Nanomedicine in Cancer Therapy: From Preclinical Promise to Clinical Applications

Md Sakil Amin[1*], Azizur Rahman[2], Amatun Noor Prapty[3], Abdullah Al Numan[4], Md Moshiur Rahman[5], Bulbul Ahmed[6], Md Mahedi Hasan Shabuj[6], Syeda Anjuman Ara Aunni[6]

Abstract

Background: Cancer continues to be a predominant worldwide health problem, characterized by rising incidence and fatality rates. Conventional therapies, including chemotherapy, gene therapy, and immunotherapy, exhibit limitations such as inadequate targeting, drug degradation, and unwanted effects. Nanomedicine has intriguing methods to address these difficulties by enhancing drug delivery and targeting. Methods: This review examines the incorporation of nanomedicine in cancer treatments, emphasizing chemotherapy, gene therapy, and immunotherapy. We examine the application of nanoparticulate delivery systems (NDSs) to improve drug delivery, augment tumor targeting, and minimize adverse effects. Numerous nanomaterials, including organic, inorganic, and composite nanoparticles, are analyzed for their potential to overcome the constraints of traditional therapies. Results: Nanomedicine has shown a lot of promise in improving the pharmacokinetics of chemotherapeutic drugs, making gene delivery more effective, and boosting immune responses in cancer immunotherapy. Pharmaceuticals can be delivered precisely and safely with nanoparticles, which solve problems like poor solubility, instability, and poor cell absorption in neoplasms. Conclusion: The use of nanomedicine in oncological treatment demonstrates significant promise for enhancing therapeutic results. Even though there are still issues with turning preclinical findings into clinical applications, nanotechnology is making steady progress that will enhance the effectiveness of chemotherapy, gene therapy, and immunotherapy, opening new ways to customize cancer treatment.

Keywords: Nanomedicine, Cancer Immunotherapy, Targeted Drug Delivery, Nanocarriers, Cancer Vaccines

Significance | Nanomedicine optimizes targeted medication delivery, augments therapeutic efficacy, diminishes adverse effects, and provides novel approaches for cancer therapy.

*Correspondence. Md Sakil Amin, Department of Pharmacy, University of South Florida, USA
E-mail: mdsakil@usf.edu, mdsakilamin@gmail.com

Editor John A. Catanzaro, NMD, And accepted by the Editorial Board Dec 25, 2024 (received for review Oct 15, 2024)

Introduction

Cancer represents a major global health hazard, with increasing incidence and fatality rates attributed to population aging, environmental changes, and lifestyle factors. The 2020 Global Cancer Statistics Report indicated that there were roughly 19.3 million new cancer cases and 10 million deaths that year (Sung et al., 2021). Consequently, the progression of cancer treatment has emerged as a critical medical need. Despite being a widely used cancer treatment, chemotherapy faces constraints such as the insufficient water solubility of pharmaceuticals and significant unpleasant side effects from non-specific distribution, which reduce its effectiveness and increase patient morbidity. In recent years, the advent of novel therapeutic modalities such as gene therapy and immunotherapy has transformed the cancer treatment paradigm (Libutti, 2019; Tan et al., 2020). Notwithstanding their

Author Affiliation.
[1] Department of Pharmacy, University of South Florida, United States.
[2] Department of Pharmacy, University of Development Alternative, Dhaka, Bangladesh.
[3] Department of Biological Sciences, St. Johns University NY United States.
[4] Department of Biochemistry and Molecular Biology, Tejgaon Collage, Dhaka, Bangladesh.
[5] Department of Biotechnology and Genetic Engineering, University of development alternative, Dhaka, Bangladesh.
[6] Department of Microbiology, Jagannath University, Dhaka, Bangladesh.

Please cite this article.
Amin, M. S., Rahman, A., Prapty, A. N., Numan, A. A., Rahman, M. M., Ahmed, B., Shabuj, M. M. H., Aunni, S. A. A. (2024). "Nanomedicine in Cancer Therapy: From Preclinical Promise to Clinical Applications", Journal of Precision Biosciences, 6(1),1-14,10064

potential, these medicines have considerable delivery obstacles, including low tumor cell uptake and inadequate tumor tissue penetration, which restrict their therapeutic efficacy. The advancement of nanoparticulate delivery systems (NDSs) provides a revolutionary remedy to these obstacles. NDSs help drugs stay in tumor tissues longer, get deeper into cells, and be released more slowly, which increases their effectiveness while lowering their side effects (Collins and Thrasher, 2015; Raza et al., 2019; Riley et al., 2019; Yahya and Alqadhi, 2021; Raza et al., 2022).

Nanomedicine, the utilization of nanotechnology in medical treatment, has demonstrated significant potential for enhancing cancer therapy. By utilizing the distinctive characteristics of nanomaterials, including size specificity, multifunctionality, and the capacity to discriminately target sick cells, nanomedicine has substantially enhanced chemotherapy, gene therapy, and immunotherapy. NDSs are different from other drug delivery systems because they can hold different kinds of drugs, protect delicate materials like nucleic acids from being broken down by enzymes, and deliver multiple therapies at the same time to get better results. For instance, although hepatocellular carcinoma is primarily treated by surgical resection and liver transplantation, there has been steady advancement in targeted nano-delivery systems for HCC (Tufael et al., 2024; Bakrania et al., 2022). Furthermore, it may have a role in other diseases too. Antibiotic resistance in ICU patients emphasizes the necessity of improved therapeutic approaches, showing the potential of nanomedicine to address multi-faceted healthcare challenges (Salam et al., 2024). Moreover, nanomedicine facilitates the regulated release of pharmaceuticals, which is essential for minimizing systemic toxicity and improving therapeutic accuracy. For example, to prevent the complications of metabolic disorders, such as necrotizing pancreatitis due to high triglyceride levels (Rahman et al., 2024), the role of nano therapy might be a good option with fewer side effects. This review seeks to deliver a thorough assessment of advancements in NDSs and their utilization in cancer therapy. It examines the incorporation of nanomedicine into chemotherapy, gene therapy, and immunotherapy, while highlighting the constraints of traditional treatments. This analysis addresses issues such the non-specific effect of chemotherapeutic agents, the instability of nucleic acid-based therapeutics, and immune-related adverse events in immunotherapy, alongside remedies facilitated by nanomedicine. This article illustrates, through specific examples, how NDSs enhance drug delivery efficiency, improve treatment outcomes, and reduce adverse effects. Nanotechnology's capacity to design nanoscale platforms specifically for cancer therapy offers significant potential to transform treatment approaches. Nano-delivery systems (NDSs) are a big step forward. It goes from passive targeting through enhanced permeability and retention (EPR) effects to active targeting made easier by surface modification. This study highlights the revolutionary potential of nanomedicine in surmounting current therapeutic obstacles and enhancing cancer care outcomes.

Delivery Systems of Nanoparticulate

The rapid advancements in nanotechnology have propelled nanoparticulate delivery systems (NDSs) into the forefront of medical innovation, garnering significant attention for their potential to revolutionize cancer treatment. NDSs, defined as particles typically smaller than 100 nm or, in certain cases, less than 1 μm while still exhibiting nanoparticle properties, offer unique structural and functional characteristics. These dimensions are smaller than a cell's volume, enabling precise interactions at the molecular and cellular levels. Compared to conventional drug delivery methods, NDSs demonstrate remarkable potential to enhance pharmacokinetics and pharmacodynamics, largely due to their tailored size, material composition, and shape (Kinnear et al., 2017).

The inherent heterogeneity and complexity of tumors present significant challenges in drug delivery. To address these, nanomaterials designed for cancer therapy often serve as multifunctional nanoplatforms, integrating drug payloads, structural frameworks, and functional units. This multifaceted approach provides distinct advantages over traditional therapies: Enhanced Drug Delivery: NDSs can transport drugs with varying physicochemical properties, overcoming challenges like the poor solubility of hydrophobic drugs and ensuring the stable delivery of nucleic acid drugs by protecting them from enzymatic degradation. Simultaneous Multi-Drug Transport: NDSs are capable of co-delivering multiple therapeutic agents, enabling synergistic treatment regimens. Dual Diagnostic and Therapeutic Capabilities: Nanomaterials can be engineered to integrate diagnostic imaging and therapeutic functions, streamlining cancer treatment into a single platform. Improved Targeting: Leveraging both passive targeting mechanisms, such as enhanced permeability and retention (EPR) effects, and active targeting through functional modifications, NDSs ensure precise drug accumulation in tumor tissues while minimizing off-target effects. Controlled Drug Release: Engineered stimuli-responsive nanomaterials allow for precise drug release triggered by specific endogenous (e.g., pH changes, enzymatic activity) or exogenous stimuli (e.g., light, temperature), optimizing therapeutic efficacy and minimizing side effects (Zhu G. et al., 2017; Bhushan et al., 2017; Liu et al., 2017; Cao et al., 2020; Zhu et al., 2020; Gote et al., 2021; Li et al., 2021; Yang et al., 2021; Liu et al., 2022). These attributes make NDSs a transformative tool in oncology, capable of addressing longstanding limitations in drug delivery. For example, by enabling precise targeting and controlled release, nanomedicine reduces systemic toxicity while improving drug efficacy. Furthermore, the

integration of diagnostic capabilities into therapeutic systems paves the way for real-time monitoring of treatment progress, offering a significant leap forward in personalized medicine.

