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Review Article

Applications Of Nanotechnology In Cancer Therapy

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ABSTRACT

Despite significant advancements in technology and medicine, cancer still claims te ns of millions of lives annually [1,2]. Years of research have consistently shown how dynamic the disease is, and despite better treatment options, there are still serious side effects from strong chemotherapies [3, 4]. Patients suffer when more severe therapy are required, particularly when aggressive tumors lie dormant and subsequently reappear [5-7]. The omnipresent establishment of resistance mechanisms is one of the biggest obstacles to developing an effective cancer treatment. After the primary oncogenic pathways are shut down, resistance mechanisms are triggered in parallel signaling pathways and reroute, enabling the growth of the tumor [8, 9]. The heterogeneity of tumor cells, patient tumors, genetic abnormalities, and epigenetic patterns can all restrict the effectiveness of therapeutic interventions and contribute to the development of drug resistance [10–13]. Clonal heterogeneity influences the biology of the entire tumor and is known to promote cancer growth and metastasis [14]. Although new medications and targets can improve cancer treatments, cancer's adaptive nature finds a way to survive.

INTRODUCTION

Finding new treatments for cancer must give way to enhancing current treatments and diagnostics in creative, efficient, and tenable ways. 66% of individuals with advanced stage cancer and 55% of cancer patients undergoing therapy report feeling pain [15]. Chemotherapies that lack specific targeting mechanisms kill both cancerous and non-cancerous cells, which worsens systemic toxicity and the quality of life of the patient [16,17]. The advantages of early detection are also obvious. Early cancer detection results in significantly improved 5-year survival rates, much lower patient financial burdens, and often less aggressive treatment regimens (Fig.1) [18–20]. Nanotechnology may hold the key to the answer by improving the targeting abilities of current medicines, boosting localized medication efficacy, reducing systemic toxicity, enhancing imaging, and improving radiation therapy [21–24].

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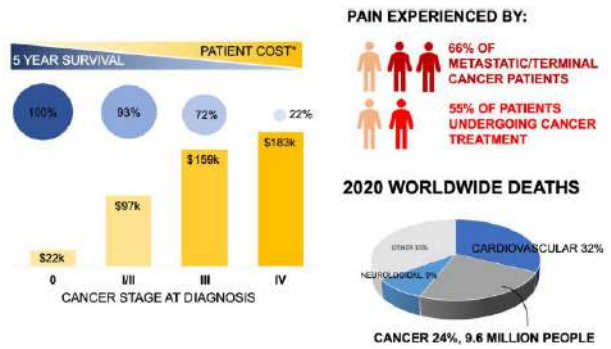

Fig.1: Urgent Need for Innovative Approaches to Improve Cancer Treatment and Diagnostics: Addressing Advanced Stage Diagnoses, Patient Expenses, Pain Management, and Global Impact.

Cancer nanomedicine has been clinically translated for many years, and the number of nano-based treatments and parts for imaging, diagnosis, and radiation therapy has continuously expanded (Table 1) [25, 26]. When used with traditional scanning technologies like magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT), nano-based imaging contrast agents like superparamagnetic iron oxide NPs (SPIONs) and gadolinium (Gd)-based contrast agents improve tumor detection and imaging in vivo [27, 28].

Table 1: Currently available cancer treatments made of nanotechnology

Product name	Compositions	Indications	First approval
ONIVYDE	Liposomal irinotecan	Advanced pancreatic cancer	US (2015)
DHP107	Paclitaxel lipid NPs (oral administration)	Gastric cancer	South Korea (2016)
Vyxeos	Liposomal daunorubicin and cytarabine	High-risk acute myeloid leukemia	US (2017)
Apealea	Paclitaxel micellar	Ovarian, peritoneal, and fallopian tube cancer	Europe (2018)
Hensify	Hafnium oxide NPs	Locally-advanced soft tissue sarcoma	Europe (2019)

By using physical modalities to destroy malignant cells, improving specificity with triggered release, and targeting numerous components with dual-drug loading, nanoformulations can combat resistance mechanisms [29,30]. Due to leaky blood arteries and inadequate lymphatic drainage, nanoscale carriers can pass through a tumor endothelium and passively collect in tumors [31]. Additionally, nanomaterials are used in very sensitive diagnostic tests because of their distinctive physico-chemical properties, which enable the early diagnosis of cancer and improve patient prognosis [32, 33]. Nanomaterials have proven to be particularly useful for biomarker identification in point-of-care liquid biopsies, which are progressively replacing invasive, time-consuming procedures in cancer diagnosis [34–36]. Additionally, certain characteristics allow for a significant advancement in imaging methods used for tumor surveillance and surgical guidance, enabling very precise surgical resection and improved treatment monitoring [37]. By acting as radiosensitizers, nanomaterials can deliver highly targeted radiation doses to tumors while sparing healthy tissue [38]. Nanomaterials' adaptability and functionality provide up a wide range of possibilities for cancer medication therapies, diagnostics, imaging, and radiotherapy. The systemic toxicities associated with conventional approaches can be eliminated, and the prognosis and patient quality of life can be enhanced by early identification, reduced radiation dosage, and increased therapy specificity [39–41].

