www.idosr.org
Prissy
©IDOSR PUBLICATIONS
ISSN: 2550-794X
International Digital Organization for Scientific Research
IDOSR JOURNAL OF SCIENTIFIC RESEARCH 10(3):54-62, 2025.
https://doi.org/10.59298/IDOSRJSR/2024/10.3.5462
IDOSRJSR10.300000

Targeting Cancer Stem Cells Using Nanotechnology: Challenges and Opportunities

Ahereza Prissy

Department of Pharmacy Kampala International University Uganda
Email: prissy.ahereza@studwc.kiu.ac.ug

ABSTRACT

Cancer stem cells (CSCs) represent a subpopulation of tumor cells with self-renewal and tumor-initiating properties, playing a central role in tumor recurrence, metastasis, and resistance to conventional therapies. Despite advances in cancer treatment, targeting CSCs remains a significant challenge due to their plasticity, quiescent nature, and resistance mechanisms. Nanotechnology offers an innovative platform for the targeted delivery of therapeutics to CSCs by exploiting unique features such as enhanced permeability and retention (EPR) effect, surface functionalization, and controlled drug release. This review critically discusses the biology of CSCs, current strategies to target them, and the application of nanotechnology-based approaches, including nanoparticles, liposomes, micelles, dendrimers, and exosomes, to overcome the limitations of conventional therapies. We highlight the design considerations for CSC-specific targeting, recent preclinical and clinical advances, and the integration of molecular markers, such as CD44, CD133, ALDH1, and EpCAM, for precise targeting. Furthermore, we examine the major challenges, including off-target effects, heterogeneity of CSCs, and translational bottlenecks, as well as future opportunities such as smart nanocarriers, combination therapies, and personalized nanomedicine. Overall, nanotechnology presents a promising frontier in eliminating CSCs and improving long-term cancer treatment outcomes.

Keywords: Cancer stem cells, Nanotechnology, Drug delivery, Tumor resistance, Targeted therapy

INTRODUCTION

Cancer continues to be one of the most pressing global health concerns, accounting for millions of deaths each year[1–3]. Despite significant advances in early detection, diagnostics, and therapy, the recurrence and metastasis of tumors remain major obstacles in achieving long-term patient survival [3, 4]. Over the past two decades, there has been growing recognition of the critical role played by a distinct subpopulation of tumor cells known as cancer stem cells (CSCs)[5–8]. These cells, which possess stem-like characteristics such as self-renewal and the ability to differentiate into heterogeneous tumor cell populations, are believed to be responsible for tumor initiation, progression, metastasis, therapeutic resistance, and relapse following treatment. Unlike the bulk of tumor cells, CSCs can survive adverse microenvironmental conditions and cytotoxic treatments, making them exceptionally resilient and difficult to eliminate through conventional therapeutic strategies[9, 10].

Conventional chemotherapy and radiotherapy are designed to target rapidly proliferating tumor cells. While this approach often leads to initial tumor shrinkage, it is typically insufficient for complete eradication because it spares the relatively quiescent CSCs[11–14]. As a result, CSCs can repopulate the tumor mass after treatment, leading to recurrence and the spread of cancer to distant sites. Furthermore, CSCs exhibit inherent resistance to therapy through various biological adaptations, including the overexpression of drug efflux pumps, enhanced DNA repair systems, and activation of anti-apoptotic pathways. These mechanisms collectively protect CSCs from genotoxic insults and promote their survival under therapeutic pressure[15–18].

In light of these challenges, targeting CSCs has emerged as a critical frontier in the development of effective and durable cancer treatments. However, this goal presents numerous biological and pharmacological hurdles. CSCs are rare and phenotypically heterogeneous, making their identification and isolation difficult [5, 10]. They often share molecular markers and signaling pathways with normal stem cells, increasing the risk of off-target toxicity when using traditional therapies. Moreover, the tumor microenvironment (TME) provides a supportive niche that helps maintain CSC plasticity and contributes to their evasion of immune surveillance and therapeutic targeting[19–21].

The emergence of nanotechnology offers promising solutions to overcome these challenges. Nanomedicine involves the design and application of materials at the nanometer scale, typically between 1 and 100 nanometers, for therapeutic and diagnostic purposes. Nanoparticles can be engineered with precise physical, chemical, and

biological properties that allow them to interact with tumor tissues in a highly specific manner[2, 22, 23]. In the context of CSC targeting, nanocarriers can be functionalized with ligands or antibodies that recognize CSC-specific surface markers, enabling selective delivery of therapeutic agents to this subpopulation while sparing normal cells. These nanocarriers can encapsulate a range of cargos, including small-molecule chemotherapeutics, siRNAs, CRISPR-Cas9 components, or immunomodulatory agents, thereby enhancing treatment efficacy and reducing systemic side effects[24–26].

Furthermore, nanoparticles can exploit the abnormal vasculature and leaky blood vessels within tumors through the enhanced permeability and retention (EPR) effect, which promotes their accumulation at the tumor site[27–29]. Stimuli-responsive nanoparticles can also be designed to release their payload in response to specific conditions within the TME, such as acidic pH, high reactive oxygen species (ROS), or specific enzymatic activity, thereby ensuring precise drug release at the site of interest[25, 30–32].

The interplay between CSC biology and nanotechnology represents a paradigm shift in the design of next-generation cancer therapeutics. By integrating our understanding of CSC-driven tumor dynamics with the precision capabilities of nanomedicine, researchers and clinicians can develop more effective interventions aimed at preventing tumor recurrence and metastasis. This review explores the biological basis of CSCs, the current state of nanotechnology-based approaches to target them, and the challenges and opportunities that lie ahead in translating these innovations into clinical practice.

2. Biology of Cancer Stem Cells

Cancer stem cells (CSCs) represent a small but critical subset of cells within a tumor that possess unique biological features distinguishing them from the majority of tumor cells[10, 33]. These cells are characterized by their ability to self-renew, differentiate into multiple cell lineages within the tumor, and initiate new tumor formation. Their discovery has reshaped our understanding of tumor heterogeneity, progression, resistance to therapy, and recurrence. Unlike the bulk tumor cells that proliferate rapidly but lack long-term self-renewal capacity, CSCs are believed to serve as a reservoir of cancer cells that sustain tumor growth and drive relapse following treatment[34, 35].