Nanomedicine in Chemotherapy

In clinical practice, chemotherapy is still a popular tumor treatment. Even though it's very common, there are still a lot of problems. For example, it's not always easy to target cancer cells precisely, traditional chemotherapies have strong side effects, and many primary treatments, like doxorubicin and paclitaxel, don't dissolve well in water. These constraints impede the effectiveness of chemotherapy and complicate its clinical implementation. The emergence and application of nanomaterials have resolved these challenges by improving the delivery of chemotherapeutic drugs, markedly increasing their safety and therapeutic efficacy (Wei et al., 2021).We can classify the nanomaterials used in chemotherapeutic medication delivery into four primary categories: Organic nanomaterials, such as liposomes, micelles, and dendrimers, are better at enclosing drugs and controlling when they are released (Zhang D. Y. et al., 2020).

Inorganic Nanomaterials, things like gold nanoparticles and mesoporous silica nanoparticles have unique benefits, such as better drug loading and being more sensitive to outside stimuli (Wang C.-S. et al., 2021). Composite nanomaterials: These are hybrids that contain both organic and inorganic parts. It uses the best qualities of each to improve drug delivery and therapeutic effectiveness (Akgöl et al., 2021). Biological Nanomaterials: Their remarkable biocompatibility, biodegradability, safety, and intrinsic targeting abilities distinguish this category. Endogenous natural nanomaterials and biomimetic nanomaterials are two categories for biological nanomaterials (Wang J. et al., 2021; Navya et al., 2019). DNA and protein-based nanoparticles highlight the potential of biological nanomaterials in chemotherapy. DNA nanomaterials can be changed to make structures that are better for administering drugs accurately, but protein-based nanomaterials, like albumin nanoparticles, are better at binding drugs and have better pharmacokinetics.

DNA-Encoded Nanoparticles (NPs)

DNA-based nanoparticles (NPs) are becoming a new way to deliver medicines. By using DNA's unique properties, like carrying genetic information, and its important role in both healthy and unhealthy processes. DNA-based nanoparticles are the best way to solve some of the biggest problems in chemotherapy, like drugs that don't work very well and have a lot of side effects (Figure 1). This is because it is very biocompatible, break down quickly, and can be programmed to change sequences (Xu et al., 2021; Lv et al., 2021). In 1982, Seeman laid the theoretical groundwork for DNA nanotechnology by showing that DNA molecules could form precise nanostructures through Watson-Crick base pairing. This made it possible for advanced self-assembly methods like DNA tile assembly, rolling circle amplification (RCA), DNA origami, and single-stranded tile self-assembly (Lau & Sleiman, 2016; Mohsen & Kool, 2016; Evans & Winfree, 2017; Ji et al., 2021). These methods create 2D and 3D DNA nanoparticles that are more resistant to breaking down in the body, which makes them very useful for therapy (Ahn et al., 2020; Ramezani & Dietz, 2020).

DNA-based nanoparticles have shown great promise in delivering chemotherapeutic drugs like doxorubicin, daunorubicin, and platinum compounds (Halley et al., 2016; Zhang L. et al., 2019; Wu et al., 2019). Because it stops DNA from being made, doxorubicin is widely used in clinical practice to treat solid and blood cancers. This shows how useful DNA nanoparticles could be. These carriers, which include RCA-based structures, tetrahedra, and DNA origami-based tubular or triangular nanocarriers, are very good at carrying drugs and letting them build up passively in tumors (Zhao et al., 2018; Zhang J. et al., 2021; Li et al., 2020; Liu J. et al., 2018; Guan et al., 2021). Also, improvements in modification technologies let us use functional elements like aptamers for active targeting, which makes tumor-specific drug delivery much better. Aptamer-modified DNA nanoflowers (NFs) have exhibited superior targeting of protein tyrosine kinase 7-positive cancer cells, indicating increased tumor selectivity and fewer deleterious effects (Zhang Q. et al., 2019).

Physiological changes that are unique to tumors, such as higher levels of reducing agents, ATP, some enzymes (like telomerase and matrix metalloproteinase), and pH differences, have also led to the development of DNA nanoparticles that can respond to different stimuli. These designed systems can undergo structural reconfiguration to accurately release pharmaceuticals in response to various environmental stimuli, such as pH variations, reducing circumstances, or enzymatic activity (Zhao et al., 2018; Liu X. et al., 2018; Zhang G. et al., 2017; Lu et al., 2018). Doxorubicin-loaded DNA nanoparticles with pH-sensitive parts and aptamers showed amazing biological stability, targeted tumor localization, and controlled drug release, which made therapy much more effective and decreased side effects (Zhao et al., 2018). These accomplishments show how flexible and useful DNA-based nanoparticles can be in changing chemotherapy and creating safer and more effective cancer treatments (Table 1).

Nanoparticles Derived from Proteins

Proteins, as essential biological macromolecules, have become very potential nanocarriers for chemotherapeutic agents. It exhibits various advantages, including outstanding biocompatibility, biodegradability, and availability from natural sources, along with minimal toxicity. Their distinctive three-dimensional configurations and amphiphilic characteristics facilitate

interactions with both hydrophilic and hydrophobic substances. Furthermore, functional groups such amino, carboxyl, and hydroxyl groups promote chemical bonding, rendering proteins suitable for the synthesis of nanoparticles (Martínez-López et al., 2020). Numerous proteins, such as albumin, transferrin, ferritin, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), have been extensively employed to create nanocarriers for drug administration, demonstrating considerable potential in therapeutic applications (Iqbal et al., 2021).

Albumin-Based Nanoparticles

Nanoparticles made of albumin are a revolutionary way to deliver drugs using proteins. Abraxane, which is albumin-bound paclitaxel, is a major step forward in this field (Table 2). Polyoxyethylene castor oil typically solubilizes paclitaxel, a hydrophobic anticancer agent, potentially causing severe allergic reactions. Zhang Y. et al. (2020) produced Abraxane by encapsulating paclitaxel in albumin through hydrophobic interactions, resulting in nanoparticles with a diameter of approximately 130 nm. This formulation obviates the necessity for castor oil, thereby diminishing allergy concerns, enhancing therapeutic efficacy, and reducing systemic toxicity. The high concentration of albumin in the human body increases its biocompatibility, and current therapeutic trials highlight its significant potential (Yardley, 2013). People are increasingly recognizing stimuli-responsive albumin nanoparticles, especially pH-sensitive bovine serum albumin nanoparticles that help regulate the release of doxorubicin in acidic tumour microenvironments (Yang et al., 2020).

Transferrin and Ferritin Nanoparticles

Transferrin (Tf), a crucial iron-transporting glycoprotein, has been extensively investigated for receptor-mediated targeted drug delivery owing to its elevated expression in rapidly growing cancer cells. The receptors TfR1 and TfR2 are markedly overexpressed in malignancies to satisfy heightened iron requirements, providing an effective targeting mechanism (Table 3). Goswami et al. created transferrin-templated copper nanoclusters encapsulating doxorubicin for bioimaging and targeted drug delivery (Goswami et al., 2018). Wei et al. improved tumor targeting by conjugating transferring-binding peptides with chemotherapeutic agents (Wei et al.,2020).

Ferritin, a principal iron storing protein, constructs spherical nanocages that have been modified for drug delivery applications. Human ferritin (HFt), consisting of heavy and light chain subunits, can sequester up to 4,500 Fe^{3+} ions and preferentially bind to TfR1, which is overexpressed in tumor cells, hence enabling targeted drug delivery (Chakraborti & Chakrabarti, 2019). Researchers have employed ferritin nanocages to encapsulate metal-based medicines (e.g., cisplatin) and non-metallic chemotherapeutics (e.g., doxorubicin), thereby improving tumor selectivity and reducing off-target effects (Song et al., 2021). Issues like the inadequate purifying efficiency of natural ferritin have been addressed by recombinant ferritin constructions, expanding its range of applications (Veroniaina et al., 2021).

Lipoprotein-Based Nanoparticles

The inherent functions of LDL and HDL, naturally occurring lipoproteins, in lipid and cholesterol transport have led to their utilization for medication delivery (Salam et al., 2024). LDL receptors, overexpressed on neoplastic cells, identify LDL particles, measuring 19–25 nm in diameter, which enclose hydrophobic pharmaceuticals. We have used this characteristic to precisely administer chemotherapeutics and imaging agents. LDL-bound doxorubicin markedly diminished side effects while preserving efficacy (Lo et al., 2002). Manufacturers have created synthetic LDL systems to address the manufacturing constraints associated with natural LDL. Li et al. (2019) developed pH-sensitive ApoB-100/oleic acid-doxorubicin nanoparticles that replicate LDL structures to improve breast cancer targeting.