Fundamentals of Nanotechnology

It is no longer unique to use nanotechnology to enhance therapies; in fact, as the advantages become clearer, nanotechnology research has increased steadily [24, 26]. The majority of cancer

nanomedicines that are currently approved use liposomal formulations and drug conjugates (protein, polymer, and/or antibody) with the goal of enhancing the PK/PD of the free medication and utilizing passive targeting. Numerous clinical research are presently examining the use of nanomaterials in imaging modalities for therapeutic and diagnostic purposes [43, 44]. The enhanced permeation and retention (EPR) effect, where NPs can preferentially concentrate within tumor vasculature, provides the foundation for passive targeting for malignancies [45]. Numerous cancers contain leaky blood arteries with openings that allow NPs to enter the tissue and aggregate there [46]. The EPR effect is not a panacea, either, as passive targeting does not stop drugs from acting in healthy tissues or from having negative effects from systemic dispersion [47]. significantly in the absence of a sick state, there are physiological barriers that prevent NPs from reaching their target, and these barriers can be significantly more challenging to overcome for cancer patients [48]. Blood flow rate, coronas, phagocytic cells, and protein- and lipid-adsorption can all lower stability and delivery capabilities [49–52]. Access to a tumor may also be restricted by extracellular matrices and interstitial pressure [53, 54]. These problems may get more complicated due to variations in cancer types, necessitating formulation optimization for each [55]. Major cancer therapies' pharmacokinetic (PK) characteristics, solubility, bioavailability, and stability have all been significantly enhanced by first-generation nanomedicines [56]. Nanomaterials can expand into new areas to incorporate highly specialized design and function as a result of the increasing accessibility of technology and information. This makes it possible for the subsequent generation of nanomedicine to employ multimodal medicines, radiation, gene therapy, targeted medication release, combination therapies, and specialized targeting. Furthermore, nanotechnology will be a crucial tool for enhancing diagnostics and bioimaging to stop metastasis as scientific breakthroughs clarify cancer genesis and survival pathways.

Optimizing dose coordination for combination therapy can be challenging because to the significant physiological differences between different forms of cancer and between individual patients, as well as the fact that drugs might have widely disparate biodistributive characteristics and relative concentrations [44, 57]. Because complementary actions can take place in a coordinated manner, co-delivery of synergistic medications within a single carrier can significantly boost synergistic potential [30]. Lipid-based, polymeric, inorganic, carbon-based, biomacromolecular, and hydrogel nanomaterials, among others, can effectively manufacture a variety of treatments with radically varied chemical properties [58–61]. Depending on the kinetics and method of action, several medications may be designed to release either concurrently or sequentially, with drug release occurring either by degradation of the carrier, drug desorption, diffusion through the nanoparticle matrix, or by triggered release [62, 63].

To reduce the risk of systemic toxicity, precise targeting employs a nanocarrier or drug combination coupled with certain molecules that have high affinity for malignant cells and decreased affinity for healthy cells [64, 65]. Targeted delivery of a nanocarrier may integrate a greater dosage of medicine and typically have more diversity for targeting modes employing dynamic nanomaterials than antibody drug conjugates, which now improve targeting [66, 67]. For instance, immunoliposomes loaded with doxorubicin (DOX) and embellished with epidermal growth factor (EGF) to target EGFR are currently undergoing clinical studies (ClinicalTrials.gov Identifier: NCT03603379).

For example, somatostatin receptors that are overexpressed in neuroendocrine tumors and only active in the tumor microenvironment (TME) can be targeted specifically using probes for tumor imaging [68].

In order to effectively deliver to the target cells, nanocarriers must be able to prevent the cargo from degrading, accomplish prolonged circulation, avoid reticuloendothelial system absorption, and achieve prolonged circulation [69-71]. As a result, correct ligand selection, carrier material selection, and ligand density selection are necessary for designing the nanoformulation. The specific mode of action also plays a crucial role in optimizing nanoformulation because certain medicines require intracellular delivery while others use cellular membrane diffusion. Targeting TME components alone may be sufficient in some situations to improve therapeutic effectiveness and specificity [72, 73].

