibility of developing multifunctional nanomedicine for CSC to effectively treat cancer. In addition to the above-mentioned applications, Table 1 also lists other recent studies on biomedical applications of different types of nanoparticles.

4. Biosafety and toxicity issues

The use of nanomaterials to help change stem cells into different types of cells is mainly controlled in three ways: using nanoparticles in a liquid, growing cells in a flat layer, or growing them in a 3D structure (Soltani et al., 2023). Besides their natural ability to help stem cells change into different types of cells, special tiny materials can also influence the basic qualities of how stem cells develop, including their hardness and direction. Many other factors are also very important for what happens to stem cells. Besides their natural ability to help stem cells change into different types of cells, special tiny materials can also influence the basic qualities of how stem cells develop, including their hardness and direction. Many other factors are also very important for what happens to stem cells. Our comprehension of the interactions between nanomaterials and stem cells remains incomplete. It continues to be a major challenge to comprehend the effects of microscopic materials and structures on the functionality and processing of stem cells in the body. In general, the technologies used to check stem cells inside the body without surgery need to be safe and gentle. They should help track the cells over a long time without causing harm to them. On the other hand, it is important to note that very few NPs have been used to monitor patients receiving treatment with stem cells. Before using NPs

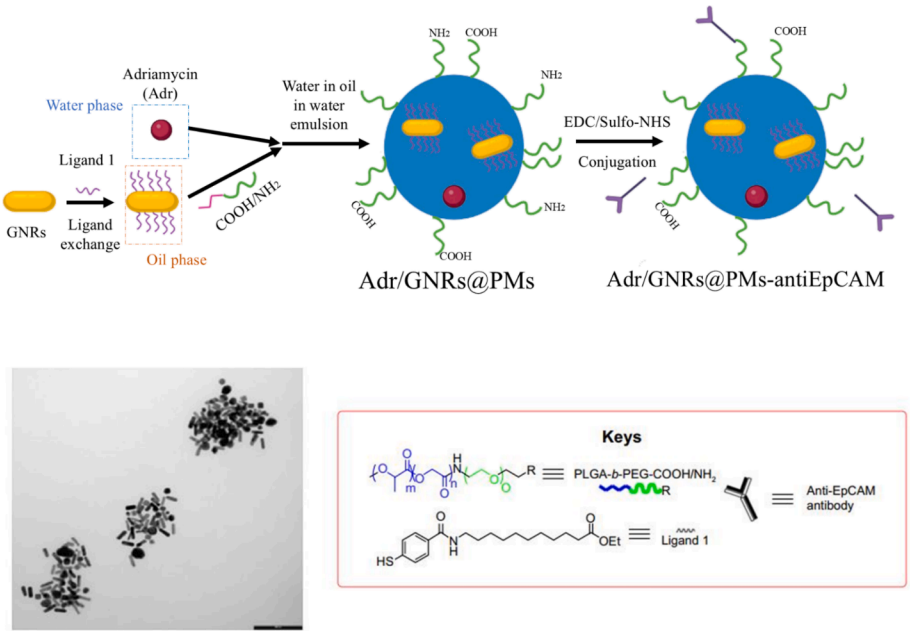

Fig. 10. Representative procedure for the synthesis of Adr/GNRs@PMs-antiEpCAM and TEM image of the final nanosystem. Reprinted from (Locatelli et al., 2019) with permission of Locatelli et al. (2019).

for treatment, it's important to carefully study them. This means looking at their chemical composition and how they affect stem cells. It is essential to evaluate the viability of the stem cells following the application of nanoparticles, as well as their mobility, differentiation into various cell types, and the potential short- and long-term adverse effects.

One potential method by which nanoparticles cause cell death could be linked to their entry mechanism into the cells. Still, some nanoparticles can get inside cells by spreading out on their own. This might cause harm by interacting directly with the cell's fluid, its parts, or its DNA. Most kinds of NPs are taken into cells by a process called endocytosis and are grouped in tiny sacs inside the cell, mainly in lysosomes or late endosomes (Augustine et al., 2020; Goyal and Malviya, 2023). However, some NPs can be affected by the harsh conditions in these cell parts, which can cause them to break down or dissolve. This results in the release of free ions or an increase in reactive surfaces. Another way nanoparticles can be harmful is by causing problems with the actin cytoskeleton. Because of endocytosis events, the cells change their internal structure. This structure is important for basic functions of the cell, including its shape, movement, division, sticking to things, and interacting with its surroundings (Abbasi et al., 2023; Khan et al., 2021). Scientists have researched nanotechnologies and stem cells a lot for treating cells, fixing genes, and healing using the body's ability to repair itself. NPs can cause harmful effects by changing how reactive oxygen species (ROS) are produced (Patra et al., 2018; Wang et al., 2017). These effects include: (a) changes in gene expression caused by NPs damaging DNA directly or by affecting the way cells read and make proteins, especially near the cell nucleus, (b) physical changes in the cell, like altering signals inside the cell, damaging proteins, or injuring cell membranes, and (c) immune system effects, such as increasing certain proteins that promote inflammation or starting an immune response to specific proteins on the surface of the NPs (Zhou et al., 2018).

In general, the pharmacological effectiveness of the majority of pharmaceuticals is linked to their localization at targeted sites within a biological system, which necessitates the achievement of a specific concentration threshold. Given the swift excretion of pharmaceuticals and their extensive distribution within bodily tissues, substantial dosages are frequently required to attain the desired therapeutic concentration, which may lead to drug inefficacy and potential harm to healthy cells (Bigham et al., 2022; Waheed et al., 2022). Nanomedicine is regarded as a potentially effective strategy for tackling these obstacles (Rahimkhoei et al., 2024). It has been empirically demonstrated that nanomedicines possess the capacity to influence the biodistribution of pharmacological agents, leading to the preferential accumulation of these agents within specific target organs or tissues (Shi et al., 2017; Zhang et al., 2020). This capability for targeted delivery has been evidenced to reduce the likelihood of adverse toxicological effects on particular sensitive tissues and cellular structures to a significant degree (Mitchell et al., 2021).

How to use current skills to create new types of nanostructures, deal with packaging and testing issues, find the best quality nanomaterials, customize these materials, and understand how they behave on the surface of solar cells are important challenges in developing effective solar cell technologies. Stem cells are very promising for medicine. As they develop for use in healing, stem cell nanotechnology is likely to help treat diseases that get worse over time soon.

5. Challenges

Targeting CSCs in oncological treatment represents a potentially effective strategy to enhance therapeutic efficacy and improve cellular responses. Recent investigations suggest that employing nanoparticles to specifically target CSCs presents a novel and promising methodology. However, this approach encounters several obstacles that necessitate resolution to augment its overall effectiveness. The following discourse delineates the advantages and challenges that require attention.

- With advancements in materials science, NPs have been fabricated utilizing a broader spectrum of materials, designs, and functionalities. Nonetheless, the nanomaterials currently accessible in this domain predominantly exhibit fundamental characteristics. Furthermore, the application of diverse fabrication techniques, morphological alterations, and the incorporation of various substances onto their surfaces can yield nanoparticles endowed with distinct capabilities. Consequently, collaboration between materials scientists and medical researchers is imperative to innovate and enhance the appeal of nanomaterials.
- The emergence and proliferation of CSCs are linked to multiple mechanisms, albeit the precise pathways remain elusive. For

Table 1
Summary of the application of nanomaterial in stem cell differentiation.