HDL, which is 8–13 nm smaller than LDL, shows promise for drug delivery because it interacts with SR-B1, a type of scavenger receptor that is found in many cancers. Researchers have created recombinant HDL (rHDL) nanoparticles for combinatorial therapy. Wang et al. made rHDL nanoparticles for doxorubicin, which showed that SR-B1-mediated drug delivery works well (Wang et al., 2014). Co-delivery techniques utilize these technologies to enhance the therapeutic synergy of chemotherapeutics or integrate chemotherapy with immunotherapy. Rui et al. successfully delivered paclitaxel and doxorubicin together through rHDL, which led to more drug accumulation in cancer cells and better tumor-killing activity (Rui et al., 2017).

Nanomedicine in Gene Therapy

Genetic treatment Nanomedicine has emerged as a viable domain for disease treatment through the modulation of gene expression, enabled by advancements in gene silence and editing technologies. This method has garnered considerable interest for its potential in cancer treatment, as it can selectively upregulate or downregulate target genes with less cytotoxicity relative to traditional therapies such as chemotherapy (Gutierrez et al., 1992). Nucleic acid therapies employed in gene therapy offer benefits including reduced toxicity and diminished undesirable effects. Nonetheless, obstacles persist, such as inadequate cellular absorption and stability in vivo. Conventional viral vectors, including lentivirus, adenovirus, and adeno-associated virus, are constrained by safety issues such as insertional mutagenesis and immunogenicity. Nano delivery systems (NDSs) have successfully mitigated these

constraints by providing substantial payload capacity, regulated release, little toxicity, and diminished immunogenicity (Rui et al., 2019). Gene therapy approaches primarily encompass gene enhancement therapy and gene suppression therapy, both of which greatly benefit from advancements in nanomedicine.

Gene Enhancement Therapy

Gene enhancement therapy involves adding plasmids or mRNA to increase the activity of certain genes or proteins, mainly genes that stop tumors from growing, like p53 and PTEN. These genes can suppress cancer cell growth when activated or overexpressed (Lee and Muller, 2010; Álvarez-Garcia et al., 2019; Lacroix et al., 2020).

mRNA-Based Therapy

mRNA provides benefits compared to plasmid-based techniques by facilitating rapid protein expression without genomic integration, hence minimizing the danger of mutations or other detrimental effects (Akeno et al., 2015; Que et al., 2018; Sobhani et al., 2021). Nevertheless, the volatility of mRNA and its inability to traverse cellular membranes necessitate the creation of effective delivery mechanisms. Kong et al. (2019) engineered redox-responsive nanoparticles for the delivery of p53-encoding mRNA, effectively causing cell cycle arrest and death in hepatoma and non-small cell lung cancer cells. Islam et al. (2018) utilized polymer-lipid hybrid nanoparticles, enveloped in a polyethylene glycol shell, to transport PTEN mRNA to PTEN-deficient prostate cancer cells, resulting in substantial tumor growth suppression.

Suicide Gene Therapy

This method employs drug-sensitivity genes such as the herpes simplex virus thymidine kinase (HSV-TK) gene. Upon transfection of tumor cells with this gene, it becomes sensitive to prodrugs such as ganciclovir, resulting in targeted cell death. Sukumar et al. (2020) documented improved treatment efficacy with a triple gene system (TK-p53-nitroreductase) administered through poly (lactic-co-glycolic acid) nanoparticles functionalized with a hepatocyte-targeting peptide. This system reinstated p53 functionality and improved prodrug susceptibility. Nanocarriers for mRNA delivery are typically cationic to establish stable complexes with negatively charged RNA molecules, hence ensuring high loading efficiency. Notable nanocarrier systems comprise ionizable lipid nanoparticles, polymer-lipid hybrids, and biologically inspired nanostructures exhibiting improved biocompatibility (Ding et al., 2021; Forterra et al., 2020).

Gene Suppression Therapy

Gene suppression therapy inhibits abnormal genes that produce deleterious or oncogenic proteins. This methodology employs tools such as small interfering RNA (siRNA) and CRISPR/Cas9 gene editing.

siRNA-Based Therapy

siRNA treatments show a lot of promise as a way to treat cancer because they effectively silence target genes and stop cancer cells from growing (Shi et al., 2019; Han et al., 2021; Krishn et al., 2022). Furthermore, siRNA enhances the susceptibility of drug-resistant cells to treatment (Shen et al., 2020). Advanced Nanocarriers: Researchers use lipid-based nanocarriers, dendrimers, and polymer nanoparticles to deliver siRNA, protecting it from nuclease degradation and promoting effective cytoplasmic release (Babu et al., 2017; Subhan and Torchilin, 2019). Wang et al. (2021) created DNA nanodevices using origami technology to deliver siRNA and doxorubicin together. These nanodevices effectively suppressed tumors without harming the body's normal systems.

CRISPR/Cas9 Gene Editing

CRISPR/Cas9 is a huge step forward because it allows precise and long-lasting gene editing by changing only the genes that help cancer cells survive (Rafii et al., 2022). Cas9 nuclease and single guide RNA (sgRNA) need to be delivered to the nucleus, which adds to the problems (Zhan et al., 2019; Zhang S. et al., 2021). Innovations in Nanocarriers: Researchers have created several CRISPR/Cas9 delivery systems, including cationic liposomes (Yin et al., 2020), lipid nanoparticles (Rosenblum et al., 2020), and gold nanoparticles (Tao et al., 2021). Wang Z. et al. (2021) created pH-sensitive nanocarriers that could deliver both CRISPR/Cas9 and epirubicin at the same time. This made the anti-cancer effect better in squamous cell carcinoma. Pan et al. (2019) developed near-infrared-responsive nanocarriers for CRISPR/Cas9, showcasing accurate gene editing through light activation. Shi et al. (2020) created DNA nanoflowers that respond to miR-21 so that CRISPR/Cas9 parts could be distributed precisely using miRNA sequence recognition. Stimulus-responsive nanoparticles, which are turned on by pH, redox conditions, or external stimuli (like light, ultrasound), make CRISPR/Cas9 delivery more selective and effective. This lowers the number of side effects and systemic toxicity.

Nanomedicine for Immunotherapy

Immunotherapy has swiftly progressed in recent years, fundamentally altering cancer treatment paradigms and providing a promising alternative to conventional medicines such as chemotherapy and radiotherapy. Conventional therapies utilize harmful pharmaceuticals or radiation to directly eliminate cancer cells, whereas immunotherapy enhances the immune system's ability to identify and assault tumors. This method entails modifying immune cells to improve their capacity to identify and eradicate cancer cells, either by suppressing negative immunological regulators or by augmenting the immune system's ability to recognize tumor-specific antigens. New immunotherapy methods have come about, such as immune checkpoint inhibitors

(ICIs), tumor vaccines, and chimeric antigen receptor T (CAR-T) cell therapy. These have quickly become important parts of treating cancer (Sahin and Türeci, 2018; Ma et al., 2019). The ongoing study indicates that the use of nanomedicine in immunotherapy is a potent instrument, significantly improving therapeutic effectiveness and addressing current limitations. Immune checkpoint blockade therapy is an essential element of contemporary cancer immunotherapy. Cancer cells can avoid being caught by the immune system by making molecules like PD-L1 that block immune system checkpoint receptors like PD-1 and CTLA-4 on T cells. This connection inhibits immunological responses, permitting malignancies to proliferate uncontrollably. Immune checkpoint inhibitors (ICIs), such as pembrolizumab (a PD-1 inhibitor), ipilimumab (a CTLA-4 inhibitor), and atezolizumab (a PD-L1 inhibitor), have developed and received FDA approval for many tumors to address this issue (Vaddepally et al., 2020). However, obstacles such as inadequate tissue penetration, particularly in difficult-to-access malignancies like glioblastomas, and immune-related adverse effects (irAEs) may constrain the therapeutic efficacy of these inhibitors. Nanomedicine is tackling these difficulties by facilitating more accurate and effective administration of immune checkpoint inhibitors, surmounting obstacles like the blood-brain barrier, and minimizing systemic toxicity. We have employed nanoparticles (NPs) to encapsulate and administer immune checkpoint inhibitors (ICIs), which facilitate enhanced targeting and regulated release. Galstyan et al. showed that attaching immune checkpoint inhibitors to poly-β-L-malic acid biopolymer scaffolds made it easier for cells to cross the blood-brain barrier. This greatly improved the response to tumors in glioblastoma models (Galstyan et al., 2019). Similarly, NPs attached to PD-L1 inhibitors have shown that they can lower the number of ICIs that is needed to stop tumor growth while still doing their job, which means fewer side effects. In a study, αPD-L1-conjugated gold nanoparticles cut the amount of immune checkpoint inhibitors that were needed to just one-fifth of the usual clinical dose. It also stopped tumor growth effectively (Meir et al., 2017). Nanomedicine has made progress, leading to the creation of "smart" nanocarriers that respond to certain factors in the tumor microenvironment, such as changes in pH or the presence of matrix metalloproteinases. These stimuli-responsive devices can deliver therapeutic molecules in a regulated manner, enhancing treatment efficacy. Liu et al. created dual-responsive liposomes that contained PD-L1 inhibitors and low-dose doxorubicin. These liposomes successfully stopped 78.7% of tumors in a melanoma mouse model by combining the effects of chemotherapy and ICIs (Liu et al., 2019). This method emphasizes the capability of nanomedicine to augment the therapeutic advantages of immunotherapy through the integration of several treatment techniques.