Nanotechnology can enhance treatment specificity by stimuli-responsive activation in addition to precise targeting. To prevent off-target effects, medicines are only released under specific chemical, biological, or physical conditions seen in tumor environments or cancer cells [24, 26]. When exposed to external stimuli such radiation, electric and magnetic fields, and hyperthermia, nanocarriers may be programmed to release medications under specified pH, glucose, enzyme, oxidative/reductive, and ion concentration conditions [32, 74–77]. The use of magnetic particles for MRI tumor imaging or theranostic applications is only one example of how these similar modalities might be used for imaging and diagnostic reasons [78, 79]. Recent developments in pH-responsive peptide-based nanoparticles (NPs) that morph into fibrils inside the TME and exhibit potent fluorescence signals and improved photodynamic treatment are described in [80]. Certain nanomaterials' intrinsic features make them perfect for bioimaging, multimodal treatments, and molecular detection for diagnostic purposes [81, 82]. Having excellent stability and less photobleaching than conventional dyes, fluorescent NPs have proven to be successful substitutes [36]. Due to their paramagnetic characteristic and high X-ray attenuation coefficient, Gd-based NPs have demonstrated tremendous utility as MRI and CT contrast agents and as radiosensitizers [83]. Optical and electrical detection, surface plasmon resonance, and fluorescence resonance energy transfer are all possible with gold nanoparticles, making them the perfect material for developing highly selective, adaptable, and sensitive biosensors [84, 85]. Using magnetic NPs functionalized with polyethyleneimine/protein corona or tannic acid in a different study, it was demonstrated that nanomaterials can enable the early identification of circulating tumor cells (CTCs) from peripheral blood [86, 87]. This review gives an overview of the present clinical applications and upcoming technologies (Fig.2), which can significantly improve cancer medicines and diagnostics thanks to the wide variety of uses of nanotechnology.

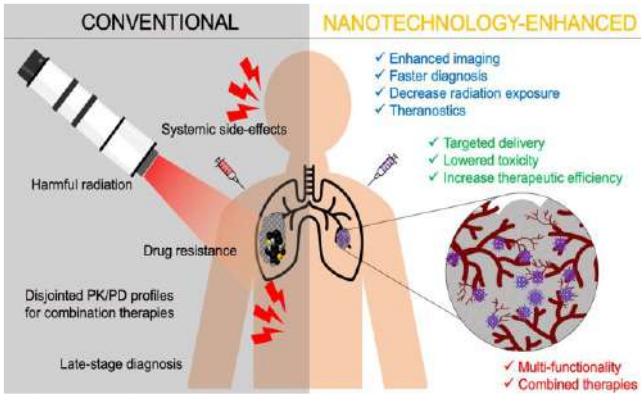

Fig.2: Nanotechnology provides many advantages over conventional treatment.

Utilizing Nanotechnology for Cancer Treatment

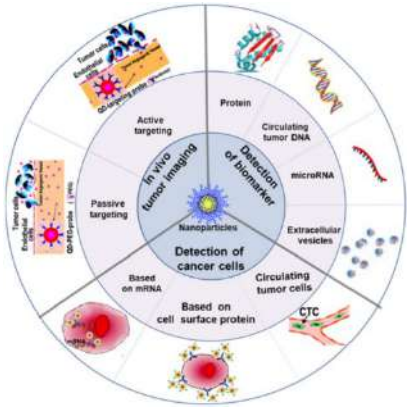

Fig.3: Schematic illustration of nanotechnology applications in cancer diagnosis.

By providing novel methods for the diagnosis, treatment, and monitoring of cancer, nanotechnology has demonstrated enormous potential for changing cancer therapy (Fig.3). Here is a quick rundown of some important applications:

Targeted Drug Delivery: Chemotherapy medications can be delivered specifically to tumor locations using nanoparticles, limiting damage to healthy cells and adverse effects. The therapeutic impact can be improved by engineering these nanoparticles to release the medicine under regulated conditions.

Photothermal Therapy: When exposed to laser light, nanoparticles can specifically kill cancer cells by absorbing light energy and converting it to heat. This method, referred to as photothermal therapy, provides localized treatment with little harm to neighboring tissues.

Hyperthermia: By heating cancer cells to a point where they die, while sparing healthy cells, nanoparticles can treat cancer. The use of hyperthermia improves the efficiency of conventional therapies like chemotherapy and radiation.

Diagnostic Imaging: Magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) all allow the use of nanoparticles as contrast agents. These substances aid in enhancing the perception of tumors and their features.

Early Detection: Nanotechnology makes it possible to create highly sensitive and focused diagnostic tools for the early identification of cancer biomarkers, which may result in earlier intervention and better patient outcomes.

Individualized Medicine: By customizing nanoparticles to each patient based on their particular genetic and molecular profiles, nanotechnology enables the development of individualized treatment strategies. This may result in medications that are more effective and have fewer negative effects.

Theranostics: Therapeutic and diagnostic properties are combined in theranostic nanoparticles. They are capable of simultaneously administering therapeutic chemicals to tumors and giving instantaneous imaging feedback on the treatment's effectiveness.

Gene Delivery: By modifying nanoparticles, it is possible to send genetic material, such as siRNA or tools for gene editing, to cancer cells. Targeting particular genes linked to the development of cancer may be possible using this strategy.

Enhancing Immunotherapy: By improving the transport of immunotherapeutic drugs directly to the tumor microenvironment, such as checkpoint inhibitors or cancer vaccines, nanoparticles can improve the immune system's response to cancer cells.

Biosensors: Nanotechnology-based biosensors can identify chemicals linked to cancer at extremely low concentrations, assisting in early illness identification and disease progression tracking.

Nanoparticle-Mediated Radiotherapy: By preferentially accumulating in tumor cells and raising their radiation sensitivity, nanoparticles can improve the effects of radiation therapy.

