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Review Article

Breaking Barriers in Cancer Treatment: An updated review on Clinical Translation of Novel Nanocarrier Systems

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ABSTRACT

Cancer remains a significant cause of illness and death globally, and it is therefore crucial to find new ways to improve treatment efficacy and patient outcomes. Chemotherapy has the potential to act effectively on cancer cells but also impacts normal cells, leading to serious side effects. In this review, we discuss how nanotechnology is overcoming these challenges through novel concepts aimed at improving the specificity and efficiency of chemotherapy delivery. Through the utilization of nanocarriers (NCs), including lipid-based, polymer-based, protein-based, carbon-based, and inorganic nanosystems (such as metallic nanoparticles, quantum dots, mesoporous silica nanoparticles, and metal-organic frameworks), as well as hybrid and responsive nanosystems, nanotechnology enables more specific and sensitive targeted drug delivery. All of these approaches can reduce undesired side effects and enhance treatment outcomes by facilitating the potential for earlier treatment and diagnosis. Our review article presents an overview of ongoing clinical trials and FDA-approved NC-based anticancer therapies, unveiling progress in the field. Utilizing nanotechnology for cancer treatment represents a significant paradigm shift, with the potential to revolutionize drug delivery, minimize side effects, and ultimately improve the lives of cancer patients. We also highlight the challenges inherent in utilizing NCs for targeted drug delivery, alongside potential strategies to tackle these obstacles, with the ultimate goal of advancing cancer therapy and improving overall survival rates for patients.

Keywords: Chemotherapy; Cancer Therapy; Clinical Trials; Drug Delivery; Nanotechnology; Nanocarriers

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Introduction

Globally, cancer causes thousands of deaths a year, ranking first or second among 183 countries in terms of causes of death before the age of 70 (1). The number of cancer-related deaths in 2020 was approximately 10 million, and in 2022, there were 20 million cancer cases and 9.7 million cancer-related deaths. For the year 2023, an estimated 1,958,310 new cases of cancer and 609,820 cancer deaths occurred in the United States. Prostate, lung, colorectal, and liver cancers are more prevalent in males, while women most commonly experience breast and ovarian cancers (2). Early cancer detection methods are complex; however, nanotechnology represents a promising and developing domain. Nanoparticles (NPs) possess a superior surface area-to-volume ratio compared to other dense materials, making them optimal for cancer detection (3). Nanoparticles gather indicators such as proteins, circulating DNA, and cancer cells, while multiple ligand bindings may enhance specificity and sensitivity. NPs, composed of materials such as gold and silver, have gained attention for molecular imaging. Detecting cancer in its early stages is possible by imaging tumor tissue with NPs. One method for detecting metastases in lung cancer involves developing immune superparamagnetic iron oxide nanoparticles (SPIONs), which can be targeted in MRI imaging (4).

Nanocarriers (NCs) used in cancer therapy include liposomes, polymeric nanoparticles, carbon nanotubes, dendrimers, and micelles (5). Liposomal formulations of adriamycin have demonstrated considerable therapeutic advantages in the treatment of metastatic ovarian cancer (6). FDA-approved nanopharmaceuticals have reduced the toxicity associated with Active Pharmaceutical Ingredients (APIs) and improved overall survival rates (7). NCs can also simultaneously deliver oligonucleotides, chemotherapy drugs, and cancer suppressor genes. These materials offer advantages such as sterilization, low inherent toxicity, diverse sizes and shapes, and real-time tracking using spectroscopic techniques (8). Nanotechnology can also eradicate cancer cells through thermosensitive drug delivery and photothermal-thermodynamic destruction (9). Progress in nanomedicine has led to the fabrication of NCs that incorporate both medications and imaging agents, known as Theranostics. These systems provide benefits including the analysis of nano-drug accumulation at target sites, visualization and quantification of drug release, and monitoring of drug biodistribution. Nanotheranostic techniques may enable distinct neoplasm therapies by integrating nanoparticles with anticancer agents.

Newly developed Nanosystems for delivery of chemotherapeutic agents

Nanoparticles (NPs) enhance drug targeting and efficacy due to their ability to carry pharmaceuticals and penetrate tumors. They are directed to specific sites using various methods, particularly in lung cancer theranostics. Active and passive targeting are key strategies for delivering nanoparticles to cancer cells (10).

Controlled-release drug delivery systems originated in the 1950s for oral and transdermal applications, using techniques such as diffusion, dissolution, osmosis, and ion exchange. However, they encountered difficulties in the 1980s due to the complexities of creating automated systems. The emergence of nanotechnology in the 21st century has generated interest in using nanoscale materials in medicine, specifically for the diagnosis, treatment, and prognosis of medical disorders, notably cancer therapy (11). These NPs include lipid-based, micellar, inorganic, polymeric, gold, and carbon nanotube types. Polymeric NPs are the most extensively researched materials for developing nanotechnology-based drug delivery systems (12).

Nanocarriers for drug delivery exhibit various forms, sizes, and conformations. Conventional nanocarriers face challenges such as non-specificity, instability, limited biocompatibility, inadequate permeability, diminished retention, drug resistance, and elevated toxicity due to tumor microenvironment barriers. Targeted stimuli-responsive nanocarriers offer greater precision, lower toxicity, enhanced biocompatibility, superior stability, increased permeability, and improved retention. These intelligent nanocarriers exhibit targeted reactions in biological environments, providing several advantages over the direct application of chemotherapeutic agents, minimizing adverse effects, and enhancing therapeutic effectiveness (13). Each type of NC (or NP) is shaped by specific elements that impact the final formulation (Figure 1).

Lipid-based Nanosystems

Lipid-based nanosystems are now more highly adopted for chemotherapeutic drug delivery, improving effectiveness and reducing side effects in cancer treatment. The nanosystem encloses and transports pharmaceuticals to the tumor site, protecting them from degradation (14). Their increased solubility and targeting behavior reduce side effects and improve the effectiveness of cancer treatment. Here we review three important classes of lipid-based nanosystems applied for chemotherapy drug delivery.