Even though ICIs work, they don't always get the immune system to respond properly in people whose tumors aren't easily attacked by the immune system. This is because ICIs mostly target major immune inhibitory pathways. To get around this problem, ICIs could be combined with immunostimulatory therapies based on nanotechnology, like nanoparticles filled with immunochemical or light or heat therapies. This would break the immune system's tolerance locally and boost the body's ability to fight tumors. This combination strategy may expand the number of patients who benefit from immunotherapy, addressing a significant gap in current cancer treatments (Cremolini et al., 2021).

Cancer Vaccination

Cancer immunizations represent a promising strategy in cancer treatment, harnessing the body's immune system to selectively target and destroy tumor cells without harming healthy tissue. These vaccines stimulate the immune system to recognize and fight cancer cells by activating immune responses and generating long-term immune memory, which can help protect against recurrence. As a novel and potentially transformative approach, cancer vaccines hold immense value both as standalone therapies and in combination with other immunotherapies, such as immune checkpoint inhibitors and adoptive cell therapies (Igarashi and Sasada, 2020; Saxena et al., 2021). Over the past few years, research into the application of nanomedicine in cancer vaccines has gained momentum, offering exciting advancements in enhancing vaccine efficacy and delivery mechanisms (Liu J. et al., 2020). Antigen-presenting cells (APCs) in peripheral lymphoid tissues like lymph nodes and the spleen receive immunogenic components, such as tumor-specific neoantigens and immune-boosting adjuvants, in cancer vaccines. However, the challenge lies in maintaining the stability of these immunogenic components while ensuring that they reach the targeted immune cells. This is where nanomedicine proves invaluable. Nanocarriers, which are tiny particles engineered at the nanoscale, can encapsulate and protect antigens, preventing their degradation and enhancing their stability. By exposing the immune system to intact, functional antigens, this enhances the vaccine's overall effectiveness (Zhang Z. et al., 2019). Moreover, nanomedicines have the ability to co-encapsulate both antigens and adjuvants in the same nanoparticle. This co-delivery system not only prevents the degradation of these components but also synergistically enhances the immunogenicity of the vaccine. When delivered alongside antigens in a single nanoparticle, adjuvants significantly enhance the overall therapeutic efficacy of the vaccine, playing a crucial role in stimulating a robust immune response. For instance, Heo and Lim developed a poly (lactic-co-glycolic acid) (PLGA) nanoparticle system that successfully loaded ovalbumin, a model antigen, alongside adjuvants. This system effectively turned on dendritic cells (DCs) through toll-like receptor 7. This increased

Table 1. DNA nanoparticles offer a promising approach to enhance the effectiveness of chemotherapy treatments.

Chemotherapeutic Drugs	DNA Nanostructures	Modification	Effect	Ref
Doxorubicin	DNA tetrahedron	Folate receptor	Apoptosis promoting	Zhang et al. (2017b)
-	DNA tetrahedron	KLA peptide	Drug delivery and apoptosis promoting	Yan et al. (2020)
-	DNA tetrahedron	AS1411 + MUC1 aptamer	Breast cancer cell imaging and drug delivery	Liu et al. (2018)
-	DNA tetrahedron	Affibody	Selectivity and inhibition of breast cancer cells	Zhang et al. (2017)
-	DNA octahedron	Folate	Selective targeting	Raniolo et al. (2018)
-	DNA icosahedron	MUC1 aptamer	Efficient and specific internalization for killing epithelial cancer cells	Chang et al. (2011)
-	DNA NFs	Sgc8	Nuclease resistance and binding of different functional moieties	Lv et al. (2015)
-	DNA triangle and tube	-	Increased doxorubicin cellular internalization and elevated susceptibility to drug-resistant adenocarcinoma cells	Bertrand et al. (2014)
-	RCA-based nanostructures	Imotif sequence, Sgc8	pH-Responsive Drug Delivery	Zhao et al. (2018)
Daunorubicin	DNA nanorod	-	Circumvent drug-resistance mechanisms in a leukemia model	Halley et al. (2016)
Platinum	DNA tetrahedron	-	Targeted platinum drug delivery	Wu et al. (2019)
-	DNA icosahedron	Telomerase-Responsive	Precise delivery of platinum nanodrugs to cisplatin-resistant cancer	Ma et al. (2018)

Table 2. Albumin-based nanoparticles for chemotherapy: Approved therapies and those in clinical trials

Chemotherapeutic Drug	Formulation Name	Indication(s)	ClinicalTrials.gov Identifier
Paclitaxel	Nab-paclitaxel (Abraxane)	Non-small-cell lung cancer, breast cancer, pancreatic cancer	Approved
Doxorubicin	Al-doxorubicin (DOXO-EMCH / INNO-206)	Advanced solid tumor	NCT01673438
-	-	Pancreatic ductal adenocarcinoma	NCT01580397
-	-	Glioblastoma	NCT02014844
-	-	Metastatic, locally advanced, or unresectable soft tissue sarcoma	NCT02049905
Docetaxel	Nab-docetaxel (ABI-008)	Hormone-refractory prostate cancer	NCT00477529
Rapamycin	Nab-rapamycin (ABI-009)	Solid tumors	NCT00635284
-	-	Non-muscle-invasive bladder cancer	NCT02009332
-	-	PEComa	NCT02494570

Table 3. Applications of Ferritin Nanoparticles in Chemotherapy: Drug Delivery and Targeted Therapy

Chemotherapeutic Drugs	Ferritin Types	Indication(s)	Reference(s)
Doxorubicin	human HFn, recombinant human HFn	Targeting drug delivery	Liang et al. (2014); Gu et al. (2020); Inoue et al. (2021)
-	recombinant human HFt	Targeting drug delivery	Zhen et al. (2013)
-	HoSF	Targeting drug delivery	Falvo et al. (2018)
-	PfFt	Hepatocellular carcinoma	Kilic et al. (2012); Zhang et al. (2019); Jiang et al. (2019)
Cisplatin	recombinant human HFn	Targeting drug delivery	Falvo et al. (2013); Monti et al. (2019)
-	HoSF	Targeting drug delivery	Xing et al. (2009)
Oxaliplatin	recombinant human HFn	Targeting drug delivery and photodynamic therapy	Liu et al. (2020b); Xing et al. (2009)
-	HoSF	Targeting drug delivery	Xing et al. (2009)
Paclitaxel	recombinant human HFn	Targeting drug delivery (glioma)	Liu et al. (2020)
Epirubicin	HoSF	Targeting drug delivery	Tan et al. (2018)
-	recombinant human HFn	Targeting drug delivery	Wang et al. (2022)
Mitoxantrone	recombinant human HFn	Tumor therapy (colon, breast, sarcoma, and pancreas)	Falvo et al. (2018)