Drug Resistance Mitigation: Using numerous therapeutic chemicals that simultaneously target

various pathways within cancer cells, nanotechnology techniques can assist overcome drug resistance.

However, it's vital to keep in mind that many cancer medicines based on nanotechnology are still in the experimental or early clinical stages. To fully grasp their clinical impact, more investigation, experimentation, and improvement are required.

1. Traditional Cancer Treatments

The majority of tumors are still treated first with chemotherapy, and medication development is continually changing and shifting toward cancer-specific targets [88]. Antimetabolites, mitotic inhibitors, topoisomerase inhibitors, alkylating agents, and antibiotics are examples of common chemotherapeutic medications that cause DNA damage and interfere with cellular reproduction, respectively [89]. Traditional chemotherapies are highly effective, yet patients still experience side effects due to their non-specificity. Traditional chemotherapies cause severe side effects for patients and are highly toxic to healthy cells while having little effect on malignant cells [90, 91].

Numerous inhibitors are presently available and in development to target the enzymes involved in the distinct signaling networks known to support and sustain cancer [92, 93]. The bulk of small molecules utilized in targeted therapy now are different inhibitors of tyrosine kinases, cyclin-dependent kinases, poly ADP-ribose polymerases, and proteasomes [94]. The TME contains elements that promote tumor growth and proliferation, including immunological and inflammatory cells, blood and lymphatic endothelial cells, cancer associated fibroblasts (CAFs), and mesenchymal stem cells generated from bone marrow [95–99]. In the PI3K/Akt/mTOR pathways, protein synthesis, glucose metabolism, and another crucial aspect of cell survival are frequently hyperactivated, frequently rerouting signals in response to early therapy [100].

Multiple mutations are frequently discovered here across a wide range of cancer types since the RAS/RAF/MEK/ERK pathway initiates cell proliferation, differentiation, and development [101, 102]. Sotorasib is the first KRAS-targeting medication to get FDA approval, and mutations in RAS proteins are one of the most often detected in human cancers [103, 104]. There are about 14 EGFR-tyrosine kinase inhibitors (TKIs) available on the market and/or in clinical studies, and EGFR mutations also have a role in oncogenesis [105, 106]. Targeting these pathways and variables that contribute to cancer progression has become a priority in the development of new therapeutic therapies, however creating new drugs is expensive and takes more than ten years from conception to FDA clearance [107, 108].

Drug resistance can be selected for by cytotoxic and targeted therapy, making full eradication practically unattainable [109]. Drug resistance can arise as a result of altered drug metabolism, adjustments to efflux/influx, hyperactivated repair mechanisms, rerouting of signal transduction, and altered drug targets [110, 111]. Multiple therapies, combined chemoradiotherapy, and tailored medicine are strategies for overcoming drug resistance [112]. Co-administration of medications with various biological targets can slow the progression of cancer adaptability and assist control cancer cell mutations [113]. New combinatorial treatments are constantly being researched in clinical trials. Effective combinations have been discovered where a medicine can increase or re-introduce sensitivity of the cancer cells to an existing therapy.

However, there are some restrictions for combination therapies because to the complementing medications' fragmented absorption and various PK/PD characteristics, which lowers their efficacy and synergistic impact. These problems can be solved and the therapeutic index raised by co-delivering anti-cancer

treatments within a single nanocarrier [56, 114]. VYXEOS, a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio, was approved by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of people with newly diagnosed acute myeloid leukemia (AML) with myelodysplastic alterations and therapy-related AML [115]. In vitro and in mouse models, it has been demonstrated that the synergistic molar ratio of daunorubicin with cytarabine increases the killing of leukemia cells [116].

2. Currently Used Nanoformulated Medicines are Being Tested in Clinical Trials

Through a variety of methods, nanotechnology offers a special set of tools for overcoming both intrinsic and acquired drug resistance, enabling the application of innovative immunotherapies such mRNA vaccines and targeted therapy [117, 118]. Induced mutagenesis or differential sensitivity are associated with tumor genetic diversity, and both can lead to treatment resistance and protracted disease [119]. Liposomes, polymer microspheres, protein conjugates, and polymer conjugates are only a few of the nanoformulations for cancer therapies currently being used in clinical settings. Novel nanomaterials are also being studied for better medication efficacy and targeting [118]. The best cancer treatment, as said, is targeted delivery because it considerably reduces the side effects of non-specific activity.

2.1 Formulations for Improved PK and Targeted Recruitment

Because of their simplicity in production and drug loading, ability to modify their surface, and utilization of biocompatible components, liposomes are a particularly desirable class of nanomaterial for drug delivery applications [44, 120, 121]. Vesicles called liposomes have an aqueous interior and a lipid bilayer that is predominantly made of amphipathic phospholipids. The phospholipid polar headgroup, the length and hydrophobicity of the fatty acid tails, other components in the membrane or on the surface, and the type of synthetic or natural lipid can all be used to tailor the liposome's properties [122]. Liposomes are among the most actively researched nanomedicines for the treatment of numerous ailments because of their adaptability and relative simplicity in manufacture.