Type of nanoparticles	Nanoparticle components	Application and Type of Stem Cell	Reference
Carbon-based nanoparticles (Graphene oxide)	Poly (L-lactic-co-glycolic acid)/Graphene Oxide/Tussah Silk Fibroin Nanofiber Multilayer graphene oxide film	Osteoblastic Differentiation of Mesenchymal Stem Cells	(Shao et al., 2017), (Puah et al., 2020)
	Micro graphene oxide (MGO) and Nano graphene oxide (NGO)	Osteogenesis of human mesenchymal stem cells	(Shen et al., 2018)
	Graphene Oxide-Incorporated Hydrogels	Chondrogenic Differentiation of Human Mesenchymal Stem Cells	(Kang et al., 2018)
	Graphene Oxide Incorporated PLGA Nanofibrous	Gene Delivery into Mesenchymal Stem Cells	(Wang et al., 2018b)
	Graphene oxide nanoparticles	Human Fetal Neural Stem cells	(Kim et al., 2017)
	Graphene Oxide Nano colloids	Mouse Embryonic Stem Cells	(Wei et al., 2019)
Carbon-based nanoparticles (Carbon nanotube)	unmodified SWCNT and carboxylic acid-functionalized SWCNT (SWCNT-COOH)	Cancer stem cells in osteosarcoma	(Miao et al., 2017)
	A natural lung surfactant added SWCNT and MWCNT	Cancer stem cell-like properties in human small airway epithelial cells	(Kiratipaiboon et al., 2019)
Polymeric-based Nanoparticles	salinomycin-loaded PLGA based polymer–lipid hybrid anti-HER2 nanoparticles (Sali-NP-HER2)	salinomycin delivery to her2-positive breast cancer stem cells and cancer cells	(Li et al., 2017a)
	Chloroquine-loaded Poly Triphenylphosphonium nanoparticles	Targeting breast cancer stem-like cells	(Stagni et al., 2020)
	poly (beta-amino ester) nanoparticles containing multiplexed cancer stem cell-regulating miRNAs	Glioblastoma growth and prolong survival	(Lopez-Bertoni et al., 2018)
	Poly (lactic-co-glycolic acid) (PLGA) nanoparticle with a layer of plasma membrane	Mesenchymal Stem Cell Membrane	(Yang et al., 2018c)
	wedelolactone-encapsulated PLGA nanoparticles (nWdl)	Breast Cancer Stem Cells	(Das et al., 2019)
	TGF-β3(growth factor)-loaded Alginate nanogels	Chondrogenic differentiation of mesenchymal stem cells	(Mahmoudi et al., 2020)
Metal-based Nanoparticles	miR-326@ superparamagnetic iron oxide nanoparticles	human endometrial carcinoma stem cells	(Gao et al., 2019b)
	anti-CD44 antibody-modified superparamagnetic iron oxide nanoparticles	Neck Squamous Cell Carcinoma Stem Cells	(Su et al., 2019)
	TEMPO-conjugated Au NPs	human mesenchymal stem cells	(Li et al., 2017b)
	Albumin-Stabilized Gold Nanoclusters	Reduction of Cancer Stem Cells	(Latorre et al., 2019)
	peptide-coated gold nanoparticles	Brain glioma stem cell	(Cho et al., 2017)
	Gold Nanoparticles	Differentiation in Teratocarcinoma Stem Cells	(Gurunathan and Kim, 2018)
	AuNPs	Differentiation of embryonic stem cells into dopaminergic neurons	(Wei et al., 2017)
Silica nanoparticles	antibody functionalized mesoporous silica nanoparticles	Targeting murine leukemic stem cells	(Mandal et al., 2018)
RNA Nanoparticles	Anti-miRNA- RNA NPs	Targeting Breast Cancer Stem Cell Marker CD133	(Yin et al., 2019)
Protein based Nanoparticles	Albumin Nanoparticle of Paclitaxel	Treatment of Triple Negative Breast Cancer Stem Cells	(Yuan et al., 2020)
	Paclitaxel −loaded albumin nanoparticles	Glioma stem cells	(Lu et al., 2019)
	Ptx-loaded SF-NPs and Sal-loaded SF-NPs	Inhibition of cancer stem cells and tumor growth	(Wu et al., 2018)
Lipid-Based Nanoparticles	Docetaxel-small interfering RNA (DTXL-siRNA) NPs	Elimination of cancer stem cells and bulk cancer cells	(Chen et al., 2018b)
Inorganic nanoparticles	Cockle Shell-Derived Aragonite CaCO3 Nanoparticles	Co-Delivery of Doxorubicin and Thymoquinone Eliminates Cancer Stem Cells	(Ibiyeye and Zuki, 2020)

instance, the processes by which CSCs differentiate into conventional tumor cells and the factors that precipitate this transformation remain undefined. Additionally, although certain pharmacological agents have demonstrated efficacy in targeting cancer stem cells, their underlying mechanisms remain ambiguous. This ambiguity contributes to a lack of focus on CSCs. A comprehensive understanding of the interactions between CSCs, tumors, and therapeutic agents is essential to facilitate the development of novel oncological treatments and refine drug development methodologies.

- Recent investigations reveal that the predominant strategy for targeting CSCs entails the conjugation of ligands to the surfaces of nanoparticles. Numerous markers associated with CSCs, including CD133 and CD44, have been extensively examined. To address multiple targets simultaneously, researchers could employ various ligands on a single nanoparticle. Consequently, this approach enhances the precision of NP targeting.
- Certain pharmacological agents have demonstrated effectiveness against cancer stem cells; however, their application is constrained by poor aqueous solubility and inadequate bioavailability. Researchers have devised a specialized delivery system that exploits the unique microenvironmental conditions present within tumors to facilitate targeted drug delivery. This innovation enhances the therapeutic efficacy of the medication while minimizing the required dosage. Nevertheless, passive targeting may not achieve the same level of effectiveness as active targeting. While the drug exerts its effects in a specific manner, the distinctive properties of nanocarriers augment its ability to accurately target designated areas, thereby enhancing therapeutic effectiveness.
- In recent studies, researchers are ingeniously employing external physical factors to improve the targeting of CSCs and diversify the methodologies utilized. For instance, the utilization of MRI to assist in targeting through imaging, the modification of photothermal conditions in laboratory settings in conjunction with targeting processes for enhanced adaptability, and similar strategies are being explored. The incorporation of these methodologies facilitates the development of more innovative and varied applications for nanoparticles.
- The behavior of tumor cells, encompassing aspects such as proliferation and migration, is profoundly influenced by the surrounding microenvironment and adjacent tissues. Consequently, the selection of appropriate tumor models is of paramount importance for the development of PNP drug delivery systems. Patient-derived xenograft models (PDX) are frequently utilized as “avatars” for cancer research. Their primary objective is to replicate the genetic characteristics and environmental conditions of tumors observed in patients with maximal fidelity. NPs possess the capability to precisely target specific tissues and cells within PDX models and exhibit responsiveness to alterations in their microenvironment.

Furthermore, PDXs serve as crucial cancer models that facilitate the evaluation and comparison of the efficacy of various delivery systems. This underscores the significance of research into diverse nanoparticle types for cancer diagnosis and therapeutic intervention (Wang et al., 2018a). The current financial implications associated with the generation of PDX systems are substantially elevated; thus, there exists a pressing need to enhance the methodologies employed in their development.