One of the hallmarks of CSCs is the expression of specific surface markers that aid in their identification and isolation. Among the most commonly used markers are CD44, CD133, epithelial cell adhesion molecule (EpCAM), and aldehyde dehydrogenase 1 (ALDH1)[36, 37]. However, the expression of these markers can vary significantly depending on the type and stage of cancer, and some markers are also shared with normal stem cells, posing a challenge for selective targeting. These surface molecules often participate in key signaling pathways such as Wnt/β-catenin, Notch, Hedgehog, and PI3K/Akt, which regulate stemness, proliferation, survival, and resistance to differentiation. Dysregulation of these pathways contributes to the malignant potential of CSCs and their capacity to evade conventional therapies[38–41].

The therapy resistance of CSCs is underpinned by several sophisticated mechanisms. One major feature is the overexpression of ATP-binding cassette (ABC) transporters, such as ABCG2 and ABCB1, which actively efflux chemotherapeutic agents out of the cell, thereby lowering intracellular drug concentrations and reducing cytotoxicity[42, 43]. CSCs also exhibit robust DNA repair mechanisms that allow them to quickly rectify DNA damage induced by radiation or chemotherapy. Moreover, they often exist in a quiescent or dormant state, cycling slowly or remaining in G0 phase, which enables them to survive treatments that target rapidly dividing cells. CSCs also upregulate anti-apoptotic proteins and express high levels of antioxidant enzymes that neutralize reactive oxygen species, further enhancing their survival under therapeutic stress[43].

The tumor microenvironment (TME) plays a pivotal role in maintaining the CSC phenotype and enhancing their resistance. Components of the TME, such as stromal cells, immune cells, extracellular matrix, cytokines, and hypoxic conditions, provide a supportive niche that nurtures CSCs and protects them from immune attack[44–46]. Hypoxia, for instance, activates hypoxia-inducible factors (HIFs) that can promote the expression of stemness-related genes and support CSC maintenance. In addition, signaling from surrounding stromal cells through paracrine mechanisms can help sustain CSC properties and shield them from drugs and immune responses[47, 48].

Given the crucial role of CSCs in tumor maintenance and recurrence, a thorough understanding of their biology is vital for developing targeted therapies. However, challenges remain in reliably identifying CSCs, as their phenotype can shift depending on environmental cues and therapeutic pressure, demonstrating considerable plasticity. Additionally, the overlap in markers and signaling pathways between CSCs and normal tissue stem cells raises concerns about potential toxicity to normal regenerative tissues during targeted therapy[47, 49].

The growing body of research into CSC biology provides a compelling rationale for the development of precision medicine strategies that exploit the unique features of these cells. Nanotechnology-based approaches, in particular, offer innovative solutions by enabling the delivery of therapeutic agents specifically to CSCs. By leveraging molecular markers and TME characteristics, nanoparticles can be tailored to recognize and disrupt CSC functions selectively[8, 50, 51]. Ultimately, combining deep biological insight into CSC behavior with the precise capabilities of nanotechnology holds great promise for eradicating the roots of cancer and achieving long-term therapeutic success.

3. Nanotechnology in CSC-Targeted Therapy

Nanotechnology enables the fabrication of drug carriers with modifiable physicochemical properties such as size, surface charge, and ligand attachment. Several nanocarriers have been investigated for CSC targeting:

3.1. Liposomes and Polymeric Nanoparticles: Liposomes and polymeric nanoparticles represent some of the most extensively studied nanocarrier systems for targeted cancer therapy, particularly in targeting cancer stem cells (CSCs)[52–54]. Liposomes are spherical vesicles composed of lipid bilayers, capable of encapsulating both hydrophilic and hydrophobic drugs in their aqueous core and lipid membrane, respectively. Their structural similarity to biological membranes confers excellent biocompatibility and minimal toxicity. Polymeric nanoparticles, typically made from biodegradable polymers such as PLGA (poly(lactic-co-glycolic acid)), offer controlled and sustained drug release profiles[53, 55]. Both platforms can be functionalized with targeting ligands, such as hyaluronic acid, peptides, antibodies, or aptamers, to facilitate active targeting of CSC-specific surface markers such as CD44, CD133, or EpCAM. This targeting enhances drug accumulation at the tumor site and improves therapeutic outcomes. Additionally, surface modifications can promote cellular uptake and endosomal escape, enhancing the intracellular delivery of chemotherapeutics or gene-editing tools[52]. Polymeric nanoparticles can also co-deliver multiple therapeutic agents, enabling synergistic treatments that address CSC drug resistance and heterogeneity. The tunability of size, surface charge, and release kinetics further enhances their versatility. Overall, these nanocarriers offer a promising avenue for eradicating CSCs while minimizing systemic toxicity and improving treatment specificity.

3.2. Micelles and Dendrimers: Micelles and dendrimers are advanced nanocarrier systems that offer distinct advantages for the targeted delivery of anti-cancer therapeutics, particularly to cancer stem cells (CSCs)[56, 57]. Micelles are self-assembling colloidal structures formed from amphiphilic molecules, typically block copolymers, in aqueous environments. Their hydrophobic core can encapsulate poorly water-soluble drugs, improving bioavailability and stability in circulation. Surface modification with targeting ligands enables selective binding to CSC markers such as CD44 or ALDH1. Dendrimers, on the other hand, are highly branched, tree-like macromolecules with well-defined architecture and multiple terminal functional groups[57]. Their structure allows for precise control over size, shape, and surface chemistry. This multivalency facilitates high drug-loading capacity and simultaneous conjugation with imaging agents, therapeutic payloads, and targeting moieties. Dendrimers such as PAMAM (polyamidoamine) can be engineered to release drugs in response to pH or enzymatic activity in the tumor microenvironmen[56, 57]t. Their nanoscale size also allows for enhanced permeability and retention (EPR) in tumor tissues. Importantly, both micelles and dendrimers can bypass multidrug resistance mechanisms by facilitating intracellular drug delivery and evading efflux pumps. As a result, they hold significant promise for overcoming therapeutic challenges associated with CSCs, such as chemoresistance, tumor relapse, and metastasis.