The FDA initially granted approval to Doxil, a liposomal version of the dangerous drug DOX, in 1995. Another liposomal daunorubicin formulation, DaunoXome®, was authorized a year later to treat advanced HIV-associated Kaposi sarcoma [44]. Vincristine sulfate liposomal sphingomyelin/cholesterol formulation Marqibo®, FDA-approved in 2012, showed improved PK/PD features over vincristine as well as improved concentration in solid tumors. In addition to Depocyt® (Cytarabine/Ara-C), Myocet® (DOX), Mepact® (Mifamurtide), and Onivyde® (Irinotecan) liposomal medicines, there are only seven now available on the market that have received clinical approval for the treatment of cancer. However, it should be mentioned that Depocyt was used on a microscale and has since stopped being used.

Due to its effectiveness against a variety of cancer types, cisplatin is one of the most commonly used chemotherapies. However, it has serious side effects, highlighting the urgent need for specificity and re-formulation [123]. The phospholipase A2-IIA isoenzyme, which is highly expressed in a variety of human solid tumors including prostatic, pancreatic, colorectal, gastric, and breast cancers, selectively hydrolyzes the liposomes in LiPlaCis, the first liposomal formulation with a triggered release mechanism to go through clinical development in oncology [124, 125]. With improved PK characteristics, increased potency, and a higher maximum tolerated dose than cisplatin, LiPlaCis provides a wider therapeutic window (ClinicalTrials.gov Identifier:

NCT01861496). Clinical trial outcomes are much more likely when Drug Response Prediction (DRP®) is used.

2.2 Nanocarriers for Gene Therapy

With the delivery of nucleic acids to express pro-apoptotic proteins, replace mutant genes, down-regulate or silence oncogenic pathways, create anti-cancer cytokines, and/or engage the immune system against cancer, gene therapy is a significant role in the fight against cancer [126]. The efficient delivery of nucleic acids to the target site while preventing degradation is one of the main difficulties in gene delivery. Patisiran (ONPATTRO®), which delivers siRNA against the gene that controls the expression of the transthyretin protein and can lead to hereditary transthyretin amyloidosis, was the first siRNA-delivery liposome to receive FDA approval in 2019. The clinical translation of gene therapy continues to be hampered by the lack of effective and secure delivery mechanisms.

Recombinant viral vectors are preferable than nonviral vectors for delivering genes, but they also have drawbacks such immune response, mass production, gene size restriction, restricted cell tropisms, and lack of surface modifiability without compromising vector integrity [127]. Non-viral vectors can be less effective in transfecting cells than viral vectors despite being less immunogenic, less complex to produce on a wide scale, and synthetically dynamic. While two SARS-CoV-2 vaccines using adenovirus vectors have recently been linked to several cases of thrombotic thrombocytopenia but remain under scientific investigation, it's interesting to note that the Moderna and Pfizer/BioNTech vaccines using lipid-based carriers show higher efficacy and have no association with thrombotic complications [128, 129].

It is still important to continue to create effective and innocuous nanocarriers for nucleic acid-based cancer therapeutics, and several are now being investigated in clinical studies. Numerous human malignancies overexpress the protein polo-like kinase 1 (PLK1), and siRNA can be used to silence PLK1 by causing mitotic arrest and death when PLK1 is inhibited. A high transition temperature phospholipid, a PEGylated lipid, and an ionizable cationic phospholipid make up stable nucleic acid lipid particles (SNALPs) [130]. High encapsulation efficiency is the end product, and nucleic acid encapsulation neutralizes the net surface charge to produce more stable vesicles than traditional cationic liposomes. Patients with primary or secondary liver cancer (ClinicalTrials.gov Identifier: NCT01437007) are currently being examined for using the SNALP formulation TKM-080301, which contains siRNA against the PLK1 gene.

TKM-080301 has already undergone clinical trials, where patients with solid tumors usually tolerated it well and it showed some preliminary anticancer activity (ClinicalTrials.gov Identifier: NCT02191878). Eph receptor A2 (EphA2) is overexpressed in a variety of cancer types and is a member of the receptor tyrosine kinase family that regulates cell differentiation, survival, and proliferation [131]. Patients with advanced and/or recurring solid tumors are being treated with 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC)-liposomes carrying EphA2 siRNA in a Phase 1 experiment (Clinical- Trials.gov Identifier: NCT01591356). The transforming growth factor-(TGF-) family of structurally related proteins regulates a wide range of cellular processes, including migration, epithelial-mesenchymal transition (EMT), differentiation, and apoptosis [132].

It has been linked to effects that promote tumor growth, especially in advanced stages of numerous cancer types. A unique polypeptide nanoparticle known as STP705 delivers siRNA against TGF-1 and cyclooxygenase-2 (COX-2) [133]. Additionally, COX-2 is overexpressed in a variety

of malignancies, aiding in carcinogenesis and causing resistance to radiation and chemotherapy. Basal cell carcinoma, hepatocellular carcinoma, and cutaneous squamous cell carcinoma are all now being treated using STP705 as a form of gene therapy (ClinicalTrials.gov Identifier: NCT04844983, NCT04676633, NCT04669808). For several cancer indications in the US, Rexin-G was the first targeted gene therapy vector to receive orphan drug priorities and fast track classification. Rexin-G is a replication-incompetent retroviral vector that targets aberrant Signature (SIG) proteins in tumors by attaching to a secret collagen-binding motif on its envelope (ClinicalTrials. gov Identifier: NCT00504998) [134].