6. Conclusion and future perspective

Nanomaterials present a compelling option as carriers for the targeted delivery of therapeutic agents to neoplastic tissues via the aberrant vasculature typically associated with tumors, a phenomenon known as the enhanced permeability and retention effect. The functionalization of NPs with hydrophilic polymers, including PEG, polyacrylic acid (PAA), and dextran (DEX), has been employed to circumvent the uptake of NPs by the mononuclear phagocyte system (MPS), thereby prolonging their circulation time and augmenting their transvascular accumulation. In addition to surface functionalization, drug-laden NPs can be directed toward CSCs residing within tumor matrices through conjugation with antibodies or ligands that specifically target biomarkers, surface receptors, enzymes, and proteins integral to CSC signaling cascades. Given that numerous CSC signaling pathways and associated biomarkers are also present in normal stem cells, the strategy of dual-targeting, utilizing two distinct ligands or antibodies against these biomarkers, significantly enhances the internalization by CSCs while minimizing off-target toxicity towards normal stem cells. Polymeric NPs formulated from PLA, PLGA, PEG, their copolymers, polylysine, lipids, hyaluronic acid, and liposomes have demonstrably served as effective carriers for the targeted delivery of therapeutic agents to CSCs. In contrast to polymeric NPs, which often exhibit a broad size distribution, inorganic NPs typically possess a narrower size distribution, thereby facilitating improved transport through tumor tissues for the specific targeting and uptake by CSCs. Inorganic NPs composed of gold, iron oxide, and silica have been utilized as vehicles for the targeted delivery of drugs to CSCs, in addition to their application in imaging modalities. Multifunctional protein NPs are particularly appealing due to their susceptibility to enzymatic degradation, their capacity for tunable self-assembly, and their innate ability to traverse the cell membrane, making them suitable for the delivery of amino-acid-based therapeutic agents, such as ribosome-inactivating proteins (RIP), which function to inhibit protein synthesis and cellular proliferation within malignant cells. Antibody-drug conjugates (ADCs) exhibit considerable efficacy in the eradication of metastatic and recurrent malignancies through the selection of antibodies that demonstrate high specificity towards CSC surface receptors, the judicious choice of therapeutic agents, and the appropriate selection of enzymatically degradable linkers for the intracellular delivery of drugs to CSCs. Extracellular vesicles (EVs), including exosomes, are particularly promising as carriers for the delivery of functional proteins, mRNAs, microRNAs, and small DNA fragments to CSCs aimed at reversing tumor progression, given their low immunogenic profile, extended circulation time, and substantial loading capacity; EVs also facilitate intercellular communication by functioning as antigen-presenting vesicles. The use of drug-loaded polymeric, inorganic, or protein NPs, ADCs, and EVs that selectively engage with various surface receptors on tumor-associated stem cells holds the potential to enhance drug bioavailability and uptake within tumor tissues, while simultaneously reducing undesirable side effects in healthy tissues, thus contributing to an improved quality of life for patients afflicted with cancer.

Furthermore, it is imperative to enhance our comprehension of the biology of cancer stem cells and their interactions with nanomaterials, as this can facilitate the advancement of more targeted and efficient nano-based therapeutic methodologies. Additionally, the expansion of clinical trials involving nanotherapeutics, particularly those aimed at cancer stem cells, is essential for substantiating their safety and efficacy across a heterogeneous population. The auspicious potential of nanotechnology in the realm of cancer treatment is becoming increasingly evident; however, it necessitates unified efforts and unwavering research endeavors. With appropriate dedication and allocation of resources, we assert that nanotechnology could profoundly alter the prognosis for patients contending with this formidable disease, thereby truly transforming the discipline of oncology.

CRediT authorship contribution statement

Vahid Rahimkhoei: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Ali Akbari:** Validation, Software, Resources, Project administration, Methodology, Investigation. **Amar Yasser Jassim:** Resources, Software, Writing – review & editing. **Uday Abdul-Reda Hussein:** Software, Validation, Writing – review & editing. **Masoud Salavati-Niasari:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The authors do not have permission to share data.

References

Abbasi, R., Shineh, G., Mobaraki, M., Doughty, S., Tayebi, L., 2023. Structural parameters of nanoparticles affecting their toxicity for biomedical applications: a review. J. Nanopart. Res. 25, 43.

Abdal Dayem, A., Lee, S.B., Cho, S.-G., 2018. The impact of metallic nanoparticles on stem cell proliferation and differentiation. Nanomaterials 8, 761.

Abdolahinia, E.D., Nadri, S., Rahbarghazi, R., Barar, J., Aghanejad, A., Omidi, Y., 2019. Enhanced penetration and cytotoxicity of metformin and collagenase conjugated gold nanoparticles in breast cancer spheroids. Life Sci. 231, 116545.

Adel, M., Keyhanvar, P., Zare, I., Tavangari, Z., Akbarzadeh, A., Zahmatkeshan, M., 2023. Nanodiamonds for tissue engineering and regeneration. J. Drug Delivery Sci. Technol. 90, 105130.

Aghebati-Maleki, A., Dolati, S., Ahmadi, M., Baghbanzhadeh, A., Asadi, M., Fotouhi, A., Yousefi, M., Aghebati-Maleki, L., 2020. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. J. Cell. Physiol. 235, 1962–1972.

Aqil, F., Munagala, R., Jeyabalan, J., Agrawal, A.K., Kyakulaga, A.-H., Wilcher, S.A., Gupta, R.C., 2019. Milk exosomes-Natural nanoparticles for siRNA delivery. Cancer Lett. 449, 186–195.

Atashzar, M.R., Baharlou, R., Karami, J., Abdollahi, H., Rezaei, R., Pourramezan, F., Zoljalali Moghaddam, S.H., 2020. Cancer stem cells: A review from origin to therapeutic implications. J. Cell. Physiol. 235, 790–803.

Augustine, R., Hasan, A., Primavera, R., Wilson, R.J., Thakor, A.S., Kevadiya, B.D., 2020. Cellular uptake and retention of nanoparticles: Insights on particle properties and interaction with cellular components. Mater. Today Commun. 25, 101692.

Bayati-Komitaki, N., Ganduh, S.H., Alzaidy, A.H., Salavati-Niasari, M., 2024. A comprehensive review of Co3O4 nanostructures in cancer: Synthesis, characterization, reactive oxygen species mechanisms, and therapeutic applications. Biomed. Pharmacother. 180, 117457.

Bellezza, I., Giambanco, I., Minelli, A., Donato, R., 2018. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochimica et Biophysica Acta (BBA)-Molecular. Cell Res. 1865, 721–733.

Bigham, A., Rahimkhoei, V., Abasian, P., Delfi, M., Naderi, J., Ghomi, M., Moghaddam, F.D., Waqar, T., Ertas, Y.N., Sharifi, S., 2022. Advances in tannic acid-incorporated biomaterials: Infection treatment, regenerative medicine, cancer therapy, and biosensing. Chem. Eng. J. 432, 134146.

Boutzen, H., Madani Tonekaboni, S.A., Chan-Seng-Yue, M., Murison, A., Takayama, N., Mbong, N., Wagenblast, E., Orouji, E., Arruda, A., Mitchell, A., 2022. A primary hierarchically organized patient-derived model enables in depth interrogation of stemness driven by the coding and non-coding genome. Leukemia 36, 2690–2704.

Campbell, E., Hasan, M.T., Pho, C., Callaghan, K., Akkaraju, G., Naumov, A., 2019. Graphene oxide as a multifunctional platform for intracellular delivery, imaging, and cancer sensing. Sci. Rep. 9, 1–9.

Cao, Y., Li, B., Zhong, G., Li, Y., Wang, H., Yu, H., Peng, F., 2018. Catalytic wet air oxidation of phenol over carbon nanotubes: Synergistic effect of carboxyl groups and edge carbons. Carbon 133, 464–473.

Chen, F., Zeng, Y., Qi, X., Chen, Y., Ge, Z., Jiang, Z., Zhang, X., Dong, Y., Chen, H., Yu, Z., 2018a. Targeted salinomycin delivery with EGFR and CD133 aptamers based dual-ligand lipid-polymer nanoparticles to both osteosarcoma cells and cancer stem cells. Nanomedicine: Nanotechnology. Biology and Medicine 14, 2115–2127.

Chen, H., Lin, J., Shan, Y., Zhengmao, L., 2019. The promotion of nanoparticle delivery to two populations of gastric cancer stem cells by CD133 and CD44 antibodies. Biomed. Pharmacother. 115, 108857.

Chen, K., Shen, S., Zhao, G., Cao, Z., Yang, X., Wang, J., 2018b. Simultaneous elimination of cancer stem cells and bulk cancer cells by cationic-lipid-assisted nanoparticles for cancer therapy. Nano Res. 11, 4183–4198.

Cho, J.-H., Kim, A.-R., Kim, S.-H., Lee, S.-J., Chung, H., Yoon, M.-Y., 2017. Development of a novel imaging agent using peptide-coated gold nanoparticles toward brain glioma stem cell marker CD133. Acta Biomater. 47, 182–192.

Cho, Y., Kim, Y.K., 2020. Cancer stem cells as a potential target to overcome multidrug resistance. Front. Oncol. 10, 764.

Choe, G., Kim, S.-W., Park, J., Park, J., Kim, S., Kim, Y.S., Ahn, Y., Jung, D.-W., Williams, D.R., Lee, J.Y., 2019. Anti-oxidant activity reinforced reduced graphene oxide/alginate microgels: Mesenchymal stem cell encapsulation and regeneration of infarcted hearts. Biomaterials 225, 119513.

