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Advances and Applications of Cancer Therapy by Nanotechnology: A Review

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Abstract
Innovations in nanotechnology have opened transformative avenues in cancer treatment. This field enables precise control over the characteristics of nanomaterials, enhancing the effectiveness of drug delivery to specific sites. Clinical studies underscore the potential of therapeutic nanoparticles to improve treatment outcomes while minimizing adverse effects, distinguishing them from conventional therapies. Driven by these promising strides, researchers are actively crafting innovative nanoparticles for drug administration, offering a fresh dimension to cancer treatment. Nanotechnology's role in cancer therapy has garnered substantial attention recently. This interdisciplinary domain, merging science, engineering, and medicine, holds vast potential. It introduces a distinct approach to combating cancer, encompassing early detection, prognosis, prevention, personalized treatment, and medication. Tailored drug delivery to targeted areas and early pathological diagnosis stand as pivotal focal points where nanotechnology could revolutionize the landscape. This review delves into the applications of cancer nanotechnology, outlining its role in advancing cancer treatment strategies.

Key words: Nanoparticles, Conventional therapies, Drug delivery, Nanotechnology.

1 INTRODUCTION:

Cancer

Cancer is a major cause of mortality more than ten million people are diagnosed with the complaint annually. Cancer is known to develop via a multistep carcinogenesis process containing multitudinous cellular physiological systems similar as cell signalling and apoptosis, making it a largely incomprehensible and complex complaint [1,2]. Originally, cancers start as localized conditions, but they're prone to spread to distant spots within the body, which makes cancer incorrigible. To date, cancer treatments have been performed on the base of clinical and pathologic

staging that's determined using morphologic individual tools, similar as conventional radiological and histopathological examinations. The most common cancer treatments are confined to chemotherapy, radiation and surgery [3]. At present, still, the early recognition and treatment of cancer remain a technological tailback. Despite numerous advances in conventional treatment options similar as chemotherapy and radiation, cancer remedy is still far from optimal because it's agonized by some downsides. Frequent challenges encountered by current cancer curatives include nonspecific systemic distribution of antitumor agents, shy medicine attention reaching the tumour point, intolerable cytotoxicity, limited capability to cover remedial responses and development of multiple medicine resistance [4 – 6]. Current individual and prognostic groups are inadequate to make prognostications for successful treatment and case outgrowth [7]. therefore, there's a critical need and major openings to develop new and innovative technologies that could help to delineate tumour perimeters, identify residual tumour cells and micro metastases, and determine whether a tumour has been fully removed.

The primary treatments for cancer are limited to chemotherapy, radiation, and surgery. The current challenges faced by these curatives include issues like non-specific distribution of anti-tumour agents throughout the body, inadequate medicine attention at tumour spots, and difficulty in monitoring treatment responses. This poor targeting can lead to problems similar as multidrug resistance. The main objects in developing remedial agents or imaging discrepancy phrasings are enhanced targeting particularity and bettered delivery effectiveness. immaculately, remedial medicines should accumulate generally in tumour regions while sparing normal tissues. One effective strategy to achieve this is by attaching remedial medicines to monoclonal antibodies[mAbs] or other ligands that widely bind to antigens or receptors overexpressed on tumour cells. various strategies employing ligand- targeted curatives, including radio ImmunoTherapeutics, medicine immunoconjugates, and immunotoxins, are under development. Despite demonstrating promising efficacity in preclinical and clinical trials when compared to traditional chemotherapy medicines, these conjugated agents still face limitations in delivery effectiveness and particularity. Studies have indicated that only a small bit of intravenously administered mAbs, rectifiers, or imaging agents [1 to 10 corridors per 100,000] successfully reach their intended targets within tissues [8,9,10]. Conventional cancer treatment styles encompass surgery, chemotherapy, radiation remedy, targeted remedy, immunotherapy, and hormone remedy [11, 12]. While chemotherapy and radiation remedy parade cytostatic and cytotoxic goods [13], they frequently come with acute side goods and a high threat of rush. Common side goods include neuropathies, bone gist repression, gastrointestinal and skin diseases, hair loss, and fatigue. Specific medicines like anthracyclines and bleomycin can induce cardiotoxicity and pulmonary toxin [14]. The emergence of targeted remedy has advanced perfection treatment [15], yet it still presents challenges similar as multi-drug resistance that curtails remedial effectiveness [14]. Immunotherapy has shown pledge in treating primary cancer, precluding distant metastasis, and reducing rush rates [16]. still, it can lead to autoimmune conditions and might be less effective against solid tumours compared to tubercles [17]. Solid tumours frequently produce an atypical extracellular matrix, making it delicate for vulnerable cells to insinuate [18]. These newer targeted curatives and immunotherapies can disrupt signalling pathways critical to both nasty actions and normal functions of the skin, performing in dermatologic adverse events[dAEs][19].

Nanoparticle- grounded medicine delivery systems have demonstrated significant advantages in the treatment and operation of cancer. These systems offer bettered pharmacokinetics, precise targeting, minimized side goods, and mitigation of medicine resistance [20,21]. With the elaboration of nanotechnology, multitudinous Nano remedial medicines have been introduced to the request and several further have progressed to clinical trials after 2010. These

advancements have contributed to enhanced medicine delivery systems and addressing anti-tumour multidrug resistance [MDR]. Nano- remedial medicines enable combination remedy and the repression of medicine resistance mechanisms, thereby expanding treatment possibilities [22]. The original operation of nanotechnology in drug dates back to the 1960s, forming from sweats at ETH Zurich [23].