Exosomes have a lipid bilayer membrane that is 30-100 nm in diameter and contains proteins, other biological components, DNA, miRNA, mRNA, and lncRNA [135]. Through membrane fusion, exosomes can enter recipient cells and affect transcriptional and translational processes [136, 137]. They have a lot of potential for cancer therapy since they are extremely biocompatible, stable, and display tumor homing [138]. Exosomes produced from healthy fibroblast-like mesenchymal cells were modified to contain siRNA or shRNA targeted at the oncogenic KRASG12D mutation, which is a frequent occurrence in pancreatic cancer (ClinicalTrials.gov Identifier: NCT03608631).

When compared to liposomes, iExosomes have an improved ability to target oncogenic Kras, which depends on CD47 and is made possible by micropinocytosis [139]. Treatment with iExosomes greatly extended overall survival in several mice models of pancreatic cancer while suppressing the disease. In this phase I trial, individuals with pancreatic cancer with the KrasG12D mutation that has progressed to other parts of the body are evaluated for the optimal dose and side effects of exosomes made from mesenchymal stromal cells that contain KrasG12D siRNA (iExosomes).

2.3 Nanotechnology Based Immunotherapeutics

In the field of immunotherapies for cancer, groundbreaking developments have been made, such as CAR-T cell therapy, immune checkpoint inhibitors, and cancer vaccines. Immunotherapy is based on the idea that the adaptive immune system can recognize tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) [140]. While TSAs are present only in tumor cells, TAAs are present in all cell types but are frequently overexpressed in tumor cells [141]. Antigen-presenting cells (APCs) take up and break down the tumor-associated protein to produce immune responses that are directed against the tumor [142]. The HLA-peptide complex is identified by the T cell receptors (TCR) after binding to patient-specific human leukocyte antigen (HLA) molecules, and upon binding, the T cell promotes tumor cell death [143].

New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a cancer-testis antigen that is typically expressed in testicular germ cells and trophoblasts of the placenta. Some TAAs can result from reactivation of embryonic genes that are ordinarily located in differentiated cells [144]. Several advanced malignancies, including melanoma (46%) and round cell liposarcoma (89-100%), neuroblastoma (82%), and ovarian cancer (43%) all exhibit significant incidences of NY-ESO-1 expression. Numerous clinical studies utilizing the NY-ESO-1 antigen have shown better immune responses and successful outcomes in some trials, proving the antigen's usefulness in the treatment of cancer.

A subset of immune cells known as invariant natural killer T (iNKT) cells are capable of recognizing glycolipid antigens delivered via the non-polymorphic MHC class I-like protein CD1d [145, 146]. In addition, iNKT agonists have strong

adjuvant effects when given concurrently, even at low dosages, since they effectively generate cytokines upon activation that excite other immune cells and increase cytotoxic T cell responses [147, 148]. The FDA and the European Medicines Agency (EMA) have given their approval for the use of polylacto-coglycolic acid (PLGA), a biodegradable polymer with low (systemic) toxicity, in numerous drug-carrying platforms. In a Phase 1 clinical investigation, PLGA-based NPs with the tumor antigen NY-ESO-1 and the iNKT cell activator IMM60 are testing anti-tumor responses in cancer patients (ClinicalTrials.gov Identifier: NCT04751786).

T cell responses can be improved by combining adjuvants and antigens within a single polymeric nanoparticle [149]. The NY-ESO-1 entire protein was encapsulated in adjuvant ISCOMATRIX in earlier experiments, and it was discovered that the majority of patients experienced specific T cell responses [150]. The NY-ESO-1 protein and peptides have already been established in prior clinical trials to be safe and tolerable in patients with advanced cancer.