3.3. Metallic and Magnetic Nanoparticles: Metallic and magnetic nanoparticles have gained considerable attention for their diagnostic and therapeutic applications in targeting cancer stem cells (CSCs)[58, 59]. Metallic nanoparticles, such as gold and silver nanoparticles, possess unique optical and physicochemical properties that make them suitable for imaging, photothermal therapy, and drug delivery. Gold nanoparticles (AuNPs), for example, can be functionalized with CSC-specific ligands like antibodies against CD133 or CD44 to enable selective binding and internalization[59, 60]. Upon exposure to near-infrared light, AuNPs convert absorbed light into heat, inducing localized hyperthermia and cell death particularly effective against CSCs known to resist conventional therapies. Silver nanoparticles exhibit antimicrobial and cytotoxic properties, although their application requires careful dose optimization to minimize toxicity[58, 61, 62]. Magnetic nanoparticles, such as superparamagnetic iron oxide nanoparticles (SPIONs), offer an additional layer of control, allowing for site-specific targeting via external magnetic fields. This magnetic guidance enhances the accumulation of therapeutics in tumor sites and reduces off-target effects. These nanoparticles can also serve as contrast agents in magnetic resonance imaging (MRI), enabling real-time tracking of biodistribution and treatment response. Furthermore, their surfaces can be functionalized for dual imaging and therapeutic functions, contributing to the development of theranostic platforms for CSC management.

3.4. Exosomes and Biomimetic Nanoparticles: Exosomes and biomimetic nanoparticles represent a new frontier in nanomedicine for targeting cancer stem cells (CSCs), offering high biocompatibility and innate targeting capabilities[10, 63]. Exosomes are nano-sized extracellular vesicles naturally secreted by cells and play essential roles in intercellular communication by transporting proteins, lipids, and nucleic acids. Their endogenous origin enables them to evade immune detection and prolong circulation time in vivo[64, 65]. Importantly, exosomes can be engineered to encapsulate therapeutic agents, such as small molecules, RNAi, or CRISPR-Cas9 components, and modified with targeting ligands to enhance CSC specificity[10, 65]. For example, exosomes can be derived from mesenchymal stem cells or cancer cells and loaded with anti-CSC drugs, offering selective delivery while minimizing systemic toxicity.

Biomimetic nanoparticles, which imitate natural cellular structures or functions, further enhance targeted delivery[66]. These include nanoparticles cloaked in cancer cell membranes, stem cell membranes, or leukocyte-derived coatings that confer homotypic targeting and immune evasion. Such systems can mimic CSC surface markers or exploit tumor tropism to home in on the CSC niche. In addition, biomimetic nanoparticles can respond to stimuli in the tumor microenvironment, such as pH or enzyme activity, to release their payload

precisely at the target site[66]. These advanced platforms hold immense potential for improving therapeutic outcomes and reducing relapse driven by CSCs.

4. Ligand-Based Targeting Strategies

The identification and exploitation of specific surface markers on cancer stem cells (CSCs) have enabled the development of ligand-based targeting strategies for more effective drug delivery[67]. CSCs express unique or overexpressed biomarkers such as CD44, CD133, EpCAM (epithelial cell adhesion molecule), and ALDH1 (aldehyde dehydrogenase 1), which distinguish them from normal cells and bulk tumor populations. By conjugating ligands such as monoclonal antibodies, aptamers, peptides, or polysaccharides to the surface of nanocarriers, researchers can achieve selective recognition and binding to CSCs[68]. For instance, anti-CD44 antibodies or hyaluronic acid (a natural ligand for CD44) can be used to decorate nanoparticles, promoting preferential binding and uptake by CD44+ CSCs. Similarly, aptamers that specifically bind CD133 can guide therapeutic payloads to CD133+ populations, common in glioblastoma and colorectal cancers[69]. EpCAM-targeting peptides and ALDH1-responsive systems have also been engineered to exploit the differential expression of these markers for enhanced specificity. Once internalized by CSCs, these ligand-functionalized nanocarriers facilitate localized drug release, improving cytotoxic efficacy while minimizing harm to non-target cells. This approach enhances therapeutic outcomes by ensuring that the cytotoxic agents directly affect the most therapy-resistant cell subpopulations[69]. However, challenges such as receptor heterogeneity, downregulation, or shedding of target markers must be addressed to avoid off-target delivery or therapeutic escape[69]. To further increase selectivity and reduce systemic toxicity, researchers are exploring dual-ligand strategies that simultaneously target two markers or combine CSC-specific ligands with tumor microenvironment (TME) cues. As nanomedicine progresses, ligand-based targeting remains a cornerstone strategy, offering a rational and adaptable method to overcome the limitations of conventional therapies by enabling the selective elimination of CSCs.

5. Therapeutic Payloads for CSC Elimination

To effectively eradicate cancer stem cells (CSCs), nanocarriers are engineered to deliver a variety of therapeutic payloads directly to these therapy-resistant cells. Among the most common payloads are conventional chemotherapeutics such as paclitaxel and doxorubicin, which are cytotoxic to proliferating cells[70]. However, CSCs often exhibit intrinsic or acquired resistance to these agents due to mechanisms like enhanced DNA repair, drug efflux, and quiescence. To overcome these barriers, modern nanocarriers have been designed to incorporate nucleic acid-based therapies, including small interfering RNA (siRNA), short hairpin RNA (shRNA), and microRNA (miRNA), which can silence genes involved in stemness, drug resistance, and survival. For instance, targeting genes involved in the Wnt/β-catenin, Notch, or Hedgehog pathways as key regulators of CSC maintenance—can sensitize these cells to additional therapies or directly induce apoptosis. Nanocarriers can also encapsulate small molecule inhibitors of these pathways, enabling precise disruption of CSC signaling cascades[71]. Additionally, photothermal therapy (PTT) and photodynamic therapy (PDT) agents have emerged as innovative payloads, where light-triggered activation leads to local heating or reactive oxygen species generation, selectively damaging CSCs with minimal invasiveness. Combination therapy approaches offer even greater promise by simultaneously attacking both bulk tumor cells and CSCs. For example, a single nanocarrier may be co-loaded with a chemotherapeutic for rapid tumor debulking and a CSC-targeting siRNA to prevent recurrence[71]. This dual-strike strategy reduces the likelihood of relapse and metastasis. Overall, the choice of therapeutic payloads is critical and must be tailored based on the molecular characteristics of the CSC population in a given cancer type. The versatility of nanocarrier systems allows for the co-delivery of diverse agents, offering a powerful means to overcome drug resistance, reduce toxicity, and improve the overall efficacy of cancer therapy by targeting the root drivers of malignancy.