2.NANOTECHNOLOGY

Nanotechnology has surfaced as a promising field in cancer treatment [24]. Nano drug, which applies nanotechnology to drug, holds great potential for transubstantiating cancer diagnostics and rectifiers. It achieves this by developing innovative biocompatible nanocomposites for medicine delivery, a crucial operation of nanoparticles [25]. In recent times, Nano carriers, particularly in the size range of 10 nm to 100 nm, have gained substantial attention as an arising remedial approach for treating cancer. specially, liposomes and albumin nanoparticles have gained blessing from the US FDA for clinical use. Examples similar as liposomal doxorubicin and albumin- bound paclitaxel [Abraxane1] highlight enhanced permeability and retention [EPR]- grounded Nano vector operations in bone cancer chemotherapy [26,27]. These Nano systems parade four distinct parcels setting them piecemeal from conventional cancer rectifiers[i] Nano systems can retain essential remedial or individual capabilities and can be acclimatized to carry substantial remedial loads.[ii] Nano systems can be linked to multivalent targeting ligands, icing strong affinity and particularity for target cells.[iii] Nano systems can accommodate multiple medicine motes, enabling concerted cancer remedy.[iv] Nano systems can bypass traditional medicine resistance mechanisms. Through unresistant and active targeting strategies, these Nano carriers can boost medicine attention within cancer cells while minimizing detriment to normal cells. This binary effect enhances anticancer efficacity and reduces systemic toxin [28].

2.1Nanoparticles

Nanoparticles (NPs) are characterized as structures having a size smaller than 100 nm, displaying unique properties not typically found in larger materials [29]. NPs exist in various dimensions, categorized as 0D, 1D, 2D, or 3D depending on their geometric shape [30]. The structure of NPs is complex, comprising the outer shell, inner core, and additional components that form the core of the NP [31].

NPs possess exceptional characteristics such as a high surface-to-volume ratio, small size, versatility, and an improved targeting mechanism, making them valuable in diverse fields. These properties enable NPs to penetrate deeply into tissues, leading to enhanced permeability and retention effects. Furthermore, surface properties play a crucial role in determining bioavailability and longevity by facilitating efficient passage through cellular barriers [32]. For example, NPs coated with the hydrophilic polymer polyethylene glycol can prevent unwanted interactions with the immune system and enhance circulation time [33]. Additionally, tailoring specific polymer attributes can optimize the release rates of drugs. Ultimately, the unique properties of NPs play a significant role in their therapeutic potential for cancer treatment. Various approaches and techniques for synthesizing nanoparticles are depicted in Figure 1. gives different approaches and methods for synthesizing nanoparticles.

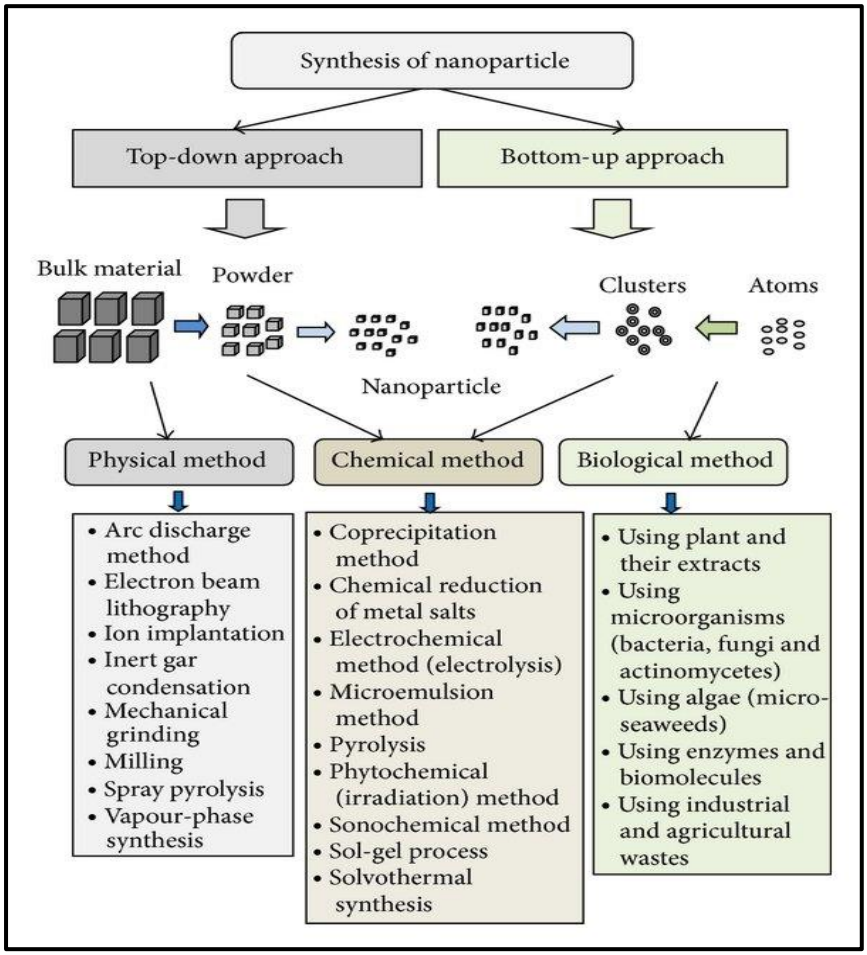

Fig 1. Different approaches and methods for synthesizing nanoparticles.

Synthesis of NPs

The creation of Nanoparticles (NPs) exhibits wide range of shapes sizes, and structures, achievable through different Synthesis methods. These methods are classified into two main categories: the bottom-up approach and the top-down approach, each with variations based on reaction conditions and procedures [Fig.2].

Bottom-up Approach

NPs are built from molecules, clusters, to more intricate formations [34]. Common techniques include spinning, sol-gel synthesis, chemical vapor deposition (CVD), tube or honeycomb template synthesis, flame pyrolysis, and biosynthesis.

Top-down Approach

The top-down approach, known as the deconstructive method, breaks down bulk materials to synthesize NPs. It breaks down larger particles into smaller units that form NPs [35]. Techniques include mechanical milling, nanolithography, chemical etching, laser ablation, sputtering, electrical explosion, and thermal decomposition. Notably, the morphological characteristics such as size, shape, and charge can be adjusted by modifying reaction conditions and synthesis parameters [36]. The growth environment also influences the chemical properties of NPs, presenting challenges for tailored synthesis.