Choi, Y.-J., Gurunathan, S., Kim, J.-H., 2018. Graphene oxide–silver nanocomposite enhances cytotoxic and apoptotic potential of salinomycin in human ovarian cancer stem cells (OvCSCs): A novel approach for cancer therapy. Int. J. Mol. Sci. 19, 710.

Chu, X., Tian, W., Ning, J., Xiao, G., Zhou, Y., Wang, Z., Zhai, Z., Tanzhu, G., Yang, J., Zhou, R., 2024. Cancer stem cells: advances in knowledge and implications for cancer therapy. Signal Transduct. Target. Ther. 9, 170.

Crous, A., Abrahamse, H., 2020. Effective Gold Nanoparticle-Antibody-Mediated Drug Delivery for Photodynamic Therapy of Lung Cancer Stem Cells. Int. J. Mol. Sci. 21, 3742.

Das, D., Patra, P., Ghosh, P., Rameshbabu, A.P., Dhara, S., Pal, S., 2016. Dextrin and poly (lactide)-based biocompatible and biodegradable nanogel for cancer targeted delivery of doxorubicin hydrochloride. Polym. Chem. 7, 2965–2975.

Das, S., Mukherjee, P., Chatterjee, R., Jamal, Z., Chatterji, U., 2019. Enhancing chemosensitivity of breast cancer stem cells by downregulating SOX2 and ABCG2 using wedelolactone-encapsulated nanoparticles. Mol. Cancer Ther. 18, 680–692.

De Francesco, E.M., Ozsvari, B., Sotgia, F., Lisanti, M.P., 2019. Dodecyl-TPP Targets Mitochondria and Potently Eradicates Cancer Stem Cells (CSCs): Synergy With FDA-Approved Drugs and Natural Compounds (Vitamin C and Berberine). Front. Oncol. 9, 615.

De Menezes, B., Ferreira, F., Silva, B., Simonetti, E., Bastos, T., Cividanes, L., Thim, G., 2018. Effects of octadecylamine functionalization of carbon nanotubes on dispersion, polarity, and mechanical properties of CNT/HDPE nanocomposites. J. Mater. Sci. 53, 14311–14327.

Dias, L.F.G., Abou-Hassan, A., 2024. Different applications, same story: Inspiring nanomedicine from photothermal catalysis to modulate the photothermal activity of nanomaterials through defects engineering. Coord. Chem. Rev. 507, 215751.

Dragu, D.L., Necula, L.G., Bleotu, C., Diaconu, C.C., Chivu-Economescu, M., 2015. Therapies targeting cancer stem cells: Current trends and future challenges. World Journal of Stem Cells 7, 1185.

Fan, Z., Wang, X., Yang, X., Li, Z., 2024. Boosting Oxidative Stress with Hydroxyethyl Starch Smart Nanomedicines to Eliminate Cancer Stem Cells. Acc. Mater. Res. 5, 1558–1570.

Farahzadi, R., Valipour, B., Fathi, E., Pirmoradi, S., Molavi, O., Montazersaheb, S., Sanaat, Z., 2023. Oxidative stress regulation and related metabolic pathways in epithelial–mesenchymal transition of breast cancer stem cells. Stem Cell Res Ther 14, 342.

Gao, C., Lin, Z., Jurado-Sánchez, B., Lin, X., Wu, Z., He, Q., 2016. Stem Cell Membrane-Coated Nanogels for Highly Efficient In Vivo Tumor Targeted Drug Delivery. Small 12, 4056–4062.

Gao, J., Liu, J., Xie, F., Lu, Y., Yin, C., Shen, X., 2019a. Co-Delivery of Docetaxel and Salinomycin to Target Both Breast Cancer Cells and Stem Cells by PLGA/TPGS Nanoparticles. Int. J. Nanomed. 14, 9199.

Gao, Y., Qian, H., Tang, X., Du, X., Wang, G., Zhang, H., Ye, F., Liu, T., 2019b. Superparamagnetic iron oxide nanoparticle-mediated expression of miR-326 inhibits human endometrial carcinoma stem cell growth. Int. J. Nanomed. 14, 2719.

Garnica-Gutiérrez, R.L., Lara-Martínez, L.A., Palacios, E., Masso, F., Contreras, A., Hernández-Gutiérrez, S., Cervantes-Sodi, F., 2018. Effect of functionalized carbon nanotubes and their citric acid polymerization on mesenchymal stem cells in vitro. Journal of Nanomaterials 2018.

Goyal, P., Malviya, R., 2023. Advances in nuclei targeted delivery of nanoparticles for the management of cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1878, 188881.

Gui, K., Zhang, X., Chen, F., Ge, Z., Zhang, S., Qi, X., Sun, J., Yu, Z., 2019. Lipid-polymer nanoparticles with CD133 aptamers for targeted delivery of all-trans retinoic acid to osteosarcoma initiating cells. Biomed. Pharmacother. 111, 751–764.

Guo, W., Qiao, T., Li, T., 2022. The role of stem cells in small-cell lung cancer: evidence from chemoresistance to immunotherapy. Seminars in Cancer Biology. Elsevier 160–169.

Gurunathan, S., Kim, J.-H., 2018. Biocompatible gold nanoparticles ameliorate retinoic acid-induced cell death and induce differentiation in F9 teratocarcinoma stem cells. Nanomaterials 8, 396.

Halim, A., Luo, Q., Ju, Y., Song, G., 2018. A mini review focused on the recent applications of graphene oxide in stem cell growth and differentiation. Nanomaterials 8, 736.

Hsu, J.C., Tang, Z., Eremina, O.E., Sofias, A.M., Lammers, T., Lovell, J.F., Zavaleta, C., Cai, W., Cormode, D.P., 2023. Nanomaterial-based contrast agents. Nat. Rev. Methods Primers 3, 30.

Hu, X., Li, X., Yin, M., Li, P., Huang, P., Wang, L., Jiang, Y., Wang, H., Chen, N., Fan, C., 2017. Nanodiamonds mediate oral delivery of proteins for stem cell activation and intestinal remodeling in Drosophila. ACS Appl. Mater. Interfaces 9, 18575–18583.

Huang, C., Dong, H., Su, Y., Wu, Y., Narron, R., Yong, Q., 2019. Synthesis of carbon quantum dot nanoparticles derived from byproducts in bio-refinery process for cell imaging and in vivo bioimaging. Nanomaterials 9, 387.

Huang, H., Liu, M., Jiang, R., Chen, J., Huang, Q., Wen, Y., Tian, J., Zhou, N., Zhang, X., Wei, Y., 2018. Fabrication and characterization of hyperbranched polyglycerol modified carbon nanotubes through the host-guest interactions. Mater. Sci. Eng. C 91, 458–465.

Ibiyeye, K.M., Zuki, A.B.Z., 2020. Cockle Shell-Derived Aragonite CaCO3 Nanoparticles for Co-Delivery of Doxorubicin and Thymoquinone Eliminates Cancer Stem Cells. Int. J. Mol. Sci. 21, 1900.

Ji, D., Yang, H., Zhang, Q., Ding, H., Zhang, S., Zhang, G., Pang, H., 2024. Iron series metal-organic frameworks and their composite nanomaterials: Controllable synthesis and clean energy applications. Nano Energy 109559.

Kang, E.-S., Song, I., Kim, D.-S., Lee, U., Kim, J.-K., Son, H., Min, J., Kim, T.-H., 2018. Size-dependent effects of graphene oxide on the osteogenesis of human adipose-derived mesenchymal stem cells. Colloids Surf. B Biointerfaces 169, 20–29.

Kang, S., Lee, J., Ryu, S., Kwon, Y., Kim, K.-H., Jeong, D.H., Paik, S.R., Kim, B.-S., 2017. Gold nanoparticle/graphene oxide hybrid sheets attached on mesenchymal stem cells for effective photothermal cancer therapy. Chem. Mater. 29, 3461–3476.

Khan, M., Khan, M.S.A., Borah, K.K., Goswami, Y., Hakeem, K.R., Chakrabartty, I., 2021. The potential exposure and hazards of metal-based nanoparticles on plants and environment, with special emphasis on ZnO NPs, TiO2 NPs, and AgNPs: a review. Environ. Adv. 6, 100128.