6. Challenges in CSC-Targeting Nanotechnology

Despite significant advances in CSC-targeting nanotechnology, numerous challenges remain that hinder its translation from the laboratory to clinical application. One of the most pressing issues is tumor heterogeneity, both intertumoral and intratumoral[72]. CSC markers are not universal; they vary widely between cancer types and even among individual tumors within the same patient. Moreover, CSCs may undergo phenotypic plasticity, altering their marker expression during disease progression or in response to therapy, complicating effective targeting. Another major concern is the potential for off-target effects[73]. Many CSC markers, such as CD44 and ALDH1, are also expressed at lower levels on normal stem or progenitor cells, raising the risk of unintended toxicity to healthy tissues. Delivery efficiency also poses a critical limitation. Nanocarriers often struggle to penetrate the dense extracellular matrix and reach the hypoxic, nutrient-deprived niches where CSCs typically reside. Limited diffusion and retention in these regions can drastically reduce therapeutic impact[73]. Additionally, concerns over immunogenicity and toxicity arise, particularly with synthetic or inorganic nanoparticles, which may trigger immune responses or accumulate in non-target organs. The biocompatibility and long-term safety of many novel nanomaterials remain inadequately assessed. Beyond biological challenges, regulatory and manufacturing hurdles persist. Large-scale production of complex, multifunctional nanocarriers with consistent quality and reproducibility is technically demanding and cost-intensive[69, 74, 75]. The regulatory pathway for approval is also not well-defined, especially for combination therapies involving novel nanomaterials and multiple active agents. These multifaceted challenges necessitate continued research and

refinement of nanoparticle design, including better biomarker identification, improved biocompatibility, and enhanced penetration strategies. Interdisciplinary collaboration between chemists, oncologists, pharmacologists, and regulatory agencies is essential to advance CSC-targeting nanotechnologies from experimental models to clinically viable treatments.

7. Opportunities and Future Perspectives

The future of CSC-targeting nanotechnology is promising, with several emerging strategies poised to overcome current limitations and revolutionize cancer treatment. One of the most exciting developments is the design of smart nanocarriers capable of responding to specific stimuli within the tumor microenvironment (TME) or CSC niches. These stimuli-responsive systems can release their therapeutic payloads in response to pH changes, enzymatic activity, or redox conditions, thereby enhancing precision and reducing systemic toxicity. Another promising avenue is the implementation of dual-targeting strategies, wherein nanocarriers are engineered to simultaneously recognize CSC-specific markers and TME features, such as angiogenic signals or immune checkpoint molecules. This dual specificity can improve targeting accuracy and therapeutic impact. The advent of personalized nanomedicine also offers transformative potential. By integrating patient-specific CSC profiles derived from biopsy or circulating tumor cell analysis, clinicians could tailor nanotherapeutics for individualized treatment regimens, improving outcomes and reducing adverse effects. Moreover, the combination of nanotechnology with immunotherapy is gaining traction. Immuno-nanotherapy involves using nanocarriers to deliver immune-modulatory agents, vaccines, or antigens that prime the immune system to recognize and eliminate CSCs. This approach can convert immunologically "cold" tumors into "hot" ones, enhancing responsiveness to checkpoint blockade or CAR-T therapies. Integration with advanced computational tools, such as artificial intelligence (AI) and machine learning, can further accelerate the development of CSC-targeting strategies. By analyzing multi-omics data—including genomics, transcriptomics, and proteomics, AI can identify novel CSC biomarkers and optimize nanocarrier design through predictive modeling. Additionally, organoid and patient-derived xenograft (PDX) models offer more accurate preclinical platforms for evaluating efficacy and safety. In the long term, regulatory frameworks and manufacturing technologies must adapt to accommodate the complexity of these multifunctional nanomedicines. Continued interdisciplinary research and public-private partnerships will be crucial in translating laboratory innovations into safe, effective, and scalable therapies targeting CSCs. These advancements hold the key to overcoming drug resistance, preventing relapse, and ultimately improving survival in cancer patients.

CONCLUSION

Cancer stem cells are pivotal in cancer progression and therapeutic resistance. Nanotechnology offers transformative tools for selective CSC targeting through smart design, ligand-specificity, and controlled release systems. While clinical translation is still in its early stages, ongoing research and technological advancements promise to overcome current challenges. With continued interdisciplinary efforts, nanotechnology may unlock new frontiers in eradicating CSCs and achieving long-lasting remission in cancer patients.

REFERENCES

1. Abbas, Z., Rehman, S., Abbas, Z., Rehman, S.: An Overview of Cancer Treatment Modalities. In: Neoplasm. IntechOpen (2018)
2. Abdullah, K.M., Sharma, G., Singh, A.P., Siddiqui, J.A.: Nanomedicine in Cancer Therapeutics: Current Perspectives from Bench to Bedside. Mol Cancer. 24, 169 (2025). https://doi.org/10.1186/s12943-025-02368-w
3. Tufail, T., Uti, D.E., Aja, P.M., Offor, C.E., Ibiam, U.A., Ukaidi, C.U.A.: Utilizing Indigenous Flora in East Africa for Breast Cancer Treatment: An Overview. Anticancer Agents Med Chem. 25, 99–113 (2025). https://doi.org/10.2174/0118715206338557240909081833
4. Alum, E.U.: AI-driven biomarker discovery: enhancing precision in cancer diagnosis and prognosis. Discov Onc. 16, 313 (2025). https://doi.org/10.1007/s12672-025-02064-7
5. Obisi, J.N., Abimbola, A.N.J., Babaleye, O.A., Atidoglo, P.K., Usin, S.G., Nwanaforo, E.O., Patrick-Inezi, F.S., Fasogbon, I.V., Chimezie, J., Dare, C.A., Kuti, O.O., Uti, D.E., Omeoga, H.C.: Unveiling the future of cancer stem cell therapy: a narrative exploration of emerging innovations. Discov Onc. 16, 373 (2025). https://doi.org/10.1007/s12672-025-02102-4
6. Fegade, B.S., Chaudhari, S.Y., Likhar, R.V., Bhole, R.P., Uttekar, P.S., Pathare, S.S., Maitra, S., Uti, D.E., Zaki, M.E.A., Alum, E.U.: Design, synthesis, molecular docking and molecular dynamics studies of some 3-methoxy flavone derivatives as an anti-breast cancer agent. Discov Onc. 16, 773 (2025). https://doi.org/10.1007/s12672-025-02491-6
7. Magadani, R., Ndinteh, D.T., Roux, S., Nangah, L.P., Atangwho, I.J., Uti, D.E., Alum, E.U., Egba, S.I.: Cytotoxic Effects of Lecaniodiscus Cupanioides (Planch.) Extract and Triterpenoids-derived Gold Nanoparticles On MCF-7 Breast Cancer Cell Lines. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry - Anti-Cancer Agents). 25, 841–850 (2025). https://doi.org/10.2174/0118715206325529241004064307
8. Uti, D.E., Atangwho, I.J., Alum, E.U., Ntaobeten, E., Obeten, U.N., Bawa, I., Agada, S.A., Ukam, C.I.-O., Egbung, G.E.: Antioxidants in cancer therapy mitigating lipid peroxidation without compromising