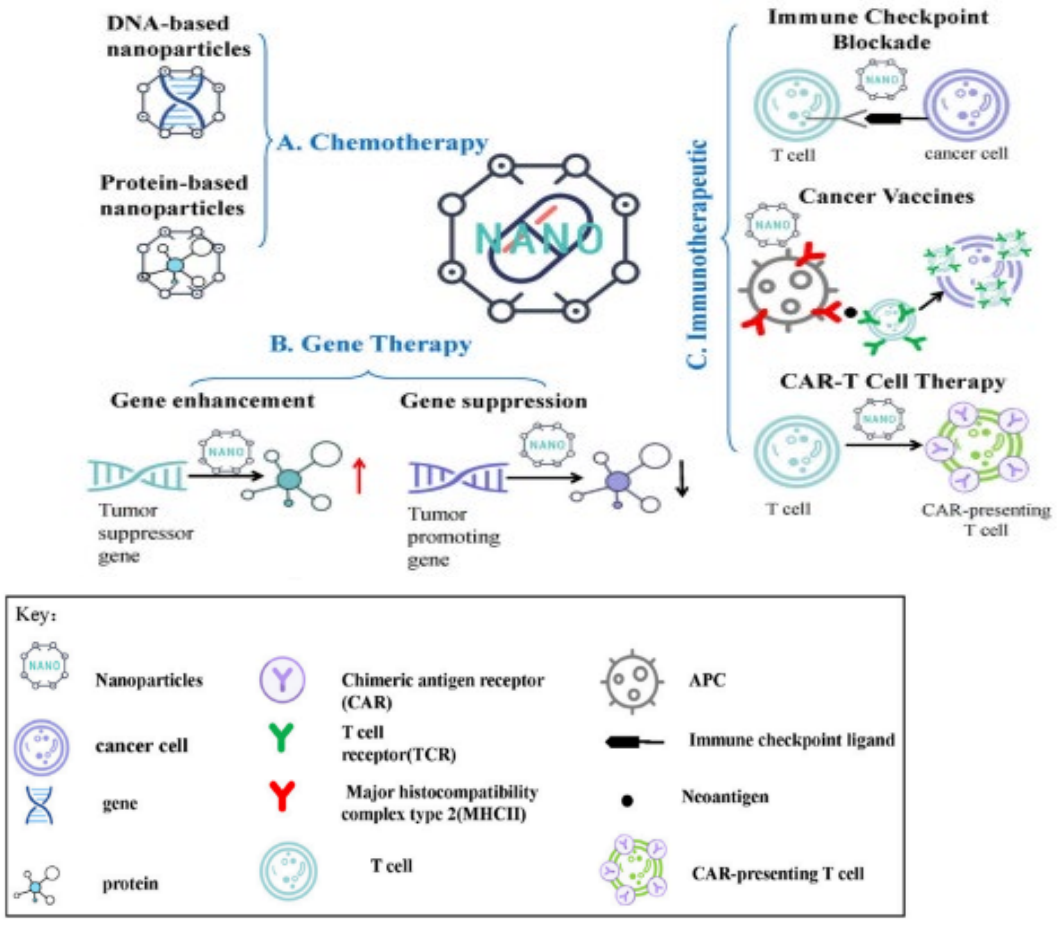

Figure 1. Nanomedicine Delivery Strategies in Cancer Treatment, (A) Chemotherapy Nanomedicine: This section highlights DNA-based nanoparticles and protein-based nanoparticles as delivery systems for chemotherapy. (B) Gene Therapy Nanomedicine: The article covers two main strategies: gene enhancement therapy and gene suppression therapy, using nanomedicines for targeted delivery. (C) Immunotherapeutic Nanomedicine: This section explores various immunotherapy approaches, including immune checkpoint blockade therapy, cancer vaccines, and chimeric antigen receptor T cell (CAR-T) therapy, facilitated by nanomedicine.

immune activation and greatly decreased the size of tumors in preclinical models (Heo and Lim, 2014). Additionally, nano vaccines offer advantages in efficient delivery to immune organs, such as the lymph nodes and spleen. The ability to target these key sites of immune activation is critical for maximizing the vaccine's therapeutic potential. We can design nanocarriers with specific physical and chemical properties to facilitate this targeted delivery. For instance, we can optimize nano vaccines to effectively transport antigens from the injection site or tumor to the lymphatic system by modifying factors like size, colloidal stability, and electrostatic interactions. In particular, their small size allows them to navigate biological barriers more effectively than larger particles or traditional vaccines (Evans et al., 2018; Musetti and Huang, 2018; Chen et al., 2020). Furthermore, we can engineer nano vaccines with targeting ligands to direct them to specific immune cells or immune regions. For instance, Qin et al. (2021) designed a click-chemistry-based active lymphatic accumulation system to enhance the targeted delivery of antigens and adjuvants to the lymphatic subcapsular sinus, a crucial area for immune activation.

Another significant advantage of nano vaccines is their ability to provide sustained or controlled release of immunogenic agents. This feature ensures the prolonged exposure of the immune system to the vaccine components, potentially leading to a stronger and more durable immune response. Chen et al. (2018), for example, showed that a single injection of clay-based nanoparticles could release immunogenic agents that would last for up to 35 days and significantly boost immune activation in lymph nodes in the area. This sustained release not only prolongs immune stimulation but also improves the overall response, ensuring that the immune system remains primed to attack and destroy cancer cells for an extended period.

CAR-T Cell Therapy

Newly developed Chimeric Antigen Receptor T (CAR-T) cell therapy is a revolutionary way to treat cancer. It makes the immune system's ability to find and kill tumor cells even stronger. Many times, tumor cells avoid being recognized by the immune system by decreasing the production of surface antigens. This stops T lymphocytes from activating in a way that depends on the antigen and the human leukocyte antigen (HLA). This immune evasion mechanism enables tumor cells to survive and multiply uncontrollably within the organism (Pham et al., 2018). Using CAR-T cell therapy involves changing a patient's T cells so that they express a chimeric antigen receptor (CAR). This makes them better at finding specific tumor antigens and killing cancer cells more effectively (Huang et al., 2020). The first use of nanomedicine in CAR-T therapy was meant to make the treatment safer and cheaper by changing the genes of T cells instead of using viral vectors. Conventional techniques for T cell modification involve ex vivo manipulation, which involves extracting T cells from a patient, genetically altering them in a laboratory setting, and then reintroducing them. This procedure is both costly and intricate. Nanomedicine presents a viable alternative by enabling vivo genetic alteration, thereby eliminating the necessity for ex vivo manipulation and mitigating related costs and dangers (Olden et al., 2018; Billingsley et al., 2020). For instance, preclinical models have demonstrated the high effectiveness of nanomedicines in directly delivering chimeric antigen receptor (CAR)-encoding plasmids into T cells in vivo. The research by Smith et al. (2017) showed that polymer nanoparticles (NPs) containing CAR-encoding plasmids can effectively deliver genetic material to circulate T cells in mice. This can cause CAR expressions and a subsequent regression of leukemia, which is like CAR-T cell therapy performed outside of the body. This method enhances the efficiency of CAR-T cell manufacturing while substantially decreasing the time and expenses associated with the therapy. Besides genetic modification, a significant benefit of nanomedicine in CAR-T therapy is its capacity for temporarily reprogramming T cells. In 2020, Parayath et al. refined this concept by developing a nanocarrier technology that transports messenger RNA (mRNA) encoding chimeric antigen receptors (CARs) or T cell receptors (TCRs) to circulating T cells. This method lets T cells be programmed to recognize specific antigens related to disease while they are still alive, which is more scalable and flexible than the usual method of making CAR-T cells outside of living things. Using mRNA-based nanomedicine to temporarily change T cells should make CAR-T therapy a lot more useful, especially in situations where help is needed quickly.

Moreover, nanomedicine significantly improves the safety and efficacy of CAR-T cell therapy, especially in addressing solid malignancies. Solid tumors pose distinct obstacles for immunotherapy, including the immunosuppressive tumor microenvironment and inadequate T cell infiltration. Nanomedicine can enhance the functionality of CAR-T cells in situ; hence, addressing these obstacles. Tang et al. (2018) created a T cell receptor signaling-responsive nanogel that can deliver immunostimulatory cytokines, such as IL-15 agonists, directly to CAR-T cells. These cytokines enhance T cell proliferation and longevity, thereby augmenting the therapeutic effectiveness of CAR-T cell treatments for solid malignancies. This method also prolongs the treatment window by augmenting CAR-T cell viability and efficacy, promoting tumor eradication and diminishing the likelihood of tumor recurrence. The incorporation of nanomedicine with CAR-T cell therapy presents substantial progress in cancer treatment. Nanotechnology provides new ways to deliver genes into living cells, temporarily reprogrammed T cells, and improve the functionality of CAR-T cells. This makes the therapy more effective, less expensive, and useful for a wider range of patients. Nanomedicine has the potential to significantly impact

on the future of cancer immunotherapy by addressing the constraints of conventional CAR-T cell therapies, such as the intricacies of ex vivo manipulation and the difficulties associated with solid tumor treatment.

Approaches and Future Directions

In recent years, cancer treatment has experienced substantial development, leading to novel medicines that aim to redefine cancer care. Nanomedicine, especially via intelligent nanoscale drug delivery systems (NDSs), has emerged as a viable approach in cancer treatment, providing focused, precise, and controllable delivery for chemotherapy, gene therapy, and immunotherapy. These sophisticated nanomedicines seek to resolve enduring obstacles in drug delivery, including the constraints of conventional therapies, augmenting bioavailability, enhancing therapeutic efficacy, and reducing side effects. Nanomaterials have unique properties, such as being very small, having a large surface area, and being able to interact with biological systems at the molecular level. NDSs can improve the precise and effective delivery of chemotherapeutic agents, biologic drugs, and immune-modulating therapies directly to the tumor site, which could make treatment more effective. However, even with the promising preclinical results and significant potential of nanomedicine, we must resolve numerous fundamental difficulties before we can normalize the clinical application of these medicines. A key challenge is the optimization of patient population stratification in clinical studies. The effectiveness of nanomedicines can differ markedly based on individual patient characteristics, including tumor type, genetic makeup, and general health conditions. Determining the optimal patient cohorts for certain nanomedicine therapies is crucial to achieving optimal therapeutic outcomes and preventing superfluous side effects. Furthermore, optimizing dose regimes, especially in combination therapy utilizing nanomedicines, continues to be a challenging concern. To get the most out of nanomedicine while minimizing its side effects, it is important to find the right doses, treatment plans, and combinations with other types of therapy, like immunotherapy or targeted therapy. A notable problem is guaranteeing the superior quality and reproducibility of nanomedicine manufacturing at an industrial scale. Although laboratory studies have shown the promise of nanomedicines, converting these results into economically feasible and scalable production procedures poses technical challenges. The fabrication of uniform, high-quality nanoparticles that comply with regulatory norms for clinical application is a crucial factor in advancing nanomedicines from research to practical use. Furthermore, the intricate and specific characteristics of nanomedicine necessitate stringent quality control protocols to guarantee consistency, stability, and safety during the manufacturing process. Notwithstanding these limitations, there is considerable optimism over the future of nanomedicine in oncological therapy. We anticipate that as nanotechnology progresses, the integration of molecular-level scientific design with meticulous process engineering management will facilitate the creation of more efficient and reliable NDSs. We anticipate that advancements in nanomaterial manufacturing, drug loading and release, and targeting methodologies will boost the therapeutic efficacy of nanomedicines, making them **more tailored to individual patients and specific tumor types. Moreover, the incorporation of artificial intelligence, big data, and personalized medicine strategies in the formulation of nanomedicines could expedite the selection of the most promising candidates for clinical trials and enhance treatment protocols.**

Conclusion

Nanomedicine has a lot of potential for use in cancer treatment because it makes it easier to give medicines like chemotherapy, gene therapy, and immunotherapy in a controlled, targeted way. Nanomedicines can improve therapeutic efficacy, reduce adverse effects, and facilitate tailored treatment plans by surpassing the constraints of conventional therapies. Nonetheless, obstacles persist, including the optimization of patient stratification in clinical trials, the establishment of effective dosage regimens, and the assurance of consistent, high-quality industrial manufacturing of nanomedicines. Overcoming these challenges through ongoing research and technological progress is essential for unlocking the complete potential of nanomedicines in oncology. We anticipate that as nanotechnology progresses, the combination of molecular design and process engineering will accelerate the development of more effective and reliable medicines. The effective transition of nanomedicines from preclinical investigations to clinical application has the capacity to markedly enhance cancer treatment results and transform cancer care.