Cellular Targeting Mechanisms

Effective treatment for cancer involves the precise targeting of tumour cells while preserving healthy bone tissue. This is accomplished through the utilization of tailored medications or gene delivery systems that can navigate through the tumour microenvironment (TME). Nanoparticles (NPs) face various natural and physiological barriers such as cell layers (like epithelium and endothelium) and structural factors (mechanical, physicochemical, enzymatic). Specific NP properties like size, biocompatibility, and surface chemistry contribute to their nonspecific targeting capacity. However, successful internalization of NPs doesn't ensure subcellular targeting, emphasizing the need for engineering and optimization for precise cellular or nuclear targeting.

Research is ongoing to develop targeted medication delivery systems based on NPs. Key characteristics for effective nano carriers include stability until entering TME, avoidance of detection by the reticuloendothelial system (RES) and mononuclear phagocyte system (MPS), accumulation in the TME via tumour blood vessels, deep penetration into tumour fluid, and direct interaction with tumour cells [37]. The functionalization of their surfaces, along with their physicochemical properties and biological characteristics, dictate the efficacy of NP-based medication delivery. Typically, NPs specialized for cancer treatment have sizes ranging from 10 to 100 nm.

A comprehensive understanding of how NP carriers interact with cancer cells and the biology of tumours necessitates a focus on targeting mechanisms. These mechanisms are broadly classified into passive targeting and active targeting, distinguishing the strategies involved in reaching and affecting cancer cells within the body.

2.2 TOOLS OF TECHNOLOGY

Liposomes: Liposomes have gained significant mileage in biology, biochemistry, and drug due to their protean structure and composition [38,39,41-43]. Examples include liposome- intermediated medicine delivery systems like Doxil and Daunoxome. Polyethylene glycol [cut]- carpeted liposomal doxorubicin [Doxil1, Caelyx1; Alza Pharmaceuticals, San Bruno, CA, USA] exhibits prolonged rotation, a half- life of 55 hours in humans [38,40,44]. These PEGylated liposomes hamper relations with tube proteins and mononuclear phagocytes, thereby extending rotation. remedial motes have been packaged within liposomes; their shells adorned using molecular' Trojan steed' technology [39,45,46]. For case, Zhang etal. [47] designed targeted PEGylated immunoliposomes with OX-26-transferrin, showing pledge in rat Parkinson's models. Folate- carpeted liposomes efficiently delivered doxorubicin and bypassed multidrug resistance [48,49].

Polymeric Micelles: Polymeric micelles, composed of amphiphilic surfactant motes, hold potential in rectifiers [50]. Genexol- PM, the first polymeric micelle paclitaxel expression, has entered clinical trials. various polymeric cut- micelle phrasings, like doxorubicin- loaded micelles, show pledge in treating solid tumours and restenosis [51 – 54]. Immunomicelles, conjugating antitumor antibodies and recapitulating medicines, target cancer cells [55]. Curcumin- loaded micelles have demonstrated bettered efficacity [56].

Dendrimers: Dendrimers, comprising branches around a core, offer adjustable size and shape for medicine delivery [57 – 60]. DNA- assembled dendrimers target cancer cells [61]. Dendrimers also serve as effective individual tools for cancer imaging, due to multivalent imaging inquiry attachment and targeting halves [62,63]. Phase I clinical trials for Star pharma's dendrimer- grounded toxic [VivaGel] are underway [64].

Nano cantilevers: Microarrays with Nano cantilevers descry bimolecular relations for complaint opinion. Anchored bars detecting cancer- associated motes suffer deviation upon commerce, enabling early molecular event discovery [65].

Carbon Nanotubes: Carbon nanotubes serve as detectors for DNA and protein discovery and carriers for medicine, vaccine, or protein delivery [66,67]. picky internalization with nanotubes aids in cancer cell destruction. Carbon nanotubes are used for imaging purposes [68 – 71].

Quantum Dots: Semiconductor amount Dots [QDs] offer multicolour imaging due to broad immersion and narrow emigration characteristics [68,72 – 75]. QDs enhance perceptivity and selectivity for in vivo tumour imaging [66]. face- functionalized QDs parade bio imaging potential [69 – 71].

Passive Targeting: Enhanced saturation and retention effect [EPR] leverages tumour blood vessel fenestrations and poor lymphatic drainage [77 – 81]. Hypoxia and neovascularization contribute to EPR. TME's acidic nature permits pH-sensitive NPs. Passive targeting relies on tumour biology, carrier attributes, and EPR effect. Over EPR, TME influences unresistant targeting. Glycolysis leads to an acidic TME, useful for pH-sensitive NP medicine release [85,86]. Passive targeting exploits tumour biology, NP attributes, and EPR for medicine delivery effectiveness [Fig.2]