Liposomes

Liposomes enhance drug solubility, circulation duration, and systemic toxicity, thereby increasing the therapeutic index of chemotherapy. A liposome-

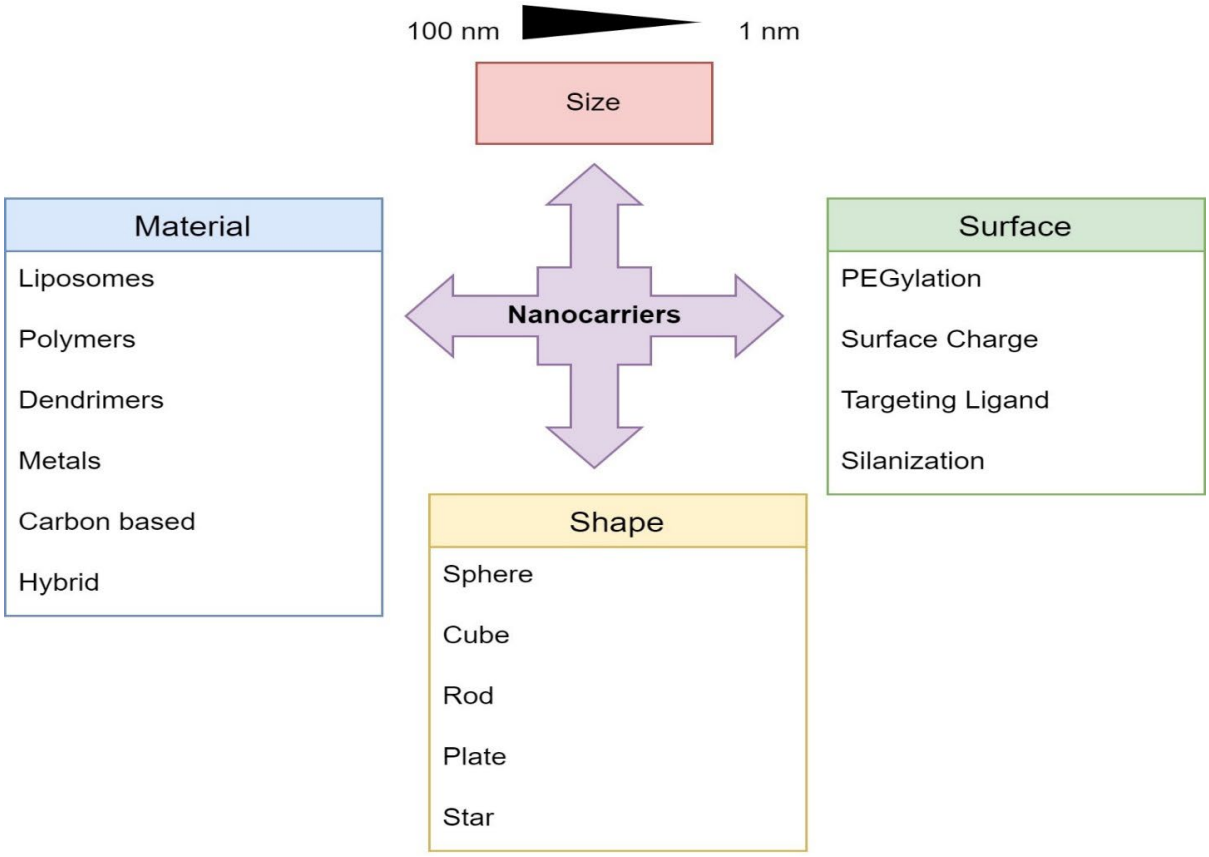

Figure 1. Nanocarriers are engineered with diverse material compositions to align with specific nanocarrier classes and functions and optimize shape, size, and targeting ligands. This approach ultimately enhances mobility and enables precise drug delivery to specific targets.

PLGA composite was developed to improve the delivery of the cancer treatment Cisplatin (CIS). Avastin®, an anti-VEGF antibody, was conjugated to the liposome to specifically target tumor cells. The resultant nanoparticles (NPs) were evaluated in cervical tumor-bearing animals and mice. The results indicated that L-PLGA-Cis-Avastin® induced cytotoxicity and decreased cell viability in SiHa cells, suggesting its potential as a targeted therapeutic agent for cervical cancer (15). Research has also led to the development of other selective nanosystems, specifically liposomes conjugated with folic acid (FA) and curcumin (LIP-CCM-FA) to target breast cancer. In vitro tests showed that LIP-CCM-FA was more cytotoxic than pure curcumin and liposomes, improving absorption and penetration of breast cancer cell spheroids. This enhanced uptake suggests a potential impact on drug delivery and folate receptor recognition (16).

Solid lipid nanoparticles (SLNs)

SLNs are biocompatible and stable drug release control systems that serve as shielding agents to prevent the enzymatic breakdown of labile drugs (17). SLNs containing gemcitabine were assessed for their cytotoxic activity against PPCL-46 and MiaPaCa-2 cancer cell lines for pancreatic cancer. Gem-SLN15 was used for entrapment, loading, cytotoxicity, and release, and it demonstrated more effective cell-killing properties against PPCL-46 cancer cells compared to GemHCl (18). Further research aimed to develop SLNs co-loaded with doxorubicin (DOX) and α-tocopherol succinate (TS) to overcome drug resistance in the MCF-7/Adr and NCI/Adr cancer cell lines. The cytotoxicity of SLNs was severe in these cell lines, and drug co-localization increased when encapsulated, helping to overcome P-glycoprotein-mediated drug efflux. SLNs co-loaded with DOX and TS exhibited strong cytotoxicity and penetrability, holding promise as a potential cancer therapy (19).

Nanostructured lipid carriers (NLCs)

The next generation of lipid nanoparticles employs a combination of solid and liquid lipids to overcome lipid matrix limitations, improving drug loading and release. NLCs enhance the solubility of water-insoluble drugs and enable tumor cell targeting. In an experiment, DOX was combined with chrysin-loaded NLCs to enhance its cytotoxic effects on MCF-7 breast cancer cells. The

study found that incubating cells with chrysin-loaded NLCs increased apoptosis, elevated the percentage of cancer cells in the sub-G1 phase, and reduced mRNA expression levels. This suggests that inhibiting drug efflux pumps and detoxifying enzymes with chrysin and NLCs may enhance DOX activity (20).

Researchers investigated NLCs for delivering DOX alongside cisplatin (CIS) or carboplatin (CDDP) in breast cancer treatment. In vitro studies demonstrated synergistic and highly cytotoxic effects on cancer cells, while in vivo results indicated that NLCs outperformed previous formulations, highlighting their potential for targeted combination therapy. Lipid-based nanosystems like NLCs are advancing cancer treatment by enabling customized drug delivery with lower toxicity, though challenges remain regarding drug encapsulation and release control (21).