treatment through nanotechnology. Discover Nano. 20, 70 (2025). https://doi.org/10.1186/s11671-025-04248-0
9. Jiang, P., Xu, C., Chen, L., Chen, A., Wu, X., Zhou, M., Haq, I.U., Mariyam, Z., Feng, Q.: EGCG inhibits CSC-like properties through targeting miR-485/CD44 axis in A549-cisplatin resistant cells. Mol Carcinog. 57, 1835–1844 (2018). https://doi.org/10.1002/mc.22901
10. Zabeti Touchaei, A., Norollahi, S.E., Najafizadeh, A., Babaei, K., Bakhshalipour, E., Vahidi, S., Samadani, A.A.: Therapeutic combinations of exosomes alongside cancer stem cells (CSCs) and of CSC-derived exosomes (CSCEXs) in cancer therapy. Cancer Cell International. 24, 334 (2024). https://doi.org/10.1186/s12935-024-03514-y
11. Aghajanzadeh, M., Zamani, M., Rajabi Kouchi, F., Eixenberger, J., Shirini, D., Estrada, D., Shirini, F.: Synergic Antitumor Effect of Photodynamic Therapy and Chemotherapy Mediated by Nano Drug Delivery Systems. Pharmaceutics. 14, 322 (2022). https://doi.org/10.3390/pharmaceutics14020322
12. Chen, N., Brachmann, C., Liu, X., Pierce, D.W., Dey, J., Kerwin, W.S., Li, Y., Zhou, S., Hou, S., Carleton, M., Klinghoffer, R.A., Palmisano, M., Chopra, R.: Albumin-bound nanoparticle (nab) paclitaxel exhibits enhanced paclitaxel tissue distribution and tumor penetration. Cancer Chemother Pharmacol. 76, 699–712 (2015). https://doi.org/10.1007/s00280-015-2833-5
13. Davodabadi, F., Sajjadi, S.F., Sarhadi, M., Mirghasemi, S., Nadali Hezaveh, M., Khosravi, S., Kamali Andani, M., Cordani, M., Basiri, M., Ghavami, S.: Cancer chemotherapy resistance: Mechanisms and recent breakthrough in targeted drug delivery. European Journal of Pharmacology. 958, 176013 (2023). https://doi.org/10.1016/j.ejphar.2023.176013
14. Franco, M.M.R., Rodriguez, E.L., Benitez, B.M., Rodriguez, L.G.V., De La Luz Sevilla Gonzalez, M., Alonso, A.A.: Association of PTP1B with Outcomes of Breast Cancer Patients who Underwent Neoadjuvant Chemotherapy. Breast Cancer (Auckl). 10, BCBCR.S40934 (2016). https://doi.org/10.4137/BCBCR.S40934
15. Ahire, V., Ahmadi Bidakhvidi, N., Boterberg, T., Chaudhary, P., Chevalier, F., Daems, N., Delbart, W., Baatout, S., Deroose, C.M., Fernandez-Palomo, C., Franken, N.A.P., Gaipl, U.S., Geenen, L., Heynickx, N., Koniarová, I., Selvaraj, V.K., Levillain, H., Michaelidesová, A.J., Montoro, A., Oei, A.L., Penninckx, S., Reindl, J., Rödel, F., Sminia, P., Tabury, K., Vermeulen, K., Viktorsson, K., Waked, A.: Radiobiology of Combining Radiotherapy with Other Cancer Treatment Modalities. In: Baatout, S. (ed.) Radiobiology Textbook. pp. 311–386. Springer International Publishing, Cham (2023)
16. Liu, Y., Zheng, C., Huang, Y., He, M., Xu, W.W., Li, B.: Molecular mechanisms of chemo- and radiotherapy resistance and the potential implications for cancer treatment. MedComm (2020). 2, 315–340 (2021). https://doi.org/10.1002/mco2.55
17. Milano, M.T., Usuki, K.Y., Walter, K.A., Clark, D., Schell, M.C.: Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy: Normal tissue dose constraints of the central nervous system. Cancer Treatment Reviews. 37, 567–578 (2011). https://doi.org/10.1016/j.ctrv.2011.04.004
18. Wu, Y., Song, Y., Wang, R., Wang, T.: Molecular mechanisms of tumor resistance to radiotherapy. Mol Cancer. 22, 96 (2023). https://doi.org/10.1186/s12943-023-01801-2
19. Cao, Y., Yi, Y., Han, C., Shi, B.: NF-κB signaling pathway in tumor microenvironment. Front. Immunol. 15, (2024). https://doi.org/10.3389/fimmu.2024.1476030
20. Chen, B., Dai, W., He, B., Zhang, H., Wang, X., Wang, Y., Zhang, Q.: Current Multistage Drug Delivery Systems Based on the Tumor Microenvironment. Theranostics. 7, 538–558 (2017). https://doi.org/10.7150/thno.16684
21. Ciepła, J., Smolarczyk, R.: Tumor hypoxia unveiled: insights into microenvironment, detection tools and emerging therapies. Clinical and Experimental Medicine. 24, 235 (2024). https://doi.org/10.1007/s10238-024-01501-1
22. Agrahari, V., and Hiremath, P.: Challenges Associated and Approaches for Successful Translation of Nanomedicines Into Commercial Products. Nanomedicine. 12, 819–823 (2017). https://doi.org/10.2217/nnm-2017-0039
23. Uti, D.E., Alum, E.U., Atangwho, I.J., Ugwu, O.P.-C., Egbung, G.E., Aja, P.M.: Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. Journal of Nanobiotechnology. 23, 336 (2025). https://doi.org/10.1186/s12951-025-03412-z
24. Ansori, A.NM., Antonius, Y., Susilo, R.JK., Hayaza, S., Kharisma, V.D., Parikesit, A.A., Zainul, R., Jakhmola, V., Saklani, T., Rebezov, M., Ullah, Md.E., Maksimiuk, N., Derkho, M., Burkov, P.: Application of CRISPR-Cas9 genome editing technology in various fields: A review. Narra J. 3, e184 (2023). https://doi.org/10.52225/narra.v3i2.184
25. Lee, H., Rho, W.-Y., Kim, Y.-H., Chang, H., Jun, B.-H.: CRISPR-Cas9 Gene Therapy: Non-Viral Delivery and Stimuli-Responsive Nanoformulations. Molecules. 30, 542 (2025). https://doi.org/10.3390/molecules30030542