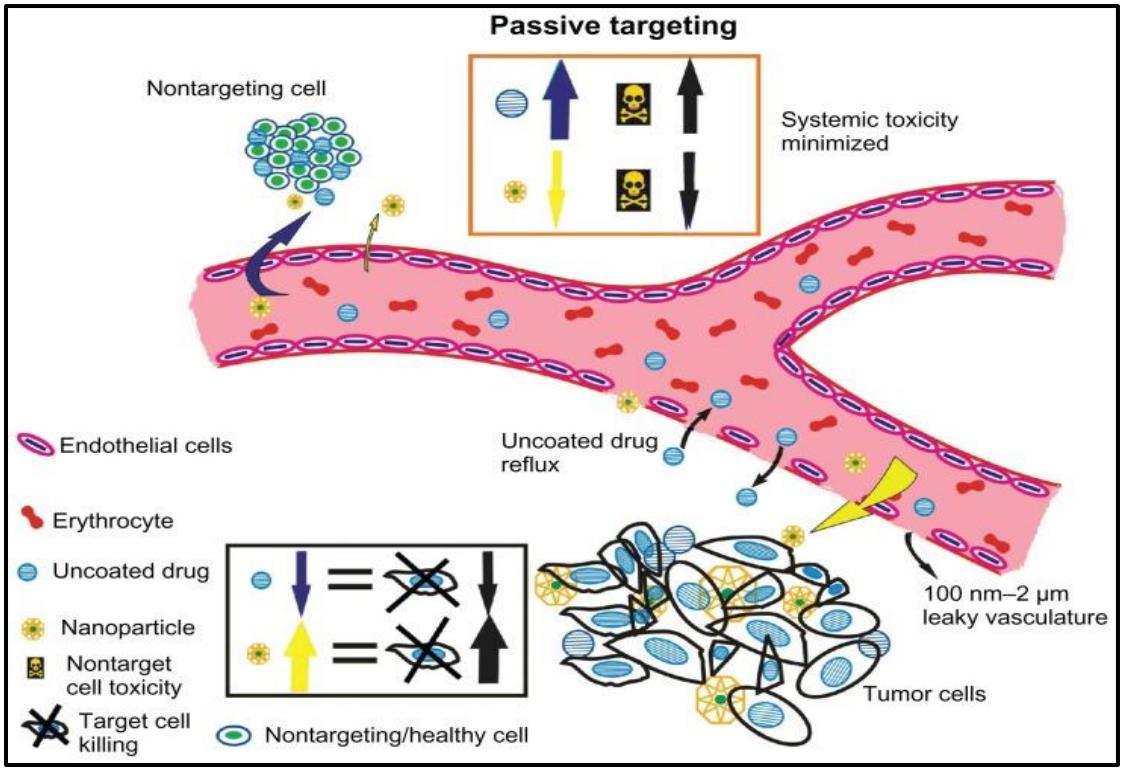

Fig 2: Passive targeting exploits tumour biology, NP attributes, and EPR for medicine delivery effectiveness

Examples of Passive Targeting

Taxanes are a highly effective group of cancer medications, particularly paclitaxel, which exhibits strong activity against various cancer forms such as bone, lung, and ovarian cancers. The US Food and Drug Administration approved Abraxane® (albumin-bound paclitaxel) by Abraxis Bio-Sciences in 2005 for advanced or metastatic bone cancer. Abraxane® works by stabilizing microtubules,

preventing their disassembly, promoting their assembly, and inhibiting the crucial reorganization needed for cellular processes, including mitosis. Paclitaxel induces unique microtubule configurations and clusters during the cell cycle and mitosis. When used in combination with gemcitabine, Abraxane® decreases the pancreatic stroma in xenograft models [87].

Genexol PM ® offers a lyophilized polymeric micellar paclitaxel expression without CrEL, with advanced MTD and elevated memoir distribution in various tissues and cancer cells. South Korea approved it for MBC, while US trials are ongoing for pancreatic cancer treatment [88]. DaunoXome® [liposomal daunorubicin; Gilead Science/ Diatos], a liposome- grounded daunorubicin, treats Kaposi's sarcoma, approved by USFDA in 1996 [89].

Despite neovascularization and angiogenesis impacting NP prolixity, elevated interstitial pressure restricts NP accumulation. Tumour cell growth diversity due to irregular blood force results in varying division rates. Irregular oohing due to high interstitial pressure hampers medicine delivery and neovascularization. EPR effect can be regulated mechanically or chemically through nitric oxide, bradykinin, ultrasound, radiation, hyperthermia, etc. Yet, limitations and contraindications live.

Active Targeting- Nanoparticle medicine Delivery

Active targeting relies on ligands binding specifically to receptors overexpressed on target cells, enabling ligand- intermediated targeting [90]. Ligand- equipped NPs, positioned near the target, enhance list and medicine penetration. This approach aims to compound NPs' relations with targets while maintaining overall bio distribution [92]. Active targeting entails ligand recognition by target substrate receptors, involving various ligands like proteins, peptides, antibodies, nucleic acids, and vitamins [93]. Studied receptors commonly include transferrin, folate, glycoproteins, and the epidermal growth factor receptor (EGFR). The interaction between ligands and receptors initiates endocytosis, facilitating the internalization of nanoparticles (NPs). Transferrin, which is often found in high levels in various tumour cells, presents a promising targeting opportunity [94]. For case, transferrin- modified NPs specifically target A2780 ovarian melanoma cells [95]. Angiogenic endothelial cells conterminous to cancer cells can also be targeted, affecting tumour vasculature, and converting hypoxia and necrosis. Tumour tissues' acidic nature due to the Warburg effect is employed; pH-sensitive liposomal medicine delivery systems are explored. Multivalence of NPs enhances ligand- NP relations with cancer cells, but design complexity arises from NP armature, ligand- target chemistry, administration route, physicochemical parcels, ligand viscosity, and NP size [97-98]. [Fig.3]