3. Potential Nanotechnologies for Improving Cancer Treatment

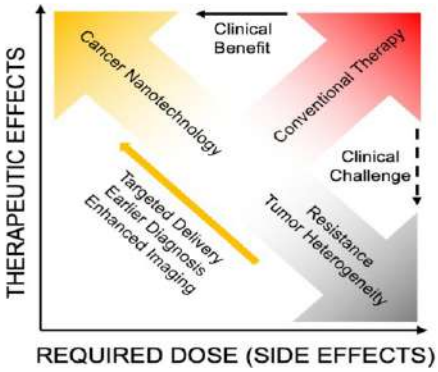

Fig.4: Nanotechnologies for improving cancer treatment

Numerous preclinical investigations are being conducted to create triggered drug release and multimodal therapies that will be extremely selective against malignant cells as developing nanotechnologies strive to increase PK/PD, effectiveness, and selectivity. Targeted drug release has the potential to reduce overall toxicity and the minimal effective dose even further, enhancing patient quality of life and efficacy (Fig.4) [30]. Therapeutics can be created to obtain the best efficacy and the least amount of toxicity when technology develops to use specialized delivery. While some targeted medicines may show tumor selectivity, their clinical efficacy may be constrained by their PK/PD or biodistribution characteristics. Because of its effectiveness against malignant cells and its ability to target them specifically while sparing healthy cells, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a perfect anti-cancer agent [151]. A short half-life and quick renal elimination of the off-targeted TRAIL make it difficult to advance through preclinical, but [152]. With 16 times longer serum half-life and continued anti-tumor activity in vivo in xenograft breast cancer and orthotopic pancreatic models, a novel TRAIL-active trimer ferritin nanocage (TRAIL-ATNC) has been developed [64]. Any therapeutic's PK/PD parameters might be improved by nanoformulation, which would allow for drug repurposing [153].

Recent studies have demonstrated that cationic liposomes' lipid tail changes can boost the loading capacity of highly hydrophobic PTX, which is useful for the development of PTX liposomal delivery systems with fewer side effects and lower costs. It was discovered that the newly synthesized DL in TAP, which contains two linoleoyl tails, has a higher loading capacity than lipid tails with one oleoyl (DOPC/DOTAP), proving that even little changes to nanoformulation can greatly enhance drug delivery systems. [122]. Stimuli-responsive carriers are intended to release payload in response to particular stimuli, such as pH changes, temperature changes, the overexpression of particular TME enzymes, elevated concentrations of intracellular substances like glutathione, and

external stimuli like radiation, ultrasound, magnetic fields, etc. [56].

In this way, medication release within the TME or other appropriate targeted locations might provide precise delivery. With the mutation occurring in up to 44% of TNBC compared to 15% in ER-positive breast tumors, TP53 is one of the most frequently mutated or deleted genes in breast cancer [154]. TNBC is the only subtype of breast cancer without any approved targeted therapies, and both the loss of TP53 and the absence of targeted therapy are significantly associated with poor clinical outcomes [155]. When treating TNBC, POLR2A in the TP53-neighboring region was shown to be a collateral vulnerability target. To increase the bioavailability and improve endo/lysomal escape, pH-activated NPs were utilized. [156]. Currently, cancer immunotherapy depends on two main strategies: using monoclonal antibodies (mAbs) to regulate effector immune cells and using chimeric antigen receptor- T cells or bispecific T cell-engaging antibodies to enable co-engagement of T cells and tumor cells. The future of cancer immunotherapy may lie in combining the two approaches into a single system, as was recently shown in a flexible antibody immobilization nanoplatform made by attaching an anti-IgG (Fc specific) antibody to the surface of a nanoparticle (Fc-NP), which allowed two different types of monoclonal antibodies to be immobilized [157]. In various mouse tumor models, immunomodulating nano-adaptors (imNAs) outperformed a combination of mABs in the T cell, natural killer cell, and macrophage driven immune response.

New nanomaterials can improve cancer immune therapy further. For instance, Gram-negative bacteria secrete outer membrane vesicles (OMVs), which are sized 30-250 nm and act as a mediator of bacterial communication and homeostasis [158]. They have ideal qualities for vaccine distribution, including small size and simplicity of manufacture scaling up, and they have intrinsic immunostimulatory capabilities. It has recently been demonstrated that tumor antigens can appear as ClyA fusion proteins on OMV surfaces and trigger T-cell-mediated, targeted anti-tumor response [159]. Additionally, a protein tag can spontaneously link to the protein catcher using the protein "Plug-and-Display" technique by forming an isopeptide bond.

After amassing in draining lymph nodes, different tumor antigens attached to protein tags can be swiftly and simultaneously displayed on the OMV surface, where they can then be processed and presented by DCs [159]. The co-delivery of several chemotherapeutic drugs has proven to be a very effective usage of nanomaterials. Co-delivery inside a single carrier can normalize distribution and delivery since drugs have a variety of biochemical properties that can be significantly different from their synergistic complement [160]. In the clinic, anti-PD-1/PD-L1 antibodies are currently utilized to disrupt the immunological checkpoint, which reverses T cell depletion and malfunction and successfully treats cancer [161].

Recent research has shown that a liposomal formulation of the histone demethylase inhibitor, 5-carboxy-8-hydroxyquinoline (IOX1), and DOX enhances T cell infiltration/activity and greatly lowers tumor immunosuppressive factors. [162]. A long-term immunological memory effect against tumor recurrence was demonstrated in in vivo investigations, which also revealed reduced growth of a variety of mice cancers (including subcutaneous, orthotopic, and lung metastasis). The study demonstrated that IOX1 inhibits P-glycoproteins (P-gp) in cancer cells via the JMJD1A/-catenin/P-gp pathway and synergistically increases DOX-induced immune-stimulatory immunogenic cell death. Depending on the intended result, nanoformulation can optimize drug release by adjusting the release kinetics for dual-drug loading [57]. Drug release can be activated in a variety of ways; therefore, the