Khoobi, M.M., Naddaf, H., Hoveizi, E., Mohammadi, T., 2020. Silymarin effect on experimental bone defect repair in rat following implantation of the electrospun PLA/carbon nanotubes scaffold associated with Wharton's jelly mesenchymal stem cells. J. Biomed. Mater. Res. A.

Kim, J., Yang, K., Lee, J.S., Hwang, Y.H., Park, H.J., Park, K.I., Lee, D.Y., Cho, S.W., 2017. Enhanced Self-Renewal and Accelerated Differentiation of Human Fetal Neural Stem Cells Using Graphene Oxide Nanoparticles. Macromol. Biosci. 17, 1600540.

Kim, K., Choi, H., Choi, E.S., Park, M.-H., Ryu, J.-H., 2019. Hyaluronic acid-coated nanomedicine for targeted cancer therapy. Pharmaceutics 11, 301.

Kiratipaiboon, C., Stueckle, T.A., Ghosh, R., Rojanasakul, L.W., Chen, Y.C., Dinu, C.Z., Rojanasakul, Y., 2019. Acquisition of cancer stem cell-like properties in human small airway epithelial cells after a long-term exposure to carbon nanomaterials. Environ. Sci. Nano 6, 2152–2170.

Kiratipaiboon, C., Voronkova, M., Ghosh, R., Rojanasakul, L.W., Dinu, C.Z., Chen, Y.C., Rojanasakul, Y., 2020. SOX2Mediates Carbon Nanotube-Induced Fibrogenesis and Fibroblast Stem Cell Acquisition. ACS Biomater Sci. Eng. 6, 5290–5304.

Kumar, S., Nehra, M., Kedia, D., Dilbaghi, N., Tankeshwar, K., Kim, K.-H., 2019. Nanodiamonds: Emerging face of future nanotechnology. Carbon 143, 678–699.

Latorre, A., Latorre, A., Castellanos, M., Rodriguez Diaz, C., Lazaro-Carrillo, A., Aguado, T., Lecea, M., Romero-Pérez, S., Calero, M., Sanchez-Puelles, J.M., 2019. Multifunctional albumin-stabilized gold nanoclusters for the reduction of cancer stem cells. Cancers 11, 969.

Laube, C., Yang, F., Naumann, M., Griebel, J., Prager, A., Lotnyk, A., Lorenz, P., Zimmer, K., Helmstedt, U., Abel, B., 2024. Nanodiamond-Polymer Composites for Decreased Laser Ablation Thresholds. ACS Appl. Nano Mater. 7, 8842–8853.

Lazovic, J., Goering, E., Wild, A.M., Schützendübe, P., Shiva, A., Löffler, J., Winter, G., Sitti, M., 2024. Nanodiamond-Enhanced Magnetic Resonance Imaging. Adv. Mater. 36, 2310109.

Lendeckel, U., Wolke, C., 2022. Redox-Regulation in Cancer Stem Cells. Biomedicines 10, 2413.

Leung, H.M., Chu, H.C., Mao, Z.-W., Lo, P.K., 2023. Versatile nanodiamond-based tools for therapeutics and bioimaging. Chem. Commun. 59, 2039–2055.

Li, J., Chen, Y., Kawazoe, N., Chen, G., 2018. Ligand density-dependent influence of arginine–glycine–aspartate functionalized gold nanoparticles on osteogenic and adipogenic differentiation of mesenchymal stem cells. Nano Res. 11, 1247–1261.

Li, J., Xu, W., Yuan, X., Chen, H., Song, H., Wang, B., Han, J., 2017a. Polymer–lipid hybrid anti-HER2 nanoparticles for targeted salinomycin delivery to HER2-positive breast cancer stem cells and cancer cells. Int. J. Nanomed. 12, 6909.

Li, J., Zhang, J., Chen, Y., Kawazoe, N., Chen, G., 2017b. TEMPO-conjugated gold nanoparticles for reactive oxygen species scavenging and regulation of stem cell differentiation. ACS Appl. Mater. Interfaces 9, 35683–35692.

Liang, H., Xu, X., Feng, X., Ma, L., Deng, X., Wu, S., Liu, X., Yang, C., 2019. Gold nanoparticles-loaded hydroxyapatite composites guide osteogenic differentiation of