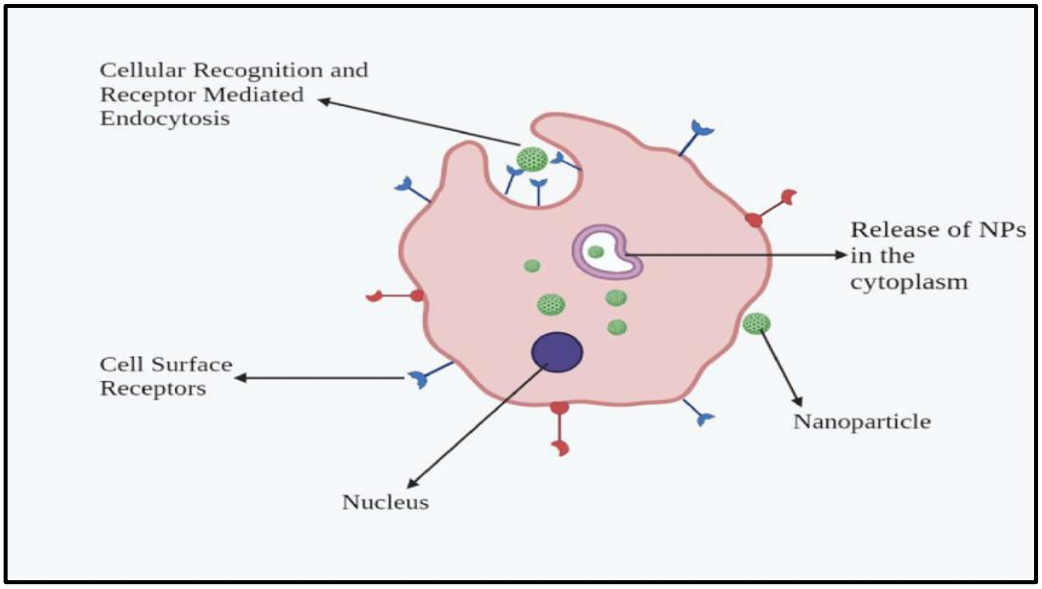

Fig 3: Multivalence of NPs enhances ligand- NP relations with cancer cells.

Examples of Active Targeting

Cancer- targeting strategies include:

1. EGFR Targeting EGFR, overexpressed in various cancers, can be targeted using gold NPs like anti-EGFR-PEG-AuNPs, showing pledge in scaled cell melanoma [48].
2. Herceptin ® targets HER2 on cancer cells in bone, while PEGylated liposomal doxorubicin focuses on HER2 to decrease the risk of anthracycline-induced heart toxicity [99].
3. VCAM- 1 Targeting NPs targeting vascular cell adhesion patch- 1[VCAM- 1] in bone cancer model indicate its potential [100].
4. Targeting of folate receptors [FR- α and FR- β] using Folate Receptor Targeting NPs is being investigated for precise cancer therapy. [101,102,103].

Overcoming Drug Resistance Mechanisms

Medicine resistance poses a significant challenge in the realm of cancer remedy and operation. This issue is pervasive across different cancer types and treatment methodologies. The emergence of medicine resistance signifies a miracle where conditions come less responsive to pharmaceutical interventions. Categorically, medicine resistance can be bifurcated into two primary forms natural and acquired [104]. natural resistance primarily emanates from pre-existing inheritable mutations in the genes responsible for regulating cell growth and apoptosis. On the other hand, acquired resistance is characterized by its development posterior to a specific anti-tumour treatment. This resistance can stem from the accession of new mutations or differences within the tumour medium during the course of treatment. using the unique capability of nanoparticles to coincidently synopsize multiple remedial agents holds pledge as a strategy to master medicine resistance in cancer- related surrounds.

Targeting Drug Efflux Transporters

Efflux transporters fall under the order of" ATP- list mail [ABC] transporters," playing a vital part in multidrug resistance [MDR]. The main function of these carriers is to remove drugs from cells, leading to a decrease in their concentration. One of these transporters, known as P-glycoprotein (P-gp), is a crucial efflux transporter that tends to be highly expressed in drug-resistant cancer cells. [105,106]. Elevated levels of P-gp have been linked to reduced treatment efficacy, specifically in cases of bone cancer [107] and ovarian cancer [108]. Nanoparticles [NPs] offer an implicit approach to fight efflux pumps. By undergoing endocytosis, nanoparticles enter cells and release medications at “perinuclear locations” that are distant from active efflux pumps. This mechanism enables them to evade these pumps [109]. By utilizing controlled methods for releasing medications such as exposure to low pH conditions and redox stimuli, nanoparticles (NPs) can effectively evade efflux pumps [110,111]. Combining different drugs in a single carrier is another approach to tackle multidrug resistance. NPs have the capability to carry multiple medications simultaneously. [112]. Inhibition of efflux transporters offers an alternative approach beyond mere evasion, focusing on developing nanoparticles that can combine obstacles of efflux pumps with anti-cancer medications [113]. Recent exploration has showcased the reversal of MDR in bone cancer cells using NPsco-delivering COX- 2 impediments and doxorubicin [114]. also, utilizing silica nanoparticles for combining miRNA-495 and doxorubicin has shown effectiveness in overcoming drug resistance in lung cancer cells [115]. A compelling research study highlighted the efficacy of targeting KDR

receptors within tumour blood vessels using NPs, proving to be a more powerful anti-tumour approach than the combination therapy with P-gp. Another strategy to overcome medicine resistance involves depleting the ATP source necessary for ABC transporter activity. One way to achieve this is by directing interventions towards mitochondria, resulting in reduced ATP production.

Targeting Apoptotic Pathways

Cancer cells evade apoptosis, leading to resistance to medication. Abnormal apoptotic pathways involving "Bcl-2" and "nuclear factor kappa B [NFκB]" contribute to this survival benefit [116]. The targeted inhibition of these anti-apoptotic proteins presents a promising approach to overcoming resistance to medication. Utilizing nanoparticles for the co-delivery of Bcl-2 siRNA and chemotherapeutics represents a viable strategy in combatting multidrug resistance [117]. Impediments to the activity of NF- κB have been investigated in conjunction with substances like “pyrrolidine dithiocarbamate [PDTC]” [118] and curcumin [119]. An alternative strategy to address resistance to medications acting on the apoptotic pathway involves enhancing pro-apoptotic factors. For example, the combination of ceramide and paclitaxel can help restore the expression of the tumour suppressor protein p53 by regulating critical pre-mRNA splicing [120]. Nanoparticles facilitating the delivery of ceramide provide a potential method to rectify p53 mutations. [121]. This combination has shown remedial efficacity in models of cancer medicine resistance. Transfecting the p53 gene using NPs has been successful in lung and bone cancer cases [122,123]. Some NP-grounded medicine delivery systems inhibit efflux pumps and promote apoptosis [124]. An innovative study employed" amphiphilic cationic NPs" loaded with paclitaxel and Bcl- 2 motor gene to address both pump- and non-pump-mediated medicine resistance in liver cancer models. This complex reduced P- gp- convinced medicine efflux while cranking apoptosis. Also, co-delivery of" doxorubicin and resveratrol reprised in NPs" demonstrated significant cellular toxin against doxorubicin- resistant bone cancer cells, downregulating Bcl- 2 and NF- κB expression, initiating apoptosis, and inhibiting efflux transporters [125]. An analogous approach was applied to multi-drug resistant prostate cancer cells using NPs recapitulating resveratrol and docetaxel, leading to downregulated anti-apoptotic gene expression and inhibited ABC transporter labels [126].