26. Lu, Y., Godbout, K., Lamothe, G., Tremblay, J.P.: CRISPR-Cas9 delivery strategies with engineered extracellular vesicles. Mol Ther Nucleic Acids. 34, 102040 (2023). https://doi.org/10.1016/j.omtn.2023.102040
27. Codullo, V., Cova, E., Pandolfi, L., Breda, S., Morosini, M., Frangipane, V., Malatesta, M., Calderan, L., Cagnone, M., Pacini, C., Cavagna, L., Recalde, H., Distler, J.H.W., Giustra, M., Prosperi, D., Colombo, M., Meloni, F., Montecucco, C.: Imatinib-loaded gold nanoparticles inhibit proliferation of fibroblasts and macrophages from systemic sclerosis patients and ameliorate experimental bleomycin-induced lung fibrosis. J Control Release. 310, 198–208 (2019). https://doi.org/10.1016/j.jconrel.2019.08.015
28. Arcos Rosero, W.A., Bueno Barbezan, A., Daruich de Souza, C., Chuery Martins Rostelato, M.E.: Review of Advances in Coating and Functionalization of Gold Nanoparticles: From Theory to Biomedical Application. Pharmaceutics. 16, 255 (2024). https://doi.org/10.3390/pharmaceutics16020255
29. Gabel, M., Knauss, A., Fischer, D., Neurath, M.F., Weigmann, B.: Surface Design Options in Polymer- and Lipid-Based siRNA Nanoparticles Using Antibodies. Int J Mol Sci. 23, 13929 (2022). https://doi.org/10.3390/ijms232213929
30. Ashrafizadeh, M., Delfi, M., Zarrabi, A., Bigham, A., Sharifi, E., Rabiee, N., Paiva-Santos, A.C., Kumar, A.P., Tan, S.C., Hushmandi, K., Ren, J., Zare, E.N., Makvandi, P.: Stimuli-responsive liposomal nanoformulations in cancer therapy: Pre-clinical & clinical approaches. Journal of Controlled Release. 351, 50–80 (2022). https://doi.org/10.1016/j.jconrel.2022.08.001
31. Hou, J., Xue, Z., Chen, Y., Li, J., Yue, X., Zhang, Y., Gao, J., Hao, Y., Shen, J.: Development of Stimuli-Responsive Polymeric Nanomedicines in Hypoxic Tumors and Their Therapeutic Promise in Oral Cancer. Polymers. 17, 1010 (2025). https://doi.org/10.3390/polym17081010
32. Mi, P.: Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 10, 4557–4588 (2020). https://doi.org/10.7150/thno.38069
33. Allemailem, K.S., Alsahli, M.A., Almatroudi, A., Alrumaihi, F., Al Abdulmonem, W., Moawad, A.A., Alwanian, W.M., Almansour, N.M., Rahmani, A.H., Khan, A.A.: Innovative Strategies of Reprogramming Immune System Cells by Targeting CRISPR/Cas9-Based Genome-Editing Tools: A New Era of Cancer Management. Int J Nanomedicine. 18, 5531–5559 (2023). https://doi.org/10.2147/IJN.S424872
34. Bisht, S., Nigam, M., Kunjwal, S.S., Sergey, P., Mishra, A.P., Sharifi-Rad, J.: Cancer Stem Cells: From an Insight into the Basics to Recent Advances and Therapeutic Targeting. Stem Cells Int. 2022, 9653244 (2022). https://doi.org/10.1155/2022/9653244
35. Cavallucci, V., Palucci, I., Fidaleo, M., Mercuri, A., Masi, L., Emoli, V., Bianchetti, G., Fiori, M.E., Bachrach, G., Scaldaferri, F., Maulucci, G., Delogu, G., Pani, G.: Proinflammatory and Cancer-Promoting Pathobiont Fusobacterium nucleatum Directly Targets Colorectal Cancer Stem Cells. Biomolecules. 12, 1256 (2022). https://doi.org/10.3390/biom12091256
36. Talukdar, S., Das, S.K., Pradhan, A.K., Emdad, L., Windle, J.J., Sarkar, D., Fisher, P.B.: MDA-9/Syntenin (SDCBP) Is a Critical Regulator of Chemoresistance, Survival and Stemness in Prostate Cancer Stem Cells. Cancers. 12, 53 (2020). https://doi.org/10.3390/cancers12010053
37. Haddadin, L., Sun, X.: Stem Cells in Cancer: From Mechanisms to Therapeutic Strategies. Cells. 14, 538 (2025). https://doi.org/10.3390/cells14070538
38. Liu, J., Xiao, Q., Xiao, J., Niu, C., Li, Y., Zhang, X., Zhou, Z., Shu, G., Yin, G.: Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Sig Transduct Target Ther. 7, 3 (2022). https://doi.org/10.1038/s41392-021-00762-6
39. Sferrazza, G., Corti, M., Brusotti, G., Pierimarchi, P., Temporini, C., Serafino, A., Calleri, E.: Nature-derived compounds modulating Wnt/β-catenin pathway: a preventive and therapeutic opportunity in neoplastic diseases. Acta Pharmaceutica Sinica B. 10, 1814–1834 (2020). https://doi.org/10.1016/j.apsb.2019.12.019
40. Song, P., Gao, Z., Bao, Y., Chen, L., Huang, Y., Liu, Y., Dong, Q., Wei, X.: Wnt/β-catenin signaling pathway in carcinogenesis and cancer therapy. Journal of Hematology & Oncology. 17, 46 (2024). https://doi.org/10.1186/s13045-024-01563-4
41. Zhang, Y., Wang, X.: Targeting the Wnt/β-catenin signaling pathway in cancer. Journal of Hematology & Oncology. 13, 165 (2020). https://doi.org/10.1186/s13045-020-00990-3
42. Cho, Y., Kim, Y.K.: Cancer Stem Cells as a Potential Target to Overcome Multidrug Resistance. Front Oncol. 10, 764 (2020). https://doi.org/10.3389/fonc.2020.00764
43. Li, Y.-C., Xiong, Y.-M., Long, Z.-P., Huang, Y.-P., Shu, Y.-B., He, K., Sun, H.-Y., Shi, Z.: ML210 Antagonizes ABCB1- Not ABCG2-Mediated Multidrug Resistance in Colorectal Cancer. Biomedicines. 13, 1245 (2025). https://doi.org/10.3390/biomedicines13051245
44. Al-Mansoori, L., Al-Jaber, H., Prince, M.S., Elrayess, M.A.: Role of Inflammatory Cytokines, Growth Factors and Adipokines in Adipogenesis and Insulin Resistance. Inflammation. 45, 31–44 (2022). https://doi.org/10.1007/s10753-021-01559-z
45. Uti, D.E., Atangwho, I.J., Omang, W.A., Alum, E.U., Obeten, U.N., Udeozor, P.A., Agada, S.A., Bawa, I., Ogbu, C.O.: Cytokines as key players in obesity low grade inflammation and related complications. Obesity Medicine. 54, 100585 (2025). https://doi.org/10.1016/j.obmed.2025.100585