human mesenchymal stem cells through Wnt/β-catenin signaling pathway. Int. J. Nanomed. 14, 6151.
Liu, D., Hong, Y., Li, Y., Hu, C., Yip, T.-C., Yu, W.-K., Zhu, Y., Fong, C.-C., Wang, W., Au, S.-K., 2020a. Targeted destruction of cancer stem cells using multifunctional magnetic nanoparticles that enable combined hyperthermia and chemotherapy. Theranostics 10, 1181.
Liu, J., Yuan, X., Deng, L., Yin, Z., Tian, X., Bhattacharyya, S., Liu, H., Luo, Y., Luo, L., 2020b. Graphene oxide activated by 980 nm laser for cascading two-photon photodynamic therapy and photothermal therapy against breast cancer. Appl. Mater. Today 20, 100665.
Locatelli, E., Li, Y., Monaco, I., Guo, W., Maturi, M., Menichetti, L., Armanetti, P., Martin, R.C., Franchini, M.C., 2019. A novel theranostic gold nanorods-and Adriamycin-loaded micelle for EpCAM targeting, laser ablation, and photoacoustic imaging of cancer stem cells in hepatocellular carcinoma. Int. J. Nanomed. 14, 1877.
Lopez-Bertoni, H., Kozielski, K.L., Rui, Y., Lal, B., Vaughan, H., Wilson, D.R., Mihelson, N., Eberhart, C.G., Laterra, J., Green, J.J., 2018. Bioreducible polymeric nanoparticles containing multiplexed cancer stem cell regulating miRNAs inhibit glioblastoma growth and prolong survival. Nano Lett. 18, 4086–4094.
Lu, L., Shen, X., Tao, B., Lin, C., Li, K., Luo, Z., Cai, K., 2019. The nanoparticle-facilitated autophagy inhibition of cancer stem cells for improved chemotherapeutic effects on glioblastomas. J. Mater. Chem. B 7, 2054–2062.
Mahmoudi, Z., Mohammadnejad, J., Razavi Bazaz, S., Abouei Mehrizi, A., Saidijam, M., Dinarvand, R., Ebrahimi Warkiani, M., Soleimani, M., 2020. Promoted chondrogenesis of hMCSs with controlled release of TGF-β3 via microfluidics synthesized alginate nanogels. Carbohydr. Polym. 229, 115551.
Mai, Y., Su, J., Yang, C., Xia, C., Fu, L., 2023. The strategies to cure cancer patients by eradicating cancer stem-like cells. Mol. Cancer 22, 171.
Makena, M.R., Ranjan, A., Thirumala, V., Reddy, A.P., 2020. Cancer stem cells: Road to therapeutic resistance and strategies to overcome resistance. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1866, 165339.
Mandal, T., Beck, M., Kirsten, N., Lindén, M., Buske, C., 2018. Targeting murine leukemic stem cells by antibody functionalized mesoporous silica nanoparticles. Sci. Rep. 8, 1–8.
Mariadoss, A.V.A., Saravanakumar, K., Sathiyaseelan, A., Wang, M.-H., 2020. J. Photochem. Photobiol. B Biol. 210, 111984.
Mengistu, B.A., Tsegaw, T., Demessie, Y., Getnet, K., Bitew, A.B., Kinde, M.Z., Beirhun, A. M., Mebratu, A.S., Mekasha, Y.T., Feleke, M.G., 2024. Comprehensive review of drug resistance in mammalian cancer stem cells: implications for cancer therapy. Cancer Cell Int. 24, 406.
Mi, Y., Huang, Y., Deng, J., 2018. The enhanced delivery of salinomycin to CD133+ ovarian cancer stem cells through CD133 antibody conjugation with poly (lactic-co-glycolic acid)-poly (ethylene glycol) nanoparticles. Oncol. Lett. 15, 6611–6621.
Miao, Y., Zhang, H., Pan, Y., Ren, J., Ye, M., Xia, F., Huang, R., Lin, Z., Jiang, S., Zhang, Y., 2017. Single-walled carbon nanotube: One specific inhibitor of cancer stem cells in osteosarcoma upon downregulation of the TGFβ1 signaling. Biomaterials 149, 29–40.
Miller-Kleinhenz, J., Guo, X., Qian, W., Zhou, H., Bozeman, E.N., Zhu, L., Ji, X., Wang, Y. A., Styblo, T., O'Regan, R., 2018. Dual-targeting Wnt and uPA receptors using peptide conjugated ultra-small nanoparticle drug carriers inhibited cancer stem-cell phenotype in chemo-resistant breast cancer. Biomaterials 152, 47–62.
Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A., Langer, R., 2021. Engineering precision nanoparticles for drug delivery. Nat. Rev. Drug Discov. 20, 101–124.
Moku, G., Layek, B., Trautman, L., Putnam, S., Panyam, J., Prabha, S., 2019. Improving payload capacity and anti-tumor efficacy of mesenchymal stem cells using TAT peptide functionalized polymeric nanoparticles. Cancers 11, 491.
Mollania, F., Hadipour, N.L., Mollania, N., 2020. CNT-based nanocarrier loaded with pyrimethamine for adipose mesenchymal stem cells differentiation and cancer treatment: The computational and experimental methods. J. Biotechnol. 308, 40–55.
Muntimadugu, E., Kumar, R., Saladi, S., Rafeeqi, T.A., Khan, W., 2016. CD44 targeted chemotherapy for co-eradication of breast cancer stem cells and cancer cells using polymeric nanoparticles of salinomycin and paclitaxel. Colloids Surf. B Biointerfaces 143, 532–546.
Murali, A., Lokhande, G., Deo, K.A., Brokesh, A., Gaharwar, A.K., 2021. Emerging 2D nanomaterials for biomedical applications. Mater. Today 50, 276–302.
Negri, V., Pacheco-Torres, J., Calle, D., López-Larrubia, P., 2020. Carbon nanotubes in biomedicine. Top. Curr. Chem. 378, 15.
Pallares, R.M., Thanh, N.T.K., Su, X., 2019. Sensing of circulating cancer biomarkers with metal nanoparticles. Nanoscale 11, 22152–22171.
Pan, F., Khan, M., Ragab, A.H., Javed, E., Alsalmah, H.A., Khan, I., Lei, T., Hussain, A., Mohamed, A., Zada, A., 2023. Recent advances in the structure and biomedical applications of nanodiamonds and their future perspectives. Mater. Des. 112179.
Park, J.S., Yi, S.W., Kim, H.J., Kim, S.M., Shim, S.H., Park, K.-H., 2016a. Sunflower-type nanogels carrying a quantum dot nanoprobe for both superior gene delivery efficacy and tracing of human mesenchymal stem cells. Biomaterials 77, 14–25.
Park, J.S., Yi, S.W., Kim, H.J., Park, K.-H., 2016b. Receptor-mediated gene delivery into human mesenchymal stem cells using hyaluronic acid-shielded polyethylenimine/pDNA nanogels. Carbohydr. Polym. 136, 791–802.
Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.d.P., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S.,, 2018. Nano based drug delivery systems: recent developments and future prospects. J. Nanobiotechnol. 16, 1–33.
Pedrosa, P., Mendes, R., Cabral, R., Martins, L.M., Baptista, P.V., Fernandes, A.R., 2018. Combination of chemotherapy and Au-nanoparticle photothermy in the visible light to tackle doxorubicin resistance in cancer cells. Sci. Rep. 8, 1–8.