Polymeric-based Nanosystems

Polymer nanosystems have revolutionized targeted drug delivery, particularly in cancer therapy, by encapsulating, protecting, and transporting therapeutic agents to specific anatomical sites. These capabilities minimize systemic adverse effects and enhance therapeutic efficacy (22).

Polymeric micelles

Colloidal self-assembling polymeric micelles are amphiphilic carriers for hydrophobic drugs. Their chemotherapeutic efficacy was enhanced by co-loading (DOX) and indocyanine green (ICG), combined with laser photothermal therapy. Folate modification improved cellular uptake. Folate-functionalized polymeric micelles (FA Co-PMs) for theranostics exhibited dual sensitivity to redox and pH conditions. Engineered for uniformity and high drug loading, these micelles utilized synergistic chemo-photothermal therapy to suppress tumors (23).

Studies on redox-sensitive hybrid micelles with upconversion nanoparticles (UCNPs) and polymers indicate potential in cancer treatment and photodynamic therapy. These micelles convert near-infrared light to visible light, generating reactive oxygen species (ROS) that boost photodynamic therapy and release DOX. This novel method could advance cancer treatment by the reduction of polypropylene sulfide (24).

Dendrimers

Dendrimers are branching macromolecules capable of precisely functionalizing therapeutic agents on their surfaces, making them ideal for targeted drug delivery. A nanoplatform for cancer therapy and diagnosis employs pyridine-functionalized generation 5 poly(amidoamine) dendrimers complexed with copper (II), enhancing radiation therapy and T1-weighted magnetic resonance imaging (MRI) for synergistic primary tumor and metastasis radiochemotherapy. These nanohybrids inhibit cancer cell proliferation, induce apoptosis, and improve MRI-based tumor visualization and therapeutic efficacy. New Cu(II)-b nanohybrids enable in vivo MRI imaging of xenografted tumors and pulmonary metastatic nodules, suggesting promising therapeutic applications for various malignancies and metastases (25). PAMAM-DMA dendrimers enhance chemotherapy by improving drug loading and controlled release. Co-injection of poly(amidoamine) dendrimers (PAMAM-DMA) and DOX has been shown to reduce tumor weight by 55.9% compared to DOX alone (26).

Nanogels

Nanogels are biocompatible, pH- and temperature-sensitive hydrogels that encapsulate therapeutic molecules and release them under specific conditions. Immunotherapeutic and chemotherapeutic drugs have been studied for chemo-immunotherapy applications. A pH-responsive nanogel (NG@M), encapsulated within a cancer cell membrane, facilitates paclitaxel (PTX) and IL-2 release for treating triple-negative breast cancer. This chemo-immunotherapy combination enhances antitumor activity and suppresses lung metastases, extending median survival to 39 days (27).

Researchers have developed a crosslinked nanogel named DSA, which enhances anticancer therapy by disulfide-linking DOX and 5-aminolevulinic acid (ALA). This approach utilizes fluorescent protoporphyrin IX (PpIX) in neoplastic cells, providing real-time imaging agents for oncological diagnosis. PpIX functions as a photosensitizer, converting oxygen into cytotoxic reactive oxygen species (ROS) to eliminate malignancies (28).

Polymeric NPs

Polymer NPs of 10 to 1000 nanometers improve drug stability and bioavailability by modulating drug distribution. Biodegradable PCEC NPs have been investigated for the dual therapy of PTX and curcumin in breast cancer treatment. These NCs released PTX and curcumin gradually, avoiding an initial peak, demonstrating dose-dependent cytotoxicity, and increasing apoptosis compared to free drugs. The NP-based drug delivery system inhibited tumor growth, prolonged life expectancy, and reduced side effects in BALB/c nude mice (29).

Carbon-based NPs

Carbon-based nanosystems have the potential to transform chemotherapy by enhancing drug delivery, precisely targeting cancer cells, increasing bioavailability, and providing multifunctionality.

Their extensive surface area and configurable surface chemistry facilitate effective drug loading and release, while functionalization reduces tissue damage and systemic side effects (30).

Carbon nanotubes (CNTs)

Cylindrical nanostructures known as CNTs, composed of hexagonal carbon atoms, have the potential to revolutionize chemotherapy due to their extensive surface area and needle-like morphology. They efficiently deliver anticancer agents into cancer cells, enhancing cellular uptake and potentially transforming chemotherapy approaches (31). Researchers have developed a three-component composite, MWNTs-Ge-Le, to improve the clinical application of gemcitabine. They successfully attached gemcitabine and lentinan to MWNTs, demonstrating superior performance compared to MWNTs alone, gemcitabine, and MWNTs conjugated with Ge (32). Subsequent research revealed that a minimal quantity of Evans Blue could diffuse and functionalize SWCNTs, resulting in a stable SWCNT/EB complex. The nanocomplex SWCNT/EB/albumin/PTX exhibits significant absorption in the near-infrared spectrum, making it suitable for integrated chemotherapy and thermal treatment. In vivo investigations demonstrated the nanocomplex's efficacy in eliminating MDA-MB-435 tumors, underscoring the synergistic impact of the combined strategy (33).

Carbon dots (CDs)

CDs, a category of nanomaterials with diameters smaller than 10 nanometers, have the potential to transform cancer chemotherapy due to their exceptional properties, including biocompatibility, tunable luminescence, large drug-loading capacity, targeted drug delivery, PTT, and biodegradability. As safe alternatives to conventional chemotherapy drugs, CDs can be engineered to emit light at therapeutic wavelengths for drug delivery tracking. Their large surface area facilitates efficient drug transport and therapy (34). CDs can achieve targeted drug delivery by immobilizing target-specific molecules on their surface to minimize drug exposure to normal tissues. Some CDs release heat upon irradiation and are used alongside standard chemotherapy agents. Their biodegradability reduces the risk of delayed health effects (35).