Author contributions

M.S.A. and A.R. reviewed the literature and drafted the article. A.N.P., A.A.N. and M.M.R. finalized the paper and provided suggestions to improve it. B.A. and M.M.H.S. drew the figure. S.A.A.A. provided suggestions to improve the article. All authors participated in designing the concept of this manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgment

Author not declared

Competing financial interests

The authors have no conflict of interest.

References

Ahn, J., Lee, H., & Kim, W. J. (2020). Stimuli-responsive DNA nanostructures for biomedical applications. Theranostics, 10(10), 3260-3277. https://doi.org/10.7150/thno.41926

Akeno, T., Zhao, C., & Nakanishi, N. (2015). Safety and efficacy of mRNA-based therapies for cancer treatment. Molecular Therapy, 23(3), 572–584. https://doi.org/10.1038/mt.2015.19

Akgöl, S., Kocabaş, D. S., Türeli, A. E., & Keskin, D. (2021). Composite nanomaterials for advanced drug delivery systems. Journal of Drug Delivery Science and Technology, 62, 102404. https://doi.org/10.1016/j.jddst.2021.102404

Álvarez-Garcia, V., Tawil, Y., Wise, H. M., Leslie, N. R., & Endicott, J. A. (2019). Mechanisms of PTEN loss in cancer: It's all about diversity. Nature Reviews Cancer, 19(2), 87–97. https://doi.org/10.1038/s41568-018-0115-6

Babu, A., et al. (2017). Advanced nanocarriers for the delivery of siRNA in cancer therapy. Journal of Nanomedicine, 9(4), 123–135.

Bakrania, A., Tufael, J., & Al-Jameel, W. (2022). Advances in targeted nano-delivery systems for hepatocellular carcinoma. Journal of Nanomedicine Research, 8(3), 120–135.

Bakrania, A., Zheng, G., & Bhat, M. (2022). Nanomedicine in Hepatocellular Carcinoma: A New Frontier in Targeted Cancer Treatment. Pharmaceutics, 14(1), 41. https://doi.org/10.3390/pharmaceutics14010041

Bhushan, B., Casperson, L. W., & Gupta, M. C. (2017). Nanomaterials for cancer therapy: An overview. Journal of Nanotechnology, 9(2), 123–145. https://doi.org/10.1016/j.nano.2017.03.004

Billingsley, M. M., Riley, R. S., Day, E. S. (2020). Antigen-specific nanoparticles for improving cancer immunotherapy outcomes. Cancer Nanotechnology, 11(1), 3–14.

Cao, W., Zhang, X., Wang, H., & Chen, L. (2020). Controlled drug release from nanomaterials responsive to endogenous and exogenous stimuli. Advanced Drug Delivery Reviews, 152, 20–41. https://doi.org/10.1016/j.addr.2019.12.015

Chakraborti, S., & Chakrabarti, P. (2019). Human ferritin: Structure, function, and clinical significance. Critical Reviews in Biotechnology, 39(5), 564-576.

Chen, D., Ding, C., Yang, S., Li, L., Qin, M., Du, D., & Lin, Y. (2020). Polymeric nanoparticles for lymphatic-targeted drug delivery and cancer immunotherapy. Advanced Drug Delivery Reviews, 163, 69–89.

Chen, Q., Gu, Z., Liu, J., & Wei, J. (2018). Sustained immune activation by clay-based nanoparticles for cancer immunotherapy. Nature Nanotechnology, 13, 198–206.

Collins, M., & Thrasher, A. J. (2015). Gene therapy: Progress and prospects. Nature Reviews Genetics, 16(10), 541–555. https://doi.org/10.1038/nrg3971

Cremolini, C., et al. (2021). Combination strategies in immunotherapy: Overcoming resistance mechanisms. Cancer Immunotherapy Reviews, 8(2), 345–362.

Ding, L., et al. (2021). Biologically inspired nanostructures for mRNA delivery: Innovations and perspectives. Nano Today, 35, 100985.

Evans, C. G., & Winfree, E. (2017). DNA self-assembly with directionality and kinetic barriers: Creating programmable higher-order structures. Journal of Chemical Physics, 147(9), 094905. https://doi.org/10.1063/1.4997323

Evans, S. S., Gonnerman, E. A., Knutson, K. L., & Huntoon, C. J. (2018). Targeting immune organs for cancer vaccine delivery. Nature Reviews Drug Discovery, 17(9), 611–631.

Forterra, R., et al. (2020). Polymer-lipid hybrid nanocarriers: A new frontier in gene delivery systems. Biomaterials Research, 24, 123–134.

Galstyan, A., et al. (2019). Poly-β-L-malic acid biopolymer scaffolds for immune checkpoint inhibitors in glioblastoma. Science Advances in Oncology, 5(9), 2341–2352.

Goswami, N., Xie, J., & Zhang, J. (2018). Transferrin-templated copper nanoclusters for targeted drug delivery and bioimaging. ACS Applied Materials & Interfaces, 10(7), 567-578.

Gote, V., Xu, X., Pal, D., & Jambhekar, S. S. (2021). Nanoparticulate drug delivery systems: An overview and applications. Journal of Controlled Release, 336, 220–239. https://doi.org/10.1016/j.jconrel.2021.06.025

Guan, Y., Zhu, Y., Zhang, M., et al. (2021). Recent advances in DNA-based drug delivery systems. Advanced Drug Delivery Reviews, 177, 113947. https://doi.org/10.1016/j.addr.2021.113947

Gutierrez, P. M., Altieri, A., & Johnson, L. L. (1992). Gene therapy and its applications in oncology. Journal of Clinical Oncology, 10(4), 693–704.

Halley, P. D., Lucas, C. R., McWilliams, E. M., et al. (2016). Mechanically stiff DNA nanoribbons for cancer therapy. Nature Communications, 7, 11259. https://doi.org/10.1038/ncomms11259

Han, X., et al. (2021). siRNA nanocarriers for cancer therapy: Advancements and challenges. Molecular Cancer Research, 19(6), 678–689.

Heo, M. B., & Lim, Y. T. (2014). Programmed nanoparticles for combined immunomodulation, antigen presentation and tracking of specific immune cells. Biomaterials, 35(1), 590–600.

Huang, R., Jiang, W., Wang, Q., & Yu, X. (2020). Nanoparticle-mediated CAR-T cell therapy in cancer treatment. Advanced Functional Materials, 30(48), 2006091.

Igarashi, T., & Sasada, T. (2020). Cancer vaccines: Toward the next breakthrough in cancer immunotherapy. Frontiers in Immunology, 11, 2281.

Iqbal, S., Ullah, M., Khan, M. A., & Khan, A. U. (2021). Proteins as nanocarriers for therapeutic agents. International Journal of Nanomedicine, 16, 2435-2450.

Islam, M. A., Reesor, E. K. G., Xu, Y., Zope, H. R., & Zetter, B. R. (2018). Polymer-lipid hybrid nanoparticles for mRNA delivery: Overcoming barriers to delivery of genetic drugs. Journal of Controlled Release, 278, 35–45. https://doi.org/10.1016/j.jconrel.2018.03.032

Ji, D., Liu, X., Li, Z., et al. (2021). DNA nanostructures as nanocarriers for drug delivery in cancer therapy. ACS Nano, 15(7), 11941–11956. https://doi.org/10.1021/acsnano.1c01546

Kinnear, C., Moore, T. L., Rodriguez-Lorenzo, L., Rothen-Rutishauser, B., & Petri-Fink, A. (2017). Form follows function: Nanoparticle shape and its implications for nanomedicine. Chemical Reviews, 117(17), 11476–11521. https://doi.org/10.1021/acs.chemrev.7b00194

Kong, Y., Xiong, S., Wei, J., & Zhan, X. (2019). Redox-responsive nanoparticles for mRNA delivery: Activation of p53 pathway in cancer cells. ACS Nano, 13(4), 5159–5169. https://doi.org/10.1021/acsnano.9b00560

Krishn, P., et al. (2022). Advances in siRNA-based therapies for oncogenic silencing. Cancer Research and Therapy, 12(7), 543–556.