Puah, P.Y., Yusoff, U.H., Lee, P.C., Moh, P.Y., How, S.E., 2020. Surface characterization, biocompatibility and osteogenic differentiation of drop-casted multilayer graphene oxide film towards human wharton's jelly derived mesenchymal stem cells. Mater. Technol. 35, 238–247.
Qi, Z., Guo, W., Zheng, S., Fu, C., Ma, Y., Pan, S., Liu, Q., Yang, X., 2019. Enhancement of neural stem cell survival, proliferation and differentiation by IGF-1 delivery in graphene oxide-incorporated PLGA electrospun nanofibrous mats. RSC Adv. 9, 8315–8325.
Qin, W., Huang, G., Chen, Z., Zhang, Y., 2017. Nanomaterials in targeting cancer stem cells for cancer therapy. Front. Pharmacol. 8, 1.
Rahimkhoei, V., Akbari, A., Zirak, M., Eftekhari-Sis, B., 2020. Ag nanoparticles stabilized on cubic polyhedral oligomeric silsesquioxane cross-linked poly (N-isopropyl acrylamide-co-itaconic acid): An efficient catalyst for 4-nitrophenol reduction. Funct. Mater. Lett. 13, 2051040.
Rahimkhoei, V., Alzaidy, A.H., Abed, M.J., Rashki, S., Salavati-Niasari, M., 2024. Advances in inorganic nanoparticles-based drug delivery in targeted breast cancer theranostics. Advances in Colloid and Interface Science.
Rahimkhoei, V., Hamadanian, M., Salavati-Niasari, M., 2025. Sol-gel auto-combustion synthesis and characterization of Eu2CrMnO6 nanostructures as a potential electrochemical hydrogen storage material. Int. J. Hydrogen Energy 102, 247–259.
Rahimkhoei, V., Padervand, M., Hedayat, M., Seidi, F., Dawi, E., Akbari, A., 2023. Biomedical applications of electrospun polycaprolactone-based carbohydrate polymers: A review. Int. J. Biol. Macromol. 126642.
Rahimkhoei, V., Rezaie, J., Akbari, A., Nourani, A., Jabbari, N., Lighvan, Z.M., Amini, M., 2021. Nano-based methods for novel coronavirus 2019 (2019-nCoV) diagnosis: A review. Cell Biochem. Funct. 39, 29–34.
Ramezanpour, A., Ansari, L., Rahimkhoei, V., Sharifi, S., Bigham, A., Lighvan, Z.M., Rezaie, J., Szafert, S., Mahdavinia, G., Akbari, A., 2024. Recent advances in carbohydrate-based paclitaxel delivery systems. Polym. Bull. 81, 1043–1069.
Rejinold, N.S., Han, Y., Yoo, J., Seok, H.Y., Park, J.H., Kim, Y.-C., 2018. Evaluation of cell penetrating peptide coated Mn: ZnS nanoparticles for paclitaxel delivery to cancer cells. Sci. Rep. 8, 1–11.
Rezaie, J., Akbari, A., Rahimkhoei, V., Lighvani, Z.M., Jafari, H., 2022. Halloysite nanotubes/carbohydrate-based hydrogels for biomedical applications: from drug delivery to tissue engineering. Polym. Bull. 79, 4497–4513.
Rheima, A.M., Al-Sharify, Z.T., Mohaimeed, A.A., Kazem, M.-A.-A.-H., Dhabab, J.M., Athair, D.M., Joseph, T.M., Mahapatra, D.K., Thomas, S., Kianfar, E., 2024. Nano biosensors: Classification, electrochemistry, nanostructures, and optical properties. Results Eng. 103428.
Saburi, E., Islami, M., Hosseinzadeh, S., Moghadam, A.S., Mansour, R.N., Azadian, E., Joneidi, Z., Nikpoor, A.R., Ghadiani, M.H., Khodaii, Z., 2019. In vitro osteogenic differentiation potential of the human induced pluripotent stem cells augments when grown on Graphene oxide-modified nanofibers. Gene 696, 72–79.
Satapathy, S.R., Nayak, A., Siddharth, S., Das, S., Nayak, D., Kundu, C.N., 2018. Metallic gold and bioactive quinacrine hybrid nanoparticles inhibit oral cancer stem cell and angiogenesis by deregulating inflammatory cytokines in p53 dependent manner. Nanomedicine: Nanotechnology. Biology and Medicine 14, 883–896.
Satpathy, M., Wang, L., Zielinski, R.J., Qian, W., Wang, Y.A., Mohs, A.M., Kairdolf, B.A., Ji, X., Capala, J., Lipowska, M., 2019. Targeted drug delivery and image-guided therapy of heterogeneous ovarian cancer using her2-targeted theranostic nanoparticles. Theranostics 9, 778.
Shafiei-Irannejad, V., Rahimkhoei, V., Molaparast, M., Akbari, A., 2022. Synthesis and characterization of novel hybrid nanomaterials based on β-cyclodextrine grafted halloysite nanotubes for delivery of doxorubicin to MCF-7 cell line. J. Mol. Struct. 1262, 133004.
Shamsian, A., Sepand, M.R., Kachousangi, M.J., Dara, T., Ostad, S.N., Atyabi, F., Ghahremani, M.H., 2020. Targeting Tumorigenicity of Breast Cancer Stem Cells Using SAHA/Wnt-b Catenin Antagonist Loaded Onto Protein Corona of Gold Nanoparticles. Int. J. Nanomed. 15, 4063–4078.
Shao, W., He, J., Wang, Q., Cui, S., Ding, B., 2017. Biomineralized poly (L-lactic-co-glycolic acid)/graphene oxide/Tussah silk fibroin nanofiber scaffolds with multiple orthogonal layers enhance osteoblastic differentiation of mesenchymal stem cells. ACS Biomater Sci. Eng. 3, 1370–1380.
Shen, H., Lin, H., Sun, A.X., Song, S., Zhang, Z., Dai, J., Tuan, R.S., 2018. Chondroinductive factor-free chondrogenic differentiation of human mesenchymal stem cells in graphene oxide-incorporated hydrogels. J. Mater. Chem. B 6, 908–917.
Shi, J., Kantoff, P.W., Wooster, R., Farokhzad, O.C., 2017. Cancer nanomedicine: progress, challenges and opportunities. Nat. Rev. Cancer 17, 20–37.
Shuai, Y., Mao, C., Yang, M., 2018. Protein nanofibril assemblies templated by graphene oxide nanosheets accelerate early cell adhesion and induce osteogenic differentiation of human mesenchymal stem cells. ACS Appl. Mater. Interfaces 10, 31988–31997.
Si, X., Ma, S., Xu, Y., Zhang, D., Shen, N., Yu, H., Zhang, Y., Song, W., Tang, Z., Chen, X., 2020. Hypoxia-sensitive supramolecular nanogels for the cytosolic delivery of ribonuclease A as a breast cancer therapeutic. J. Control. Release 320, 83–95.
Simon, J., Flahaut, E., Golzio, M., 2019. Overview of carbon nanotubes for biomedical applications. Materials 12, 624.
Smith, A.G., Macleod, K.F., 2019. Autophagy, cancer stem cells and drug resistance. J. Pathol. 247, 708–718.
Soltani, N., Khayatkashani, M., Ebrahimian, J., Tavakkoli, N., Rezaei, A., Ryadh, A., Salavati-Niasari, M., 2023. A novel modified CPE using CE-Zno-Lapis lazuli nanocomposite as a sensitive electrochemical sensor for the determination of anti-cancer drug of etoposide. J. Alloy. Compd. 968, 171900.
Song, G., Guo, X., Zong, X., Du, L., Zhao, J., Lai, C., Jin, X., 2019. Toxicity of functionalized multi-walled carbon nanotubes on bone mesenchymal stem cell in rats. Dent. Mater. J. 38, 127–135.