To address the issue of multidrug resistance (MDR) during cancer treatment, a novel method employing a poly(amidoamine) (PAMAM) dendrimer/carbon dot nanohybrid has been developed. The novel platform provides dual functionality, enabling both concurrent drug delivery and the monitoring of cancer cells via fluorescence imaging. Blue luminescent CDs derived from sodium citrate are used as the delivery vehicle for the potent anticancer drug DOX in the nanohybrid. The system is expected to be favorable, offering optimal colloidal stability and considerable cell growth inhibition due to the use of TPGS (36). Similarly, a fluorescent CD-based platform targeting CIS resistance in cancer treatment was developed in a different study. This platform incorporates full-color emissive carbon dots (CDs−Pt(IV)−DOX) for CIS and DOX delivery, and the synergistic anticancer activity of CIS and DOX proved effective and potent against A2780 and A2780cis cancer cells exhibiting CIS resistance (37).

Fullerenes

Fullerenes, a distinctive category of nanomaterials characterized by a spherical or cage-like architecture, are attractive candidates for cancer treatment owing to their exceptional biocompatibility, substantial internal cavities, adjustable surface chemistry, free radical scavenging capabilities, and potential for photodynamic therapy. Their porous architecture facilitates targeted medication administration and improves biocompatibility. Fullerenes may neutralize free radicals, which damage healthy cells and contribute to cancer progression. Certain fullerenes may be photoactivated, producing ROS that can kill cancer cells (38). Research on fullerenes for chemotherapy is still under development, with obstacles such as improving solubility and biodistribution.

A new fullerene-based system, C60–PEI–DOX, has been created to enhance cancer treatment efficacy. This advanced technology employs a fullerene core covalently linked to the polymer poly(ethyleneimine) (PEI), facilitating the encapsulation and delivery of the anticancer agent DOX. PEI may be tailored to selectively direct distribution to cancer cells, improving therapy accuracy. The release of DOX from C60–PEI–DOX is contingent upon the ambient pH, facilitating regulated drug release within the tumor microenvironment. C60–PEI–DOX exhibits substantial antitumor activity alone, although its efficiency is markedly augmented when used in combination with photodynamic therapy, greatly improving overall cancer treatment outcomes. In vivo investigations indicate that C60–PEI–DOX demonstrates enhanced antitumor efficacy with minimal toxicity to normal organs, making it a viable candidate for future cancer therapies (39).

Scientific research has uncovered a new approach to reversing the harmful effects of chemotherapy by using amino acid derivatives of fullerene (AADFs). The AADF antioxidant effectively neutralizes excess ROS produced as by-products of chemotherapy. In the research, two amino acids, L-lysine and β-alanine, were chemically modified using C70 fullerene. The L-lysine derivative (C70-Lys) exhibited enhanced

radical scavenging activity relative to the β-alanine counterpart (C70-Ala). In vivo investigations demonstrated that C70-Lys mitigated chemotherapy-induced organ damage, specifically hepatotoxicity and cardiotoxicity. The findings suggest that AADFs, particularly C70-Lys, may improve patient tolerance and enable more intensive treatment protocols (39).

Graphene oxide (GO) NPs

Graphene oxide nanoparticles (GO NPs) are a promising class of nanomaterials with tremendous potential in cancer treatment. Graphene-based NPs are highly biocompatible and possess a large surface area, making them practical for targeted drug delivery, drug release control, and combination therapy. They exhibit photothermal characteristics, enabling the eradication of cancer cells via thermal means. Certain GO NPs may be engineered for multiple imaging modalities, such as fluorescence imaging and MRI, facilitating real-time observation of drug distribution and therapy progression (40). The promise of GO NPs in cancer treatment includes improved drug delivery, targeted therapy, regulated drug release, combination therapy, and real-time monitoring. These properties enable the effective encapsulation and targeted delivery of high concentrations of chemotherapeutic drugs directly to cancer cells, thus reducing side effects and minimizing exposure to healthy tissues (41). Research on the application of graphene oxide NPs in chemotherapy is ongoing, with challenges such as achieving optimal biocompatibility and improving stability under physiological conditions. Nevertheless, continuous research holds significant potential to overcome these obstacles and realize the full capabilities of GO NPs in cancer treatment. A novel cancer treatment approach utilizing dual drug-loaded graphene oxide NPs has been developed, integrating drug delivery with photothermal therapy to facilitate the targeted administration of effective anticancer agents to malignant cells. Research indicates that this dual drug-loaded graphene oxide system, combined with near-infrared laser irradiation, demonstrates significantly higher cytotoxicity than treatment with a single drug, a drug combination, or blank graphene oxide NPs with laser irradiation. This method shows potential for overcoming inherent resistance to chemotherapeutic agents by integrating targeted drug delivery with direct cell killing mediated by photothermal therapy (PTT) (42). Carbon nanosystems such as CNTs, CDs, fullerenes, and GO NPs are transforming chemotherapy by improving drug delivery, targeted therapy, controlled drug release, combination therapy, and real-time monitoring. However, obstacles remain, including the enhancement of biocompatibility, the mitigation of stability concerns, and the overcoming of clinical translation barriers.

Hybride and Inorganic Biosystems

Metallic NPs

Metallic NPs composed of metals such as gold, silver, or iron oxide possess distinctive features that make them promising candidates for revolutionizing chemotherapy. These NPs may enhance drug delivery by allowing targeting molecules to be directed to their surface and releasing the drug payload precisely at the required location. They also improve therapeutic efficacy by protecting chemotherapy drugs from degradation within the body, enabling the administration of higher doses and more potent treatments. Some NPs also serve as imaging agents, permitting physicians to visualize tumors more effectively upon diagnosis and assess therapy efficacy in real-time (43). Researchers are developing a novel breast cancer treatment using metallic NPs. Gold or silver NPs coated with citrate are employed as drug carriers for anticancer drugs such as 6-Mercaptopurine (6-MP). The findings were promising, as gold and silver NPs loaded with 6-MP exhibited enhanced cytotoxicity (cell death) compared to the drug or NPs alone. Gold nanoparticles (AuNPs) appeared to be more efficient transporters at lower concentrations (44).

Superparamagnetic iron oxide nanoparticles (SPIONs) coated with silica (SiO2) are under investigation for oncological therapy due to their capability to transport pharmaceuticals and generate thermal energy for tumor eradication. However, their safety is a concern due to the potential release of iron ions inside the body. To address this issue, scientists have developed techniques to coat SPIONs with silica using various methods, significantly improving the safety of the nanoparticles and modifying their surface properties. Laboratory experiments using human lung cells demonstrated that both coated and uncoated SPIONs exhibited low toxicity to the cells (45).