Targeting Hypoxia: Hypoxia exacerbates MDR, as certain tumour cells abiding in hypoxic regions shirk chemotherapy due to shy medicine penetration. Hypoxia fosters tumour diversity and overexpression of efflux proteins [127]. Hypoxia-inducible factor 1α (HIF-1α) plays a vital role in this mechanism. Targeting HIF-1α or suppressing its genetic expression is a strategy to combat drug resistance [128]. The use of nanoparticles containing HIF-1α siRNA can reduce resistance caused by hypoxia [129]. Blockade of the HIF-1α signalling loop in a circular manner can be achieved, much like inhibiting the PI3K/Akt/mTOR pathway that regulates HIF-1α levels. Disrupting this pathway increases the sensitivity of MDR cells to treatment [130]. PLGA- PEG and PEGylated/non-PEGylated liposomes can be instrumental in this strategy. Additionally, HIF-1 transcriptional activity heavily relies on the crucial role of heat shock protein 90 (HSP90); reducing HIF-1α expression is achieved through HSP90 inhibition [131]. NPs loaded with HSP90 impediments, like" 17AAG," have shown bettered MDR treatment issues in bladder cancer [132].

Nanoparticles and Proteomics

When nanoparticles are introduced into living organisms, they engage with cellular and serum proteins, resulting in the creation of a "protein corona" [PC][133]. The proteins exhibit either a "hard corona" or a "soft corona" around NPs based on their affinities. The "Vroman effect" guides the

replacement of proteins with higher affinities over those initially present in the PC. [134]. Developing nanoparticles (NPs) with specific characteristics is vital. Techniques such as mass spectrometry (MS), liquid chromatography-mass spectrometry (LC-MS), SDS polyacrylamide gel electrophoresis (SDS-PAGE), and isothermal titration calorimetry (ITC) are utilized for this purpose [135]. The physicochemical properties influence how NPs interact in biological environments, consequently affecting their potential applications. In the realm of cancer research, proteomic analyses are key in examining proteins within cancer cells and blood serum, aiding in the diagnosis, treatment, and prediction of outcomes. [136]. It illuminates the processes involved in cancer development and the mechanisms behind drug resistance. In addition to traditional chemotherapy and kinase inhibitors, nanoparticles are combined with innovative agents like siRNA, mRNA, and gene editing to improve treatment outcomes.

Nanotechnology in Small Interfering RNA [siRNA] Delivery Small interfering RNAs [siRNAs] are short double-stranded RNA molecules [approximately 21 nucleotides long] that can suppress gene expression in specific targets through a process called "RNA interference." Clinical investigations are currently underway for siRNA-based nanoparticles, including ALN-TTR01 designed to target the transthyretin gene for treating transthyretin-mediated amyloidosis, and Atu027, a liposomal siRNA targeting protein kinase N3, and TKM-ApoB which downregulates ApoB expression [137, 138].

Nanotechnology in Tumour micro-RNA Profiling and Delivery

MicroRNAs, or miRNAs, are single-stranded RNA molecules that do not code for proteins. They play a role in regulating gene expression after the process by either blocking translation or causing mRNA instability. MiRNAs are crucial biomarkers used in cancer-related areas such as diagnosis, therapy, and treatment. The utilization of nanotechnology in profiling miRNAs involves methods like biosensors and surface Plasmon resonance imaging, in conjunction with processes from molecular biology. Nanotechnology is especially important in the delivery of miRNAs [139]. For example, there have been promising results with biodegradable polycationic prodrugs in managing polyamine metabolism. Furthermore, the use of microRNA-loaded polycation-hyaluronic acid nanoparticles, together with single-chain antibody fragments, has proven effective in reducing the production of "surviving expression" in highly metastatic lung cancer models.

DNA Nanotechnology for Cancer Therapy

DNA nanotechnology applications include DNA sensors for nucleic acid identification, DNA-coated gold nanoparticles for lead detection, molecular scaffold assembly, and medical drug delivery systems. Nanotechnology presents a new frontier in cancer treatment, focusing on precise targeting of cancer cells while sparing healthy ones [140]. This approach introduces innovative materials and methods like nanoparticles with tailored properties, enabling minimally invasive treatments once deemed impossible. Nanotechnology advancements support cutting-edge cancer therapies such as photodynamic therapy, radiotherapy, radiofrequency therapy, and personalized theragnostic approaches.

Nanotechnology in Gene Therapy

Gene therapy involves inserting external genes into cancer cell genetic material to trigger cell death. While viruses have traditionally been employed to transport genes, they carry the risk of stimulating immune and inflammatory reactions. Non-viral methods of gene transfer, such as utilizing liposomes with cationic polymers and nanoparticles, offer safer options with benefits like minimal toxicity and repeatable use. The physical characteristics of nanoparticles, like their size, electrical

charge, and durability, play a crucial role in determining their effectiveness as vehicles for non-viral gene delivery. Noteworthy applications have included silencing the Akt1 protein by delivering Akt1 small-interference RNA using nanoparticles [141].

Nanotechnology-Enhanced Photodynamic Therapy

Photodynamic therapy [PDT] offers a low-morbidity alternative to conventional adjuvant therapy. It involves administering a photosensitizing drug that, upon light activation, releases reactive oxygen species to kill tumour cells and their associated vasculature. Polymeric nanoparticles improve targeting and delivery of photosensitizers, enhancing PDT's precision and effectiveness. PDT can be administered repeatedly without immunosuppressive effects and is compatible with other treatments like surgery, chemotherapy, or radiotherapy.