release rate can be quite specific to the increases of stimuli-responsiveness [71]. Arsenic trioxide (ATO) and PTX were recently developed for co-delivery and dual-pH responsive sequential release using mesoporous silica NPs (MSNs) coated with polyacrylic acid (PAA) and pH-sensitive lipid (PSL) (PL-PMSN-PTX/ ATO) [163]. The modification of MSNs with the tumor-targeting peptide F56 provided a target-specific transport to cancer and endothelial cells during neoangiogenesis. The drug-loaded NPs showed a sequential drug release profile and dual-pH responsiveness (pHe 6.5, pHendo 5.0). While ATO was primarily released at pH 5.0 in PSL, PTX was released preferentially at pH 6.5. ATO and PTX co-delivered NPs demonstrated a substantial synergistic effect against MCF-7 cells, displaying more cell-cycle arrest in treated cells and more activation of apoptosis-related proteins than free medicines. Drug-free carriers revealed modest cytotoxicity toward MCF-7 cells.

There are many innovative nanotechnologies that significantly advance cancer treatments, but there are still several barriers to their use in clinical settings, such as scalability, homogeneity, and regulatory requirements.

4. Clinical Applications of Emerging Nanotechnologies For Radiation Therapy

Since nanomaterials have unique features that are favorable to atomic-level interactions with radiation and tumoral accumulation, RT can benefit from advancements in nanotechnology. It has been demonstrated that high atomic number NPs improve the Compton and photoelectric effects of conventional RT, and that some nanomaterials can be used to stimulate medication release in response to radiation while others can act as radiosensitizers [164,165].

A chelating agent called DOTA (1,4,7,10-tetra-azacyclododecane-1-glutaricanhydride-4,7,10-triacetic acid) is covalently attached to the paramagnetic contrast enhancer Gd in a nanoparticle called AGuIX [166,167]. The enormous magnetic moment and consequent huge local magnetic field produced by the placement of AGuIX in a magnetic field can increase the pace at which adjacent protons relax, boosting the MRI signal in tumor tissues where protons have gathered. The increased radiation effects of AGuIX NPs were subsequently clarified and linked to the production of low-energy photoelectrons and Auger electron interactions [168]. The ultra-small NPs, less than 5 nm in diameter, enable for quick renal clearance and reduced toxicity.

DNA damage is brought on by standard X-ray radiation through the production of ROS following contact with water molecules. Hafnium oxide nanoparticles (NBTXR3) were developed to boost energy deposit because of high electron density, leading to increased oxidative stress in tumor cells and ensuing physical ablation [169]. However, locally advanced soft tissue sarcomas (high risk and typically unresectable) frequently necessitate pre-operative radiotherapy, making them ideal cancer types for testing NBTXR3 [170]. Soft tissue sarcomas of the limbs or trunk allow direct injection of NPs into the tumor, where the radiotherapy enhancement can be localized to cancerous tissue.

High risk of RILD after stereotactic body radiation (SBRT) has been linked to hepatic cirrhosis in patients with hepatocellular carcinomas (HCC), chemotherapy-induced hepatic atrophy, or hepatosteatosis in patients with liver metastases [171,172]. However, by switching from nuclear medicine to MRI-guided radiation with SPION on 1.5 Tesla MRLinac, hepatotoxicity can be significantly decreased [173]. In order to increase the safety of liver stereotactic body radiotherapy in patients with pre-existing liver conditions, MRI-SPION radiotherapy is anticipated to facilitate detection and maximize avoidance of residual, functionally-active hepatic parenchyma from

over-the-threshold irradiation (ClinicalTrials. gov Identifier: NCT04682847).

CONCLUSION

This review article explores the amazing developments in cancer treatment made possible by the incorporation of nanotechnology. By providing creative solutions to the drawbacks of conventional medicines, the use of nanotechnology in cancer treatment has completely altered the field of oncology. Nanotechnology has shown the ability to greatly increase the efficacy and decrease the negative effects of cancer medicines through precise drug delivery systems, improved imaging methods, and individualized treatment plans. With their distinctive features, nanoparticles have made it possible to deliver therapeutic drugs specifically to tumor locations, reducing harm to healthy tissues and raising the overall therapeutic index. Additionally, real-time viewing and monitoring of treatment responses have been made possible by the integration of nanoparticles with imaging technologies, allowing doctors to make wise judgments during the course of therapy.

Since therapies can be customized to individual patients based on their genetic and molecular profiles, personalized nanotechnology-based treatments hold promises for more effective outcomes. This may help treat patients that were previously difficult to treat and overcome drug resistance. Although there is no denying the potential of nanotechnology in the treatment of cancer, a number of issues need to be resolved before wide-scale clinical application. These include problems with long-term impacts, scalability, governmental approval, and safety. To realize the full potential of nanotechnology in revolutionizing cancer therapy, it will be crucial to carry out ongoing interdisciplinary research, team up with regulatory authorities, scientists, engineers, doctors, and other healthcare professionals, as well as conduct thorough clinical studies.

In summary, the use of nanotechnology in cancer therapy has created new opportunities for precise and efficient therapies, igniting hope for a time when nanotechnology will be crucial to the eradication of cancer and the enhancement of patient quality of life on a global scale.

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