Quantum dots (QDs)

Quantum dots are emerging as a promising tool for cancer therapy due to their distinctive features, including controllable fluorescence. These semiconductor NPs may be engineered to regulate the wavelength of emitted light, facilitating targeted drug administration, imaging, diagnostics, and theranostics. QDs may be fabricated to attach to specific molecules on cancer cells, enabling the targeted delivery of chemotherapeutic agents directly to the tumor while minimizing harm to healthy tissues. They may also generate heat, known as photothermal therapy (PTT), which can be used to eliminate cancer cells in a localized manner (46). Their impact is substantial, offering a future in which chemotherapy is more precise, effective, and tailored, instilling optimism for improved prognoses for cancer patients. Researchers have developed a nanocarrier system integrating chemotherapy and phototherapy

to enhance cancer treatment efficacy. This strategy employs carbon quantum dots (CQDs) to deliver DOX and a light-reversible drug (5-ALA) to cancer cells. Under illumination of a specific wavelength, 5-ALA produces ROS, inducing apoptosis in cancer cells and synergistically enhancing the effect of the chemotherapeutic agent (47). A novel drug delivery system utilizing cyclic RGD-functionalized graphene quantum dots (R-GQDs) has also been developed. These minute nanocarriers operate via a "Trojan horse" mechanism, delivering the highly effective chemotherapeutic drug DOX into cancer cells. The specific targeting of cancer cells by R-GQDs has the potential to reduce damage to healthy tissues. Studies have demonstrated that R-GQDs are efficiently internalized by cancer cells, facilitating the co-delivery of both a light-activated moiety and the chemotherapy agent. This combined treatment has exhibited significantly greater anticancer activity compared to the individual administration of each agent (48).

Mesoporous Silica nanoparticles (MSNs)

MSNs represent a viable approach in cancer therapy due to their distinctive characteristics, including substantial drug-loading capacity, biocompatibility, and the ability to release their contents in response to specific stimuli. MSNs may be tailored for particular pharmaceuticals and directed toward cancer cells, minimizing the likelihood of significant adverse effects. They may also transport imaging agents, enabling physicians to track the NPs and assess therapeutic efficacy (49). A sophisticated nanoparticle drug carrier, chitosan-capped pH-responsive hollow mesoporous silica nanoparticles (HMSN-GM-CS-FA), has been engineered to execute a twofold attack on cancer cells. This carrier consists of an acid-sensitive biodegradable silica sphere coated with folic acid, which responds to the acidic tumor microenvironment by triggering drug release, thereby enhancing therapeutic effects on cancer cells while minimizing damage to normal tissues. This discovery represents a significant breakthrough in intelligent drug delivery systems, with the potential to revolutionize cancer therapy by precisely targeting therapeutic drug combinations to tumors, thereby reducing side effects (50). A novel cancer treatment method, Electrodynamic Therapy (EDT), has been recently introduced. EDT utilizes a direct current (DC) or square-wave alternating current (AC) electric field to initiate an electro-driven catalytic reaction on platinum nanoparticles (PtNPs), leading to the generation of reactive oxygen species (ROS). Mesoporous silica-based nanocomposites have been engineered to expand the potential applications of EDT, enabling the uniform eradication of large tumors with a comparatively modest electrical input (51).

Hybrid Nanosystems

Hybrid nanomaterials are nanocomposites with complex structures and the organization of multiple NPs. These hybrid particles exhibit remarkable properties that are unattainable with a single type of NP alone. Hybrid nanosystems are used in biomedical applications and drug delivery, consisting of multiple drug carriers with at least one dimension within the nanoscale range. These carriers may be composed of organic or inorganic components or a mixture of both. The resulting material possesses new properties and performance characteristics shaped by molecular or supramolecular interface interactions. The functionality of hybrid NPs is directly proportional to the enhancement of physicochemical properties (52).

Inorganic Hybrid Nanosystems

Inorganic hybrid nanosystems, which consist of an inorganic material combined with other materials, have significantly enhanced drug delivery systems through the integration of distinctive properties. They also provide advantages in combating antitumor multidrug resistance by facilitating combination therapy and inhibiting specific drug resistance mechanisms (53). Metal nanocarriers, primarily gold and silver NPs, effectively deliver medicines and therapeutic substances. AuNPs are extensively used in cancer therapy due to their stability, photosensitization, surface plasmon resonance, and facile functionalization, providing a versatile drug delivery platform (54). Internal stimulation approaches leverage tumor-specific microenvironments, such as pH levels and enzyme activity, to initiate drug release. AuNPs encapsulating chemotherapeutic agents may selectively target cancer cells via enzymatic interactions with tumor-specific enzymes such as matrix metalloproteinases (MMPs) and hyaluronidases (HAase). HA-functionalized AuNPs selectively targeted breast cancer cells exhibiting elevated CD44 receptor expression, effectively delivering therapeutics (55). AuNPs, characterized by a surface plasmon resonance (SPR) band in the near-infrared (NIR) region, may be stimulated by external factors such as laser optoporation and ultrasonic vibrations, producing heat via the photothermal effect. This facilitates remote activation of drug release by breaking thermosensitive connections (56). Lin et al. developed APP-DOX, a nano-drug delivery system for treating mouse liver tumors. This system was well-tolerated and resulted in tumor regression, particularly when combined with NIR laser therapy. Histological analysis revealed reduced cancer cell proliferation and increased tumor cell death in the APP-DOX-treated groups, especially with the addition of NIR laser therapy (57).

Hybrid nanosystems such as carbon-based

nanoparticles (CNTs), graphene oxide (GO), graphene quantum dots (GQDs), fullerenes (C60), and diamond nanocrystals are under investigation for their ability to traverse cell membranes and administer medicinal compounds. These nanomaterials exhibit pH sensitivity, making them suitable for drug delivery applications, such as graphene oxide for transporting anticancer therapeutics (58). MSNPs can encapsulate a central nanoparticle and serve as chemotherapy vehicles. Additives can enhance the mesoporous properties of MSNPs. A study on a core-shell configuration (GNRs-ICG@rGO-DOX) demonstrated excellent drug-loading capacity and pH-responsive release behavior, indicating its potential as a cancer therapy drug carrier (59).