Advances in Nanotechnology-Driven Radiotherapy and Radiofrequency

Therapy Enhancing radiation dose with high atomic number [Z] materials has long been explored. Gold nanoparticles have shown dose-enhancing effects, concentrating radiation in tumours while sparing surrounding tissues. Gold nanoparticles also facilitate non-invasive radiofrequency ablation of tumours. These nanoparticles enable targeted cancer cell destruction in a non-invasive radiofrequency field, showcasing potential in cancer therapy.

Nanotechnology for Theragnostic Approaches

Theragnostic combines diagnosis and therapy for enhanced precision and efficiency. Nanoparticles serve as carriers for diagnostic agents and drugs, enabling non-invasive diagnosis and targeted therapy. By combining these strategies, treatment can be accelerated, side effects reduced, and cure rates improved. Plasmonic Nano bubbles around gold nanoparticles are being investigated for their potential in optical generation and detection in individual living cells [145]. Additionally, magnetic nanoparticles hold promise for simultaneous molecular imaging and drug delivery [146].

Innovative Nanotechnology in Combined Cancer Diagnosis and Therapy Nanotechnology allows for the integration of diagnosis and therapy, a concept known as theragnostic. This approach aims to increase the accuracy of diagnosis and treatment by targeting specific diseased tissues or cells. Nanoparticles are being explored as carriers for both diagnostic agents and drugs, providing potential for non-invasive diagnosis and precise cancer therapy. For instance, combining small-interfering RNA-encapsulating polyplexes with gold nanoparticles has demonstrated multimodal optical imaging and enhanced gene silencing responses [147].

Tradename	Material	Drug	Company	Indication	Year(s) approved
Doxil®	Liposome-PEG	Doxorubicin	Janssen	MBC, metastatic ovarian cancer	1995
Eligard®	PLGA	Leuprolide acetate	Tolmar	Prostate Cancer	2002
Abraxane®	Albumin	Paclitaxel	Celgene	Metastatic breast cancer	2005
Genexol PM®	mPEG-PLA	Paclitaxel	Samyang Corporation	Metastatic breast cancer	2007
Onivyde®	Liposome	Irinotecan	Merrimack	Pancreatic cancer	2015

Benefits of Nanoparticles in Cancer Therapy

The incorporation of nanotechnology in cancer diagnosis, treatment, and management has brought about a significant shift in the field. Nanoparticles present various benefits through active and passive targeting, improving drug concentration in cells while reducing toxicity in healthy tissues.

Customized nanoparticles can be designed with pH or temperature sensitivity, allowing for controlled drug release. pH-responsive delivery systems excel in releasing medications in the acidic tumour microenvironment, while temperature-sensitive nanoparticles react to magnetic fields or ultrasound waves, delivering drugs precisely to the target area [148].

The "physicochemical attributes" of nanoparticles, such as shape, size, molecular weight, and surface properties, play a crucial role in targeted drug delivery systems. Moreover, nanoparticles can be tailored to focus on specific elements, providing personalized therapeutic strategies [149]. Conventional chemotherapy and radiation therapy face challenges regarding effectiveness and side effects due to uneven distribution and cytotoxicity, necessitating precise dosing for effective cancer cell eradication with minimal toxicity [150].

Traversing through various obstacles is vital for drugs to reach their intended destination. Drug metabolism is complex, involving passage through the tumour microenvironment, reticuloendothelial system, blood-brain barrier, and renal clearance [151]. The reticuloendothelial system, which includes blood monocytes, macrophages, and immune cells, interacts with drugs, activating macrophages or leukocytes that rapidly eliminate the drug, resulting in a short half-life. To counteract this, surface-modified nanoparticles, like those coated with PEG, avoid this process and extend the drug's half-life [152].

Facilitating kidney penetration is essential for reducing nanoparticle-induced toxicity, while breaching the blood-brain barrier is crucial for treatments related to the brain [153]. Nanoparticles exhibit the ability to cross the blood-brain barrier through methods like the enhanced permeability and retention effect, focused ultrasound, peptide-modified endocytosis, and transcytosis. Some nanoparticles, such as glutathione PEGylated liposomes containing methotrexate, have demonstrated enhanced drug uptake in animal studies. Gold nanoparticles are also utilized for efficient drug transportation and apoptosis induction.

Nanoparticles serve not only as carriers but also play a crucial role in increasing drug stability by safeguarding the enclosed content from deterioration. They can accommodate substantial medication doses without triggering chemical responses. Compared to liquid nano products, solid dry dosage forms offer superior stability, which can be further enhanced with stabilizers. The utilization of porous nanoparticles represents an additional strategy for boosting stability.

Tumours exhibit specific pathophysiological traits, such as extensive angiogenesis, irregular vascular structure, and compromised lymphatic drainage. Nanoparticles leverage these characteristics to effectively target tumour tissue, taking advantage of reduced venous return and limited lymphatic drainage. This phenomenon, referred to as the EPR effect, enables nanoparticles to accumulate within tumours. Moreover, targeting adjacent tissues aids in the delivery of drugs specifically to tumour cells [154].

Nanoparticles can be administered through various means, including oral, nasal, parenteral, and intraocular routes. Their high surface-to-volume ratio and efficient cellular uptake have been proven to outperform microparticles as superior vehicles for drug delivery. Research emphasizes the heightened efficacy of nanoparticles in drug delivery when compared to larger microparticles. [155].