46. Chen, X., Zheng, Y., Zhang, Q., Chen, Q., Chen, Z., Wu, D.: Dual-targeted delivery of temozolomide by multi-responsive nanoplatform via tumor microenvironment modulation for overcoming drug resistance to treat glioblastoma. Journal of Nanobiotechnology. 22, 264 (2024). https://doi.org/10.1186/s12951-024-02531-3
47. Liu, Y., Si, L., Jiang, Y., Jiang, S., Zhang, X., Li, S., Chen, J., Hu, J.: Design of pH-Responsive Nanomaterials Based on the Tumor Microenvironment. Int J Nanomedicine. 20, 705–721 (2025). https://doi.org/10.2147/IJN.S504629
48. Mafi, S., Mansoori, B., Taeb, S., Sadeghi, H., Abbasi, R., Cho, W.C., Rostamzadeh, D.: mTOR-Mediated Regulation of Immune Responses in Cancer and Tumor Microenvironment. Front Immunol. 12, 774103 (2022). https://doi.org/10.3389/fimmu.2021.774103
49. Labani-Motlagh, A., Ashja-Mahdavi, M., Loskog, A.: The Tumor Microenvironment: A Milieu Hindering and Obstructing Antitumor Immune Responses. Front Immunol. 11, 940 (2020). https://doi.org/10.3389/fimmu.2020.00940
50. Ammar, M.M., Ali, R., Abd Elaziz, N.A., Habib, H., Abbas, F.M., Yassin, M.T., Maniah, K., Abdelaziz, R.: Nanotechnology in oncology: advances in biosynthesis, drug delivery, and theranostics. Discov Onc. 16, 1172 (2025). https://doi.org/10.1007/s12672-025-02664-3
51. Krsek, A., Baticic, L.: Nanotechnology-Driven Therapeutic Innovations in Neurodegenerative Disorders: A Focus on Alzheimer's and Parkinson's Disease. Future Pharmacology. 4, 352–379 (2024). https://doi.org/10.3390/futurepharmacol4020020
52. Austria, E., Bilek, M., Varamini, P., Akhavan, B.: Breaking biological barriers: Engineering polymeric nanoparticles for cancer therapy. Nano Today. 60, 102552 (2025). https://doi.org/10.1016/j.nantod.2024.102552
53. Cavalcante de Freitas, P.G., Rodrigues Arruda, B., Araújo Mendes, M.G., Barroso de Freitas, J.V., da Silva, M.E., Sampaio, T.L., Petrilli, R., Eloy, J.O.: Resveratrol-Loaded Polymeric Nanoparticles: The Effects of D-α-Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) on Physicochemical and Biological Properties against Breast Cancer In Vitro and In Vivo. Cancers (Basel). 15, 2802 (2023). https://doi.org/10.3390/cancers15102802
54. Nair, A., Chandrashekhar H., R., Day, C.M., Garg, S., Nayak, Y., Shenoy, P.A., Nayak, U.Y.: Polymeric functionalization of mesoporous silica nanoparticles: Biomedical insights. International Journal of Pharmaceutics. 660, 124314 (2024). https://doi.org/10.1016/j.ijpharm.2024.124314
55. Yu, Z., Shen, X., Yu, H., Tu, H., Chittasupho, C., Zhao, Y.: Smart Polymeric Nanoparticles in Cancer Immunotherapy. Pharmaceutics. 15, 775 (2023). https://doi.org/10.3390/pharmaceutics15030775
56. Abedi-Gaballu, F., Dehghan, G., Ghaffari, M., Yekta, R., Abbaspour-Ravasjani, S., Baradaran, B., Dolatabadi, J.E.N., Hamblin, M.R.: PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy. Appl Mater Today. 12, 177–190 (2018). https://doi.org/10.1016/j.apmt.2018.05.002
57. Pérez-Ferreiro, M., M. Abelairas, A., Criado, A., Gómez, I.J., Mosquera, J.: Dendrimers: Exploring Their Wide Structural Variety and Applications. Polymers. 15, 4369 (2023). https://doi.org/10.3390/polym15224369
58. Anderson, S.D., Gwenin, V.V., Gwenin, C.D.: Magnetic Functionalized Nanoparticles for Biomedical, Drug Delivery and Imaging Applications. Nanoscale Res Lett. 14, 188 (2019). https://doi.org/10.1186/s11671-019-3019-6
59. Estelrich, J., Sánchez-Martín, M.J., Busquets, M.A.: Nanoparticles in magnetic resonance imaging: from simple to dual contrast agents. Int J Nanomedicine. 10, 1727–1741 (2015). https://doi.org/10.2147/IJN.S76501
60. Kajani, A.A., Rafiee, L., Samandari, M., Mehrgardi, M.A., Zarrin, B., Javanmard, S.H.: Facile, rapid and efficient isolation of circulating tumor cells using aptamer-targeted magnetic nanoparticles integrated with a microfluidic device. RSC Adv. 12, 32834–32843. https://doi.org/10.1039/d2ra05930d
61. Nguyen, M.D., Tran, H.-V., Xu, S., Lee, T.R.: Fe3O4 Nanoparticles: Structures, Synthesis, Magnetic Properties, Surface Functionalization, and Emerging Applications. Applied Sciences. 11, 11301 (2021). https://doi.org/10.3390/app112311301
62. Okeke, I.S., Echeweozo, E.O., Ogu, A.C., Aondona, P.Y., Ezema, F.I.: Iron oxide Nanoparticles; A Review on the role of Transition Metal doping on its magnetic properties and particle size for imaging and therapeutic applications. Hybrid Advances. 7, 100322 (2024). https://doi.org/10.1016/j.hybadv.2024.100322
63. Araujo-Abad, S., Berna, J.M., Lloret-Lopez, E., López-Cortés, A., Saceda, M., de Juan Romero, C.: Exosomes: from basic research to clinical diagnostic and therapeutic applications in cancer. Cell Oncol. 48, 269–293 (2025). https://doi.org/10.1007/s13402-024-00990-2
64. Bamodu, O.A., Chung, C.-C., Pisanic, T.R.: Harnessing liquid biopsies: Exosomes and ctDNA as minimally invasive biomarkers for precision cancer medicine. J Liq Biopsy. 2, 100126 (2023). https://doi.org/10.1016/j.jlb.2023.100126