Due to their unique magnetic properties, inorganic hybrid magnetic nanoparticles (MNPs) are used for targeted drug and heat delivery. Coated with carbon, gold, or silica shells, they exhibit biocompatibility and stability, making them suitable for biomedical applications, including cancer therapy and magnetic hyperthermia. Inorganic hybrid NPs are effective carriers for small chemotherapeutic drugs like DOX and CIS, as well as large molecular structures. Hybrid layered double hydroxides (LDHs) with a lamellar structure offer improved therapeutic effectiveness and reduced side effects in disease treatment due to their high surface-to-volume ratio (60). Researchers have developed a robust strategy against cancer treatment resistance by integrating inorganic hybrid nanostructures with advanced drug delivery methods. This approach facilitates precise drug release and tailored therapy, with carbon-based NPs enhancing accuracy and magnetic NPs enabling selective cell death and improved drug transport, leading to more effective treatments with fewer adverse effects (61).

Organic hybrid nanosystems

Organic hybrid nanosystems (ONPs) are extensively used in biomedical applications due to their superior biocompatibility, reduced bodily clearance, and improved drug solubilization and transport, which may be tailored according to the surface polymer utilized (60). The hybrid approach offers several advantages, including enhanced circulation duration, structural integrity, stability, avoidance of premature release, elevated encapsulation rates, and more precise release kinetics, thereby eliminating the need for expensive and time-intensive molecule synthesis (62).

Lipid-polymer Hybrid NPs

Lipid nanoparticles (LNPs) are secure and effective carriers composed of synthetic or natural lipids, including fatty acids, glycerides, steroids, and phospholipids. They exhibit varied architectures, such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), micelles, and liposomes. However, LNPs face challenges such as limited cargo-loading capacity, rapid drug degradation, susceptibility to aggregation, and instability in biological fluids. Recent research has explored the use of lipid and polymeric substances in novel carrier systems, including polymer-coated liposomes and lipid-polymer hybrid nanoparticles (LPHNPs). These methods are being investigated for the loading and delivery of functional chemicals, including anticancer medications (63). LPHNPs consist of three components: an external lipid-PEG layer that facilitates systemic circulation, a central lipid monolayer that safeguards the encapsulated pharmaceuticals and the polymer core, and a lipid monolayer encasing the polymer core. This architecture ensures stability and controlled drug release over time (63). LPHNPs surpass polymeric nanoparticles (PNPs) and liposomes in terms of durability, biocompatibility, drug cargo capacity, chemotherapeutic drug release management, prolonged circulation time, and in vivo effectiveness. They can transport both hydrophobic and hydrophilic pharmaceuticals, making them versatile in therapeutic applications, particularly cancer therapy (64).

Lipid-phospholipid nanoparticles (LPNs) have demonstrated the ability to enhance drug pharmacokinetics and therapeutic efficacy, leading to prolonged circulation times and reduced tumor burden in animal models. Yalcin et al. optimized the formulation of gemcitabine-loaded LPHNPs compared to the commercial product Gemko®, demonstrating superior pharmacokinetic performance in rats. GEM-loaded LPHNPs exhibited greater chemotherapeutic efficacy in breast cancer treatment, showing increased cytotoxicity due to effective nanoparticle absorption through interactions between the lipid shell and cancer cells (65). Gao and colleagues developed LPHNPs incor-porating iRGD peptides and isoliquiritigenin (ISL), demonstrating enhanced anti-breast cancer efficacy in vitro and in vivo. The ISL-iRGD NPs exhibited greater cytotoxicity and inhibited breast cancer cell lines more effectively than ISL alone. Biodistribution studies using fluorescently labeled NPs (Cy5-iRGD NPs) revealed improved tumor targeting compared to free Cy5 and Cy5 NPs. This enhanced targeting is attributed to the iRGD peptide's tumor-homing ability and the enhanced permeability and retention (EPR) effect. These findings suggest that incorporating iRGD peptides can improve the delivery and efficacy of nanotherapeutics for breast cancer (66).

Similar research has indicated that LPHNPs have significant implications for improving oral drug administration, enhancing stability, optimizing systemic distribution, advancing cancer therapy

through improved drug targeting, and overcoming therapeutic challenges (67).

Protein-polymer hybrid NPs

Protein-polymer hybrid complexes are ideal drug carriers for cancer treatments due to their non-toxic nature, enhanced water solubility, and biocompatibility. They enable sustained drug release and targeted pharmaceutical distribution, improving therapy efficacy while reducing side effects. Proteins play essential roles in biological processes, making them highly suitable for drug delivery applications. Protein-based NPs offer advantages such as bioengineering without chemical manufacturing, facile modification, and genetic alteration for antigen epitope display. Their amphipathic nature allows them to bind hydrophobic drugs with maximum encapsulation efficiency (68). Saleh et al. investigated how curcumin (CUR) improves the therapeutic effectiveness of breast cancer cell therapy through its encapsulation in human serum albumin (HSA) NPs. An HER2-binding aptamer (HB5) was attached to the surface of albumin NPs for the targeted delivery of drugs to breast cancer cells that overexpress HER2 receptors. Cellular uptake and viability tests demonstrated increased internalization of aptamer-conjugated NPs in HER2-positive cells, along with improved efficacy in reducing cell viability in these cells compared to free curcumin or non-targeted NPs. Aptamer-modified NPs exhibited no significant cytotoxicity changes against HER2-negative cells, indicating their potential for targeted treatment of HER2-positive breast cancer (69). Ge and coworkers synthesized bovine serum albumin-PMMA NPs containing camptothecin within the hydrophobic PMMA core. These NPs, approximately 100 nm in diameter, possess tunable size and charge, allowing for chemical modifications and efficient cellular uptake. They demonstrated enhanced anti-tumor activity in laboratory experiments and animal models, highlighting the potential of organic hybrid nanosystems for biomedical applications (70).

Targeted Nanosystems

Antibody-drug conjugates (ADCs), referred to as "smart chemotherapy," are a novel category of anticancer treatments that utilize tumor antigen-specific monoclonal antibodies to transport small molecules to neoplastic cells. This approach enhances chemotherapy effectiveness while reducing systemic exposure and toxicity. ADCs typically consist of a tumor-specific monoclonal antibody, a potent cytotoxic payload, and a chemically synthesized linker. The success of ADC development hinges on the careful selection of the target antigen, monoclonal antibody, payload, linker, and conjugation strategies. ADCs can exhibit a bystander effect, eliminating nearby cells regardless of their antigen expression, which is crucial for treating heterogeneous malignancies (71).