Song, Y., Tang, W., Han, L., Liu, Y., Shen, C., Yin, X., Ouyang, B., Su, Y., Guo, X., 2023. Integration of nanomaterial sensing layers on printable organic field effect transistors for highly sensitive and stable biochemical signal conversion. Nanoscale 15, 5537–5559.
Stagni, V., Kaminari, A., Sideratou, Z., Sakellis, E., Vlahopoulos, S.A., Tsiourvas, D., 2020. Targeting breast cancer stem-like cells using chloroquine encapsulated by a triphenylphosphonium-functionalized hyperbranched polymer. Int. J. Pharm. 585, 119465.
Su, L.-J., Wu, M.-S., Hui, Y.Y., Chang, B.-M., Pan, L., Hsu, P.-C., Chen, Y.-T., Ho, H.-N., Huang, Y.-H., Ling, T.-Y., 2017. Fluorescent nanodiamonds enable quantitative tracking of human mesenchymal stem cells in miniature pigs. Sci. Rep. 7, 45607.
Su, Z., Liu, D., Chen, L., Zhang, J., Ru, L., Chen, Z., Gao, Z., Wang, X., 2019. CD44-targeted magnetic nanoparticles kill head and neck squamous cell carcinoma stem cells in an alternating magnetic field. Int. J. Nanomed. 14, 7549.
Sun, R., Liu, Y., Li, S.-Y., Shen, S., Du, X.-J., Xu, C.-F., Cao, Z.-T., Bao, Y., Zhu, Y.-H., Li, Y.-P., 2015. Co-delivery of all-trans-retinoic acid and doxorubicin for cancer therapy with synergistic inhibition of cancer stem cells. Biomaterials 37, 405–414.
Suo, X., Eldridge, B.N., Zhang, H., Mao, C., Min, Y., Sun, Y., Singh, R., Ming, X., 2018. P-glycoprotein-targeted photothermal therapy of drug-resistant cancer cells using antibody-conjugated carbon nanotubes. ACS Appl. Mater. Interfaces 10, 33464–33473.
Suryaprakash, S., Li, M., Lao, Y.-H., Wang, H.-X., Leong, K.W., 2018. Graphene oxide cellular patches for mesenchymal stem cell-based cancer therapy. Carbon 129, 863–868.
Taylor, A.C., González, C.H., Miller, B.S., Edgington, R.J., Ferretti, P., Jackman, R.B., 2017. Surface functionalisation of nanodiamonds for human neural stem cell adhesion and proliferation. Sci. Rep. 7, 1–11.
Teli, D., Satasia, R., Patel, V., Nair, R., Khatri, R., Gala, D., Balar, P.C., Patel, K., Sharma, A., Vadodariya, P., 2024. Nature Meets Technology: Harnessing Nanotechnology to Unleash the Power of Phytochemicals. Clinical Traditional Medicine and Pharmacology 200139.
Tinwala, H., Wairkar, S., 2019. Production, surface modification and biomedical applications of nanodiamonds: A sparkling tool for theranostics. Mater. Sci. Eng. C 97, 913–931.
Turdo, A., Veschi, V., Gaggianesi, M., Chinnici, A., Bianca, P., Todaro, M., Stassi, G., 2019. Meeting the challenge of targeting cancer stem cells. Front. Cell Dev. Biol. 7, 16.
Uniyal, S., Choudhary, K., Sachdev, S., Kumar, S., 2024. Nano-bio fusion: Advancing biomedical applications and biosensing with functional nanomaterials. Opt. Laser Technol. 168, 109938.
Vajhadin, F., Mazloum-Ardakani, M., Hemati, M., Moshtaghioun, S.M., 2023. Facile preparation of a cost-effective platform based on ZnFe2O4 nanomaterials for electrochemical cell detection. Sci. Rep. 13, 4962.
Waheed, S., Li, Z., Zhang, F., Chiarini, A., Armato, U., Wu, J., 2022. Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. J. Nanobiotechnol. 20, 395.
Wang, B., Hu, S., Teng, Y., Chen, J., Wang, H., Xu, Y., Wang, K., Xu, J., Cheng, Y., Gao, X., 2024a. Current advance of nanotechnology in diagnosis and treatment for malignant tumors. Signal Transduct. Target. Ther. 9, 200.
Wang, H., Agarwal, P., Zhao, S., Xu, R.X., Yu, J., Lu, X., He, X., 2015. Hyaluronic acid-decorated dual responsive nanoparticles of Pluronic F127, PLGA, and chitosan for targeted co-delivery of doxorubicin and irinotecan to eliminate cancer stem-like cells. Biomaterials 72, 74–89.
Wang, H., Cui, Y., 2019. Nanodiamonds for energy. Carbon Energy 1, 13–18.
Wang, L., Hu, C., Shao, L., 2017. The antimicrobial activity of nanoparticles: present situation and prospects for the future. Int. J. Nanomed. 1227–1249.
Wang, Q., Li, S., Xu, C., Wang, X., Yang, T., Wang, C., Xiong, Y., Zhang, Z., Yang, X., Li, Z., 2024b. Glutaminolysis inhibition boosts photodynamic therapy to eliminate cancer stem cells. Biomaterials 306, 122497.
Wang, W., Shang, S., Wang, Y., Xu, B., 2024c. Utilization of nanomaterials in MRI contrast agents and their role in therapy guided by imaging. Front. Bioeng. Biotechnol. 12, 1484577.
Wang, W., Su, H., Wu, Y., Zhou, T., Li, T., 2019. Biosensing and Biomedical Applications of Graphene: A Review of Current Progress and Future Prospect. J. Electrochem. Soc. 166, B505.
Wang, Y., Sun, S., Zhang, Z., Shi, D., 2018a. Nanomaterials for cancer precision medicine. Adv. Mater. 30, 1705660.
Wang, Z., Shen, H., Song, S., Zhang, L., Chen, W., Dai, J., Zhang, Z., 2018b. Graphene oxide incorporated PLGA nanofibrous scaffold for solid phase gene delivery into mesenchymal stem cells. J. Nanosci. Nanotechnol. 18, 2286–2293.
Wei, M., Fu, Z., Wang, C., Zheng, W., Li, S., Le, W., 2019. Graphene oxide nanocolloids induce autophagy-lysosome dysfunction in mouse embryonic stem cells. J. Biomed. Nanotechnol. 15, 340–351.
Wei, M., Li, S., Yang, Z., Zheng, W., Le, W., 2017. Gold nanoparticles enhance the differentiation of embryonic stem cells into dopaminergic neurons via mTOR/p70S6K pathway. Nanomedicine 12, 1305–1317.
Wu, P., Liu, Q., Wang, Q., Qian, H., Yu, L., Liu, B., Li, R., 2018. Novel silk fibroin nanoparticles incorporated silk fibroin hydrogel for inhibition of cancer stem cells and tumor growth. Int. J. Nanomed. 13, 5405.
Wu, S., Tan, Y., Li, F., Han, Y., Zhang, S., Lin, X., 2024. CD44: a cancer stem cell marker and therapeutic target in leukemia treatment. Front. Immunol. 15, 1354992.
Xiao, C., Wang, X., Li, S., Zhang, Z., Li, J., Deng, Q., Chen, X., Yang, X., Li, Z., 2025. A cuproptosis-based nanomedicine suppresses triple negative breast cancers by regulating tumor microenvironment and eliminating cancer stem cells. Biomaterials 313, 122763.
Xu, K., Chen, W., Fu, G., Mou, X., Hou, R., Zhu, Y., Cai, K., 2019. In situ self-assembly of graphene oxide/polydopamine/Sr2+ nanosheets on titanium surfaces for enhanced osteogenic differentiation of mesenchymal stem cells. Carbon 142, 567–579.
Yang, H., Wang, Q., Li, Z., Li, F., Wu, D., Fan, M., Zheng, A., Huang, B., Gan, L., Zhao, Y., Yang, X., 2018a. Hydrophobicity-Adaptive Nanogels for Programmed Anticancer Drug Delivery. Nano Lett. 18, 7909–7918.
Yang, J.-W., Hsieh, K.Y., Kumar, P.V., Cheng, S.-J., Lin, Y.-R., Shen, Y.-C., Chen, G.-Y., 2018b. Enhanced osteogenic differentiation of stem cells on phase-engineered graphene oxide. ACS Appl. Mater. Interfaces 10, 12497–12503.
Yang, N., Ding, Y., Zhang, Y., Wang, B., Zhao, X., Cheng, K., Huang, Y., Taleb, M., Zhao, J., Dong, W.-F., 2018c. Surface functionalization of polymeric nanoparticles with umbilical cord-derived mesenchymal stem cell membrane for tumor-targeted therapy. ACS Appl. Mater. Interfaces 10, 22963–22973.
Yang, X., Zhao, Q., Chen, Y., Fu, Y., Lu, S., Yu, X., Yu, D., Zhao, W., 2019. Effects of graphene oxide and graphene oxide quantum dots on the osteogenic differentiation of stem cells from human exfoliated deciduous teeth. Artif. Cells Nanomed. Biotechnol. 47, 822–832.
Yi, Y., Kim, H.J., Zheng, M., Mi, P., Naito, M., Kim, B.S., Min, H.S., Hayashi, K., Perche, F., Toh, K., 2019. Glucose-linked sub-50-nm unimer polyion complex-assembled gold nanoparticles for targeted siRNA delivery to glucose transporter 1-overexpressing breast cancer stem-like cells. J. Control. Release 295, 268–277.
Yin, H., Xiong, G., Guo, S., Xu, C., Xu, R., Guo, P., Shu, D., 2019. Delivery of anti-miRNA for triple-negative breast cancer therapy using RNA nanoparticles targeting stem cell marker CD133. Mol. Ther. 27, 1252–1261.
Yong, T., Zhang, X., Bie, N., Zhang, H., Zhang, X., Li, F., Hakeem, A., Hu, J., Gan, L., Santos, H.A., 2019. Tumor exosome-based nanoparticles are efficient drug carriers for chemotherapy. Nat. Commun. 10, 3838.
Yuan, H., Guo, H., Luan, X., He, M., Li, F., Burnett, J., Truchan, N., Sun, D., 2020. Albumin Nanoparticle of Paclitaxel (Abraxane) Decreases while Taxol Increases Breast Cancer Stem Cells in Treatment of Triple Negative Breast Cancer. Mol. Pharm. 17, 2275–2286.
Zeng, Y.-B., Yu, Z.-C., He, Y.-N., Zhang, T., Du, L.-B., Dong, Y.-M., Chen, H.-W., Zhang, Y.-Y., Wang, W.-Q., 2018. Salinomycin-loaded lipid-polymer nanoparticles with anti-CD20 aptamers selectively suppress human CD20+ melanoma stem cells. Acta Pharmacol. Sin. 39, 261–274.
Zhang, G.-C., Song, K., Wang, X.-F., He, Z., Du, J., Sun, J.-L., Xu, R.-C., Liu, Z.-Y., Wang, F., Qi, Z.-R., 2025. Bismuth-based mesoporous nanoball carrying sorafenib for synergistic photothermal and molecularly-targeted therapy in an orthotopic hepatocellular carcinoma xenograft mouse model. Colloids Surf. B Biointerfaces 245, 114279.
Zhang, P., Zhang, Y., Ding, X., Shen, W., Li, M., Wagner, E., Xiao, C., Chen, X., 2020. A multistage cooperative nanoplatform enables intracellular co-delivery of proteins and chemotherapeutics for cancer therapy. Adv. Mater. 32, 2000013.
Zhang, Z., Deng, Q., Xiao, C., Li, Z., Yang, X., 2022. Rational design of nanotherapeutics based on the five features principle for potent elimination of cancer stem cells. Acc. Chem. Res. 55, 526–536.
Zhao, N., Song, M., Zhang, X., Xu, W., Liu, X., 2024. Nanodiamond Coating in Energy and Engineering Fields. Synthesis Methods, Characteristics, and Applications. Small, 2401292.
Zhao, Y., Zhao, W., Lim, Y.C., Liu, T., 2019. Salinomycin-loaded gold nanoparticles for treating cancer stem cells by ferroptosis-induced cell death. Mol. Pharm. 16, 2532–2539.
Zhou, M., Lozano, N., Wychowaniec, J.K., Hodgkinson, T., Richardson, S.M., Kostarelos, K., Hoyland, J.A., 2019. Graphene oxide: a growth factor delivery carrier to enhance chondrogenic differentiation of human mesenchymal stem cells in 3D hydrogels. Acta Biomater. 96, 271–280.
Zhou, X., Yuan, L., Wu, C., Luo, G., Deng, J., Mao, Z., 2018. Recent review of the effect of nanomaterials on stem cells. RSC Adv. 8, 17656–17676.