65. Butreddy, A., Kommineni, N., Dudhipala, N.: Exosomes as Naturally Occurring Vehicles for Delivery of Biopharmaceuticals: Insights from Drug Delivery to Clinical Perspectives. Nanomaterials (Basel). 11, 1481 (2021). https://doi.org/10.3390/nano11061481
66. Liu, H., Su, Y.-Y., Jiang, X.-C., Gao, J.-Q.: Cell membrane-coated nanoparticles: a novel multifunctional biomimetic drug delivery system. Drug Deliv Transl Res. 13, 716–737 (2023). https://doi.org/10.1007/s13346-022-01252-0
67. Cao, J., Bhatnagar, S., Wang, J., Qi, X., Prabha, S., Panyam, J.: Cancer stem cells and strategies for targeted drug delivery. Drug Deliv Transl Res. 11, 1779–1805 (2021). https://doi.org/10.1007/s13346-020-00863-9
68. Mazloomi, M., Doustmihan, A., Alimohammadvand, S., Hamishehkar, H., Hamblin, M.R., Jahanban Esfahlan, R.: Advanced drug delivery platforms target cancer stem cells. Asian J Pharm Sci. 20, 101036 (2025). https://doi.org/10.1016/j.ajps.2025.101036
69. Wickens, J.M., Alsaab, H.O., Kesharwani, P., Bhise, K., Amin, M.C.I.M., Tekade, R.K., Gupta, U., Iyer, A.K.: Recent advances in hyaluronic acid-decorated nanocarriers for targeted cancer therapy. Drug Discov Today. 22, 665–680 (2017). https://doi.org/10.1016/j.drudis.2016.12.009
70. Nair, P.R.: Delivering Combination Chemotherapies and Targeting Oncogenic Pathways via Polymeric Drug Delivery Systems. Polymers (Basel). 11, 630 (2019). https://doi.org/10.3390/polym11040630
71. Bailly, C., Thuru, X., Quesnel, B.: Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. NAR Cancer. 2, zcaa002 (2020). https://doi.org/10.1093/narcan/zcaa002
72. Sun, S., Yang, Q., Jiang, D., Zhang, Y.: Nanobiotechnology augmented cancer stem cell guided management of cancer: liquid-biopsy, imaging, and treatment. Journal of Nanobiotechnology. 22, 176 (2024). https://doi.org/10.1186/s12951-024-02432-5
73. Huang, X., He, T., Liang, X., Xiang, Z., Liu, C., Zhou, S., Luo, R., Bai, L., Kou, X., Li, X., Wu, R., Gou, X., Wu, X., Huang, D., Fu, W., Li, Y., Chen, R., Xu, N., Wang, Y., Le, H., Chen, T., Xu, Y., Tang, Y., Gong, C.: Advances and applications of nanoparticles in cancer therapy. MedComm – Oncology. 3, e67 (2024). https://doi.org/10.1002/mog2.67
74. Abbasi, H., Kouchak, M., Mirveis, Z., Hajipour, F., Khodarahmi, M., Rahbar, N., Handali, S.: What We Need to Know about Liposomes as Drug Nanocarriers: An Updated Review. Adv Pharm Bull. 13, 7–23 (2023). https://doi.org/10.34172/apb.2023.009
75. Attia, M.F., Anton, N., Wallyn, J., Omran, Z., Vandamme, T.F.: An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. Journal of Pharmacy and Pharmacology. 71, 1185–1198 (2019). https://doi.org/10.1111/jphp.13098

CITE AS: Ahereza Prissy (2025). Targeting Cancer Stem Cells Using Nanotechnology: Challenges and Opportunities. IDOSR JOURNAL OF SCIENTIFIC RESEARCH 10(3):54-62. https://doi.org/10.59298/IDOSRJSR/2024/10.3.5462