ADCs have demonstrated promise in treating certain tumors, and more than one hundred are currently being investigated in clinical trials (72). Trastuzumab emtansine (T-DM1) is a thioether-linked drug that reduces toxicity and enhances targeting, enabling selective delivery of DM1 into HER2-overexpressing cancer cells. Verma et al.'s EMILIA trial demonstrated T-DM1's effectiveness in treating advanced HER2-positive breast cancer, yielding improved outcomes and reduced side effects (73). Enfortumab vedotin (EV) is designed to target the overexpression of Nectin-4 in bladder cancer. Upon internalization of the EV-Nectin-4 complex, cytotoxic MMAE is released, halting cell division and initiating apoptosis (74). Nectin-4 has emerged as a promising target for systemic treatment in cases of locally advanced or metastatic urothelial carcinoma. In a phase I dose-escalation trial, 112 patients with metastatic urothelial carcinoma received EV, with a confirmed objective response rate of 43% and a response duration of 7.4 months (75).

Stimuli-responsive Nanosystems

Stimuli-sensitive nanosystems are highly sophisticated drug delivery systems designed to address challenges such as nonspecific biodistribution and premature drug release. These NPs dynamically respond to specific stimuli, providing regulated control over drug release, distribution, and dosage. Heterogeneous nanocarriers—including liposomes, polymers, metallic NPs, and nanogels—enhance drug delivery efficiency and enable personalized treatment approaches (76).

pH-responsive NPs

pH-sensitive nanocarriers are utilized in cancer therapy to regulate drug release or activation within the tumor microenvironment while preserving their stealth characteristics in normal tissues, where pH levels remain neutral. NPs can facilitate drug release, alter surface charge, and induce the disintegration of inorganic components through protonation. These acid-labile NPs can transition from hydrophilic to hydrophobic surfaces, aiding drug accumulation in tumor tissues and modifying their chemical properties (77). Various materials are employed to fabricate pH-responsive nanocarriers, including liposomes, polymer micelles, and polymer capsules (78). PEG NPs containing curcumin and DOX were conjugated with transferrin to create nanocomplexes that enable drug release in mildly acidic environments. Research indicates that at pH levels of 5.0 and 7.4, 79.2% and 57.6% of DOX, respectively, were released over 24 hours. Pandey et al. developed a

delivery system using HA-coated MOFs to encapsulate Titanocene and 5-FU, demonstrating pH sensitivity and enhanced anti-cancer activity by reducing intracellular IL-6 and TNFα levels (79).

Temperature-responsive NPs

Thermosensitive nanostructures represent a promising class of drug delivery systems that exploit temperature variations for targeted drug release, particularly in diseased or tumor tissues. These mechanisms can retain their payload at ambient temperature and discharge it upon exposure to the elevated temperatures characteristic of tumor tissues. Thermoresponsive NPs are engineered polymers that undergo phase transitions in response to temperature fluctuations. Li et al. developed temperature-sensitive polymer nanomicelles to encapsulate the anticancer medication DOX and magnetic nanoparticles (MNPs), enabling controlled drug release at elevated temperatures. The micelles could rapidly dissolve and reassemble, and a fast release of DOX was observed under mild microwave irradiation. The study determined that DOX encapsulated in thermosensitive nanocarriers could overcome DOX resistance in small-cell lung cancer by specifically targeting intracellular organelles, particularly mitochondria, thereby augmenting intracellular drug concentration and tumor-selective absorption (80).

Light-responsive NPs

Light-sensitive nanocarriers, activated by UV, visible (Vis), and near-infrared (NIR) wavelengths, enable precise drug delivery management and remote manipulation within biological systems, particularly in cancer cells and tumors. These nanocarriers can modify molecular conformations, sever chemical bonds, initiate drug release, facilitate imaging, generate reactive oxygen species (ROS), and induce photothermal effects for tumor ablation. Upon exposure to light, thermoresponsive NPs undergo structural modifications, allowing targeted drug release. Chen et al. developed a multifunctional UCNP-based micelle for near-infrared light-mediated drug release, integrating photodynamic therapy and chemotherapy for a comprehensive cancer treatment strategy (81). Yue et al. synthesized camptothecin conjugated with a thioketal linker (TL-CPT) for cancer optical imaging, photodynamic therapy, and chemotherapy. These NPs could modulate light wavelengths, activate Ce6 to generate ROS for photodynamic therapy, and enable controlled CPT release for chemotherapy. In vitro release studies demonstrated precise drug release, and Ce6-CPT-UCNPs exhibited efficient tumor targeting, therapeutic efficacy, and minimal toxicity to essential organs (82).

Ongoing Clinical Trials

NP-mediated drug delivery systems are in clinical trials now, aiming to improve chemotherapy's effectiveness and lower side effects. Clinical trials in Supplementary Table 1 compare PEGylated, micellar, liposome, and AuNPs in breast, lung, glioblastoma, and pancreatic cancers. Liposomal doxorubicin, cisplatin, and vincristine are studied from Phase I to III. Nanotechnology improves medicine absorption, tumor targeting, and side effects compared to chemotherapy. Nanoformulations are being used to treat cancer from clinical trials to market. Nano-drugs like Abraxane®, Doxil®, and Onivyde® improve liposomal, polymeric, and albumin-bound drug delivery (Supplementary Table 2). Intravenous formulations are used to treat breast, ovarian, pancreatic, and leukemia. They stabilize drugs and concentrate therapy but have the side effect of causing cardiomyopathy, neuropathy, and myelosuppression. The fact that nanoformulations were developed and approved suggests that nanomedicine may improve chemotherapy and patient outcomes. Supplementary Table 1 summarizes current clinical trials exploring NPs for delivering chemotherapy drugs, while Supplementary Table 2 presents an overview of commercial nanoformulations developed for cancer treatment.

Conclusion and Future Directions

Nanotechnology has emerged as a transformative force in cancer diagnosis, treatment, and monitoring, offering unprecedented precision and personalization. While significant progress has been made in the development of nanoscale drug delivery systems, imaging agents, and theranostic platforms, translating these innovations from bench to bedside remains a key challenge. Issues related to biocompatibility, long-term toxicity, immune response, and large-scale manufacturing must be thoroughly addressed to ensure clinical success. Moreover, regulatory frameworks must evolve to keep pace with the unique characteristics of nanomedicines, ensuring safety and efficacy while fostering innovation.