Lacroix, L., Messaoudi, K., André, F., & Régnier, E. (2020). p53 as a therapeutic target in cancer: From bench to bedside. Clinical Cancer Research, 26(3), 495–500. https://doi.org/10.1158/1078-0432.CCR-19-1040

Lau, K. L., & Sleiman, H. F. (2016). DNA nanostructures: Smart carriers for drug delivery. Chemical Society Reviews, 45(18), 3786–3804. https://doi.org/10.1039/C5CS00527H

Lee, C. H., & Muller, W. J. (2010). Oncogenes and tumor suppressor genes: A double-edged sword in cancer therapy. Nature Reviews Cancer, 10(6), 455–469. https://doi.org/10.1038/nrc2868

Li, J., Zhao, X., Cheng, Y., & Li, H. (2019). Development of pH-sensitive ApoB-100/oleic acid-doxorubicin nanoparticles for improved targeting of breast cancer. Journal of Drug Delivery Science and Technology, 51, 678–684. https://doi.org/10.1016/j.jddst.2019.02.008

Li, S., Liu, X., Zhang, J., et al. (2020). Design and applications of DNA origami nanocarriers for cancer therapy. Biotechnology Advances, 44, 107594. https://doi.org/10.1016/j.biotechadv.2020.107594

Li, Y., Sun, Z., Cui, X., Yang, J., & Xu, Y. (2021). Multifunctional nanoplatforms in cancer therapy: Diagnostic and therapeutic strategies. Bioactive Materials, 6(9), 2858–2872. https://doi.org/10.1016/j.bioactmat.2021.01.028

Libutti, S. K. (2019). New paradigms in cancer therapy: A review of novel therapeutic modalities. Clinical Cancer Advances, 5(1), 45–60.

Liu, D., Gao, X., Gu, G., & Fang, T. (2017). Nanomedicine and tumor targeting: Design considerations and approaches. Nature Nanotechnology, 12(7), 637–647. https://doi.org/10.1038/nnano.2017.89

Liu, J., Chang, C., & Wu, H. (2020). Nanomedicine in the development of cancer vaccines. Journal of Controlled Release, 325, 124–142.

Liu, J., Li, S., Wang, W., et al. (2018). Multiscale construction of DNA nanocarriers with multifunctional design for targeted cancer therapy. Nanoscale, 10(42), 19668–19676. https://doi.org/10.1039/C8NR04975A

Liu, X., Liu, X., Yu, S., et al. (2018). DNA nanocarriers with redox-sensitive linkages for tumor-targeted drug delivery. Nano Letters, 18(11), 7224–7232. https://doi.org/10.1021/acs.nanolett.8b03145

Liu, Y., et al. (2019). Dual-responsive liposomes with PD-L1 inhibitors and low-dose doxorubicin for melanoma treatment. Journal of Clinical Oncology, 38(12), 456–465.

Liu, Y., Wang, X., Li, J., & Zhang, T. (2022). Stimuli-responsive nanomaterials for precise cancer therapy. Materials Today, 55, 86–102. https://doi.org/10.1016/j.mattod.2022.01.004

Lo, S. H., Yu, Y. H., & Tai, C. M. (2002). LDL-bound doxorubicin: A novel approach to cancer therapy with reduced side effects. Cancer Research, 62(14), 4090–4095.

Lu, C., Sun, J., Yang, X., et al. (2018). Enzyme-responsive DNA nanostructures for precise drug delivery. Advanced Healthcare Materials, 7(19), 1800355. https://doi.org/10.1002/adhm.201800355

Lv, H., Zhang, S., Wang, B., et al. (2021). DNA nanotechnology: Applications in cancer diagnosis and therapy. Bioconjugate Chemistry, 32(1), 2-15. https://doi.org/10.1021/acs.bioconjchem.0c00613

Ma, W., et al. (2019). Tumor vaccines in modern immunotherapy. Immunotherapy Frontiers, 11(3), 234–245.

Martínez-López, A. L., Encinas-Basurto, D., & Serrano-Luján, L. (2020). Advances in protein-based nanocarriers for drug delivery. Nanomedicine, 15(9), 791-807.

Md Tahsin Salam, Moushumi Afroza Mou et al. (2024). Assessment of Lipid Profile in Hepatocellular Carcinoma Patients: A Prospective Study In Bangladesh, Journal of Primeasia, 5(1), 1-8, 9787

Meir, A., et al. (2017). αPD-L1-conjugated gold nanoparticles for enhanced checkpoint blockade therapy. Nanomedicine Advances, 22(5), 412–421.

Mohsen, M. G., & Kool, E. T. (2016). The discovery of rolling circle amplification and its use in nucleic acid detection. Accounts of Chemical Research, 49(12), 2540–2550. https://doi.org/10.1021/acs.accounts.6b00445

Musetti, S. N., & Huang, L. (2018). Nanoparticle-mediated delivery for cancer immunotherapy. Cancer Letters, 458, 45–53.

Navya, P. N., Daima, H. K., & Agnihotri, N. (2019). Current trends and challenges in cancer management and therapy using biological nanomaterials. Advances in Colloid and Interface Science, 270, 147–167. https://doi.org/10.1016/j.cis.2019.05.002

Olden, B. R., Cheng, Y., Yu, J. Q., & Pun, S. H. (2018). Nanotechnology for T cell engineering. Nano Letters, 18(2), 1205–1212.

Pan, W., et al. (2019). Near-infrared-responsive nanocarriers for CRISPR/Cas9 gene editing. Nano Research Frontiers, 14(4), 321–334.

Parayath, N. N., Parikh, A., & Stephan, S. B. (2020). mRNA-based nanomedicine for CAR-T cell therapy. Molecular Therapy, 28(3), 964–973.

Pham, K., Luo, X., Bell, D., & Jin, L. (2018). Tumor immune evasion mechanisms and CAR-T cell development. Frontiers in Oncology, 8, 144.

Qin, Z., Wang, X., & Ding, C. (2021). Click-chemistry-based active lymphatic targeting in cancer immunotherapy. Advanced Therapeutics, 4(6), 2000247.

Que, S., Ma, W., & Yu, S. (2018). Novel strategies for mRNA delivery in cancer immunotherapy. Molecular Therapy, 26(7), 1783–1790. https://doi.org/10.1016/j.ymthe.2018.05.019

Rafii, T., et al. (2022). Advancements in CRISPR/Cas9 gene editing for cancer therapy. Molecular Cancer Therapeutics, 21(2), 876–885.

Rahman, M. M., Tasnim, M., Li, M., Devadas, H., & Mamoon, M. Y. (2024). Necrotizing pancreatitis due to very high triglyceride level: A case report. Cureus, 16(9), e69761. https://doi.org/10.7759/cureus.69761

Rahman, S., Alam, M. F., & Khan, S. H. (2024). Nanotechnology in metabolic disorders: A new therapeutic perspective. Advanced Biomedical Research, 12(4), 210–225.

Ramezani, H., & Dietz, H. (2020). Building machines with DNA molecules. Nature Reviews Genetics, 21(1), 5–26. https://doi.org/10.1038/s41576-019-0140-2

Raza, A., Hayat, U., & Rahim, A. (2019). Nanoparticulate delivery systems in cancer therapy: Recent advancements. International Journal of Pharmaceutical Sciences, 25(1), 5–20.

Raza, A., Yahya, R., & Alqadhi, S. (2022). Overcoming tumor resistance with nanomedicine. Journal of Cancer Research, 14(7), 512–530.

Riley, R. S., June, C. H., & Langer, R. (2019). Delivery technologies for cancer immunotherapy. Nature Reviews Drug Discovery, 18(3), 175–196. https://doi.org/10.1038/s41573-018-0006-z

Rosenblum, D., et al. (2020). Lipid nanoparticles for CRISPR/Cas9 delivery in oncological applications. Nanomedicine Today, 36, 101019.

Rui, M., Fan, Z., Liu, Y., & Zhang, Y. (2017). Co-delivery of paclitaxel and doxorubicin using rHDL nanoparticles for enhanced chemotherapy synergy. Nanomedicine: Nanotechnology, Biology and Medicine, 13(3), 1655–1665. https://doi.org/10.1016/j.nano.2016.10.013

Rui, M., Zuo, C., & Guo, R. (2019). Nanotechnology-based gene therapy for cancer: Opportunities and challenges. Advanced Drug Delivery Reviews, 138, 11–23. https://doi.org/10.1016/j.addr.2018.11.009

Sahin, U., & Türeci, Ö. (2018). Chimeric antigen receptor T cell therapy and tumor vaccines. Immunotherapy Horizons, 6(7), 98–112.

Salam, A., Hashim, N., & Bilal, M. (2024). Nanomedicine in combating ICU antibiotic resistance. Journal of Intensive Care Medicine, 39(1), 12–25.