Nanoparticles in Immunotherapy

The immune system plays a crucial role in the development and advancement of cancer cells. The rise of immunotherapy has led to a significant transformation in the treatment methods for cancer. Nanoparticles [NPs] not only enable precise drug delivery for chemotherapy but also show promise in conjunction with immunotherapy techniques. Diverse approaches in immunotherapy aim to stimulate the immune system's response against cancer cells [156], such as "immunotherapy using

immune checkpoint blockade" and "cancer vaccine therapy". Chimeric antigen receptor [CAR]- cell therapy," as well as "immune system modulator therapy"[157-159] are part of NP-based immunotherapies which include "Nano vaccines," "artificial antigen-presenting cells [aAPCs]," and "immunosuppressed tumour microenvironment [TME] targeting."

Nano vaccines are designed to target "tumour-associated antigens" [TAAs] and "adjuvant" specifically to antigen-presenting cells such as dendritic cells [DCs] [160]. "They can act as enhancers to increase the display of antigens by cells that present antigens [APC] and support the maturation of DCs, subsequently initiating responses from cytotoxic T cells against tumours [161, 162]. "Liposomes, PLGA nanoparticles, and gold nanoparticles have shown the capacity to transport tumour-associated antigens (TAAs) into dendritic cells (DCs) located in the cytoplasm [163]. Mesoporous silica, which is among the most commonly used inorganic nanoparticles, demonstrates adjuvant properties that boost immune responses. [164]. Artificial antigen-presenting cells (APCs) directly engage with MHC-antigen complexes, interacting with T cells and co-stimulatory molecules to trigger T cell responses [165].

Targeting the immunosuppressive tumour microenvironment (TME) is an area where nanoparticles (NPs) show great promise in immunotherapy. This strategy involves guiding NPs specifically towards key cell types in the TME, such as tumour-associated macrophages (TAMs), regulatory T cells, and myeloid-derived suppressor cells (MDSCs). Additionally, the combination of chemotherapy and immunotherapy has proven to be effective in treating cancer. For instance, a study illustrated the enhanced proliferation of cytotoxic CD8[+] T cells and the activation of the immune response by co-loading the chemotherapeutic drug Nutlin-3a and the cytokine GM-CSF into NPs modified with spermine-acetylated dextran (AcDEX) [166].

Critical immune checkpoints include "programmed cell death protein 1 [PD-1]" and "programmed cell death ligand 1 [PD-L1]" [167]. To target these checkpoints, immune checkpoint inhibitors are employed, often utilizing NPs. A study found that conventional PD-L1/PD-1 immune checkpoint inhibitors exhibited inconsistent responses. To improve bonding efficacy, multivalent poly [amidoamine] dendrimers were employed, resulting in enhanced PD-L1 blockade and improved drug accumulation at tumour sites [168].

Nanoparticles in Cryosurgery

Cryosurgery, an innovative method involving the freezing and elimination of cancerous tissue, presents a less invasive option in contrast to traditional procedures (Figure 4). Despite its advantages, addressing issues such as limited freezing capacity and the potential harm to nearby cells is necessary [169]. The emergence of nanotechnology has brought NPs into the field of cryosurgery. Nano cryosurgery entails the introduction of NPs with specific characteristics into cancer cells, effectively triggering the process of freezing [170]. Within this procedure, the formation of ice inside cells results in cellular damage, which is a vital process well-suited for the application of NPs. Utilizing the thermal conductivity properties of NPs allows for the efficient freezing of tumour tissue, which ultimately leads to tumour damage [171]. Their rapid cooling ability facilitates control over the "growth direction" and "ice ball direction."

When faced with the challenge of cryosurgery due to tumour location or proximity to neighbouring organs, there is a persistent risk of harming healthy tissues. To address this issue, advanced methods involve utilizing phase change materials [PMs] made of NPs to protect surrounding healthy tissue during cryosurgery [172]. For instance, liposome-based microencapsulated phase change NPs have exhibited remarkable success in protecting surrounding healthy tissue [173]. These NPs

possess significant latent heat capacity and low thermal conductivity, rendering them highly suitable for cryosurgery applications.

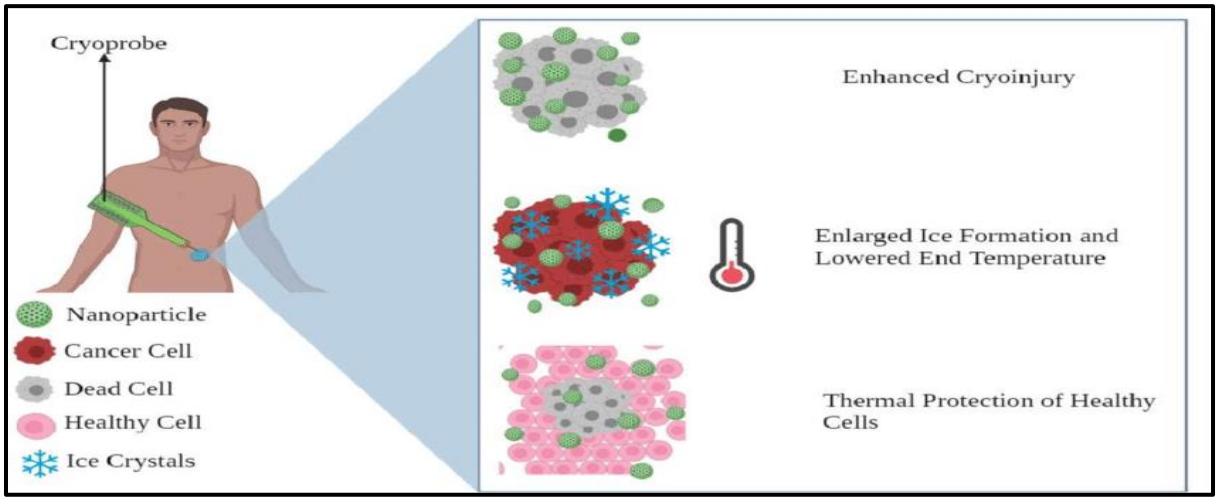

Fig 4: Cryosurgery, an innovative method involving the freezing and elimination of cancerous tissue.

Challenges in the Clinical operation of Nanoparticles