Looking ahead, future research should prioritize the development of smarter and more responsive nanoplatforms capable of navigating the complex tumor microenvironment, targeting heterogeneous cancer cell populations, and releasing therapeutic agents in a controlled, stimuli-responsive manner. The integration of nanotechnology with cutting-edge fields such as artificial intelligence, systems biology, immunotherapy, and gene editing holds immense promise for the advancement of highly personalized and adaptive cancer treatments. Furthermore, progress in bioinformatics and single-cell analysis could refine the design of nanomedicines tailored to individual tumor profiles, further expanding the possibilities of precision oncology.

Supplementary Table 1. Current clinical trials are investigating the use of NPs to deliver chemotherapy drugs.

NCT Number / Phase /Enrollment	Nanocarriers / Drug/Molecule	Cancer Type	Last Update Posted
NCT05456022/ II / 1000000	PLGA-PEG / Quercetin	Squamous cell carcinoma	2022-07-13
NCT02043288 / III / 310	Micellar nanoparticle / Cisplatin	Metastatic pancreatic cancer	2020-04-15
NCT04366648 / I / 25	PEG / Irinotecan	Solid Tumor	2021-11-17
NCT02982395 / III / 36	PEG-PLA / Docetaxel	Non Muscle Invasive Bladder Cancer	2019-08-30
NCT00080002 / II / -	PEG / Camptothecin	Gastroesophageal Cancer	2012-09-06
NCT01036113 / II / 160	PEG / SN38	Metastatic Breast Cancer	2022-02-14
NCT04413227 / I / 30	PEG / Docetaxel	Non-small Cell Lung Cancer	2020-06-02
NCT01644890 / III / 436	Micellar nanoparticle / Paclitaxel	Metastatic or recurrent breast cancer	2019-07-29
NCT00734682 / I / 34	liposome / CPT-11	Recurrent High-Grade Gliomas	2015-01-07
NCT00046787 / II / 47	liposome / Lurtotecan	Recurrent Small Cell Lung Cancer	2011-10-20
NCT03504644 / IB/II / 74	liposome / Vincristine	Relapsed or Refractory T-cell or B-cell Acute Lymphoblastic Leukemia	2023-06-23
NCT00102531 / I/II / 19	liposome / Cisplatin	Osteosarcoma Metastatic	2017-08-01
NCT04887298 / IB/II / 36	liposome / Annamycin	Soft-Tissue Sarcomas With Pulmonary Metastases	2023-10-25
NCT01094548 / II / 34	liposome / Tecemotide	Multiple Myeloma	2016-02-22
NCT00944801 / I/II / 63	liposome / Doxorubicine	Glioblastoma	2009-07-23
NCT00441376 / I / 30	Thermally Sensitive Liposome / Doxorubicin	Primary and Metastatic Tumors of the Liver	2019-02-07
NCT00046540 / I / 40	Liposome / SN38	Advanced Cancer	2011-07-04
NCT02833766 / II / 48	liposome / anti-EGFR-doxorubicin	Breast Cancer	2021-09-29
NCT01464593 / II / 2	Thermal Ablation and Lyso-Thermosensitive Liposome / Doxorubicin	Metastatic Colorectal Cancer Liver Lesions	2022-10-13
NCT00356980 / I / 60	AuNPs / rhTNF	Advanced Solid Organ Malignancies	2012-03-15
NCT03020017 / Early Phase I / 8	AuNPs / RNAi for Bcl2L12	Gliosarcoma	2022-08-26
NCT04138342 / I / 30	QD (CdS/ZnS) / Veldoreotide	Breast and Skin Cancer	2019-10-24
NCT00328497 / II / 31	Nanocrystalline / 2-methoxyestradiol	Carcinoid Tumor	2010-03-10

Supplementary Table 2. Summary of commercial nanoformulations based on nanomedicine developed for cancer treatment.

Name	Formulation	Usage	Administration	Dosage	Main Adverse Reactions	Ref
Abraxane®	Albumin-bound paclitaxel	Metastatic Breast cancer, Non-small cell lung cancer, Pancreatic adenocarcinoma	Intravenously	Varies by cancer type	Decreased blood cell counts, Neuropathy, Sepsis, Lung problems	(83, 84)
Doxil®	Doxorubicin HCl liposome	Ovarian cancer, Kaposi's Sarcoma, Multiple Myeloma	Injection	20 mg/10 mL or 50 mg/25 mL	Cardiomyopathy, Infusion Reactions, Hand-Foot Syndrome	(85, 86)
DaunoXome®	Liposomal daunorubicin	HIV-associated Kaposi sarcoma	Intravenously	40 mg/m2 every 2 weeks	Neutropenia, Alopecia, Arrhythmia, Mucositis, Vomiting	(87, 88)
Marqibo®	Liposomal vincristine	Acute lymphoblastic leukemia	Intravenously	2.25 mg/ every 7 days	Neurologic Toxicity, Myelosuppression, Constipation	(89, 90)
Lupron Depot®	PLGA leuprolide acetate	Prostatic cancer	Intramuscular	Varies (7.5 mg - 45 mg)	Changes in Bone Density, Pituitary apoplexy	(91, 92)
Eligard®	PLGA leuprolide acetate	Prostate cancer	Subcutaneously/ Injection	Varies (7.5 mg - 45 mg)	Malaise, Fatigue, hot flashes, Testicular atrophy	(92, 93)
Onivyde®	Liposomal irinotecan	Pancreatic Cancer	Intravenous infusion	70 mg/m2 two weeks	Diarrhea, Fatigue, Vomiting, nausea, Decreased appetite	(94, 95)
Patisiran®	Lipid nanocarrier RNAi	Hereditary transthyretin-mediated amyloidosis	Injection	10 mg/5 mL	Infusion-related reactions, Reduced vitamin A levels	(96, 97)
Vyxeos®	Liposomal combination of daunorubicin & cytarabine	Acute myeloid leukemia (t-AML) or AML-MRC	Intravenous infusion	Daunorubicin 29 mg/m^2 & cytarabine 65 mg/m^2	Hemorrhagic events, Febrile neutropenia, Rash, Edema, Nausea	(98)

Conflict of interests

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, S.S.; writing-original draft preparation, S.F-K., F.D., S.S[#]., F.U-K., H.U-P., and B.H-A.; writing-reviewing and editing, J.A., S.S., F.D., S.M.; supervision, final draft, S.S. All authors have read and agreed to the published version.

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