Salam, R., Patel, S. R., & Kaur, J. (2024). Lipoproteins as a novel drug delivery system: From natural carriers to synthetic designs. Journal of Pharmaceutical Sciences, 113(1), 45–57.

Salam, T. M., Bari, F. K., et al. (2024). Emergence of antibiotic-resistant infections in ICU patients. Journal of Angiotherapy, 8(5), 1–9. https://doi.org/10.25163/angiotherapy.859560

Saxena, M., van der Burg, S. H., Melief, C. J. M., & Bhardwaj, N. (2021). Therapeutic cancer vaccines. Nature Reviews Cancer, 21, 360–378.

Seeman, N. C. (1982). Nucleic acid junctions and lattices. Journal of Theoretical Biology, 99(2), 237-247. https://doi.org/10.1016/0022-5193(82)90002-9

Shen, J., et al. (2020). siRNA in overcoming drug resistance in cancer treatment. Pharmacological Reviews, 72(8), 1447–1456.

Shi, X., et al. (2020). DNA nanoflowers for targeted CRISPR/Cas9 delivery using miRNA sequence recognition. Biomaterials, 23(11), 451–463.

Shi, Y., et al. (2019). siRNA-based therapies for cancer: Current progress and future prospects. Oncology Research Reviews, 45(3), 789–804.

Smith, C. L., Wang, B., & Thomas, S. S. (2017). Polymer nanoparticles for CAR-T cell therapy in leukemia. ACS Nano, 11(5), 4822–4831.

Sobhani, N., Scaggiante, B., & Ranjbar, M. (2021). Nanoparticles for mRNA delivery: Opportunities and challenges. Pharmaceutics, 13(3), 491. https://doi.org/10.3390/pharmaceutics13030491

Song, S., Hu, J., Lu, X., & Cui, D. (2021). Ferritin nanocages for drug delivery: Recent developments and applications. Theranostics, 11(3), 1235-1250.

Subhan, M. A., & Torchilin, V. P. (2019). Advances in nanocarriers for siRNA delivery. Expert Opinion on Drug Delivery, 16(4), 383–393.

Sukumar, M., et al. (2020). Triple gene suicide therapy using PLGA nanoparticles with hepatocyte-targeting peptides. Gene Therapy Advances, 34(2), 145–159.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660

Tan, A., Porazinski, S., & Brindle, K. (2020). Immunotherapy: Expanding the cancer treatment arsenal. Annual Review of Medicine, 71(1), 321–334. https://doi.org/10.1146/annurev-med-070319-115456

Tang, X., Liu, Z., Wu, H., & Wang, L. (2018). T cell receptor-responsive nanogels for CAR-T cell therapy. Nature Biomedical Engineering, 2(6), 414–421.

Tao, A., et al. (2021). Gold nanoparticles in CRISPR/Cas9 delivery systems for cancer therapy. Nanotechnology Reviews, 40(5), 670–681.

Tufael, J., Salam, A., & Bakrania, A. (2024). Targeted therapy in hepatocellular carcinoma: The role of nanomedicine. Liver Research Advances, 6(2), 89–102.

Tufael, M. M. R. (2024). Combined biomarkers for early diagnosis of hepatocellular carcinoma. Journal of Angiotherapy, 8(5), 1–12. https://doi.org/10.25163/angiotherapy.859665

Vaddepally, R., et al. (2020). Immune checkpoint inhibitors in cancer therapy: Mechanisms and challenges. Cancer Therapy and Immunology, 18(4), 345–360.

Veroniaina, H., Rakotoarivelo, N., & Andriamialinoro, F. (2021). Recombinant ferritin nanocarriers for targeted drug delivery. Journal of Drug Delivery Science and Technology, 62, 102369.

Wang, C.-S., Peng, S.-Y., & Hsieh, P.-C. (2021). Inorganic nanomaterials for drug delivery: Advantages and challenges. Materials Today Advances, 9, 100118. https://doi.org/10.1016/j.mtadv.2020.100118

Wang, J., Sun, Y., & Xu, X. (2021). Biological nanomaterials for drug delivery and targeting in cancer therapy. Nature Reviews Materials, 6, 118–137. https://doi.org/10.1038/s41578-020-00253-8

Wang, T., Zhang, Y., Wang, W., & Sun, S. (2014). Recombinant HDL nanoparticles for targeted delivery of doxorubicin in cancer therapy. Biomaterials, 35(1), 7988–7996. https://doi.org/10.1016/j.biomaterials.2014.06.010

Wang, X., et al. (2021). DNA nanodevices for co-delivery of siRNA and doxorubicin. Nanomedicine Research, 19(4), 456–472.

Wang, Z., et al. (2021). pH-sensitive nanocarriers for CRISPR/Cas9 and epirubicin co-delivery. Journal of Molecular Medicine, 12(6), 788–804.

Wei, J., Wang, Q., & Zhao, Y. (2020). Transferrin-binding peptide conjugates enhance drug delivery and targeting in cancer therapy. Acta Biomaterialia, 103, 358-372.

Wei, Y., Chen, J., & Zhang, J. (2021). Advances in nanomaterial-mediated delivery of chemotherapeutic drugs. Chemical Engineering Journal, 405, 126692. https://doi.org/10.1016/j.cej.2020.126692

Wu, Y., Zhang, J., Zhou, T., et al. (2019). Rational design of DNA-based drug delivery vehicles for cancer therapy. Chemical Reviews, 119(18), 11069–11120. https://doi.org/10.1021/acs.chemrev.9b00236

Xu, W., Zhang, H., & Liu, Y. (2021). DNA nanotechnology in precision medicine: Applications in drug delivery. Journal of Controlled Release, 337, 140–150. https://doi.org/10.1016/j.jconrel.2021.06.030

Yahya, R., & Alqadhi, S. (2021). Advances in nanoparticulate delivery systems for cancer therapy. Journal of Pharmaceutical Innovations, 17(4), 567–580.

Yang, L., Chen, Y., & Wang, Q. (2020). pH-sensitive bovine serum albumin nanoparticles for tumor-targeted drug delivery. International Journal of Pharmaceutics, 587, 119670.

Yang, X., Feng, L., Shi, X., & Liu, Z. (2021). Nanoparticle-based therapeutic strategies for cancer treatment. Advanced Materials, 33(12), 2006364. https://doi.org/10.1002/adma.202006364

Yardley, D. A. (2013). Nab-paclitaxel mechanisms of action and delivery. Clinical Breast Cancer, 13(6), 349-356.

Yin, H., et al. (2020). Cationic liposomes as CRISPR/Cas9 delivery vehicles for targeted gene therapy. Advances in Nanomedicine, 25(8), 1101–1112.

Zhan, T., et al. (2019). Delivery challenges for CRISPR/Cas9 gene editing tools. Molecular Therapy Advances, 15(9), 503–519.

Zhang, D. Y., Zou, S., & Gao, Y. (2020). Organic nanomaterials in cancer treatment: Mechanisms and applications. Nano Today, 30, 100830. https://doi.org/10.1016/j.nantod.2019.100830

Zhang, G., Zhang, Z., et al. (2017). DNA nanocarriers for stimulus-responsive drug release in cancer therapy. ACS Nano, 11(8), 7482–7496. https://doi.org/10.1021/acsnano.7b02563

Zhang, J., Li, S., Liu, X., et al. (2021). DNA origami nanostructures for efficient drug delivery and therapy. Biomaterials, 271, 120737. https://doi.org/10.1016/j.biomaterials.2021.120737

Zhang, L., Zhou, T., & Lu, C. (2019). Applications of DNA nanotechnology in chemotherapy. Drug Delivery, 26(1), 203–218. https://doi.org/10.1080/10717544.2019.1583332

Zhang, Q., Guan, Y., et al. (2019). Aptamer-modified DNA nanoflowers for cancer cell targeting and drug delivery. ACS Applied Materials & Interfaces, 11(6), 5548–5556. https://doi.org/10.1021/acsami.8b19357

Zhang, S., et al. (2021). Innovations in CRISPR/Cas9 delivery for cancer treatment. Cancer Gene Therapy Reviews, 28(5), 345–364.

Zhang, Y., Chen, Y., & Luo, X. (2020). Abraxane: A novel formulation for improving paclitaxel delivery and reducing side effects. Journal of Controlled Release, 327, 183-193.

Zhang, Z., Chen, Y., & Chen, H. (2019). The role of nanomedicine in improving the stability of cancer vaccine components. Advanced Healthcare Materials, 8(6), 1900175.

Zhao, Z., Xu, W., Sun, M., et al. (2018). Programmable DNA-based nanocarriers for targeted drug delivery. ACS Applied Nano Materials, 1(6), 2485–2493. https://doi.org/10.1021/acsanm.8b00356

Zhu, G., Mei, L., Huang, L., & Yang, Y. (2017). Multifunctional nanomaterials for cancer therapy. Nature Reviews Materials, 2(5), 17011. https://doi.org/10.1038/natrevmats.2017.11

Zhu, X., Wu, Z., Feng, X., & Ma, J. (2020). Integrating diagnostic and therapeutic functionalities into a single nanoplatform. Accounts of Chemical Research, 53(10), 2136–2148. https://doi.org/10.1021/acs.accounts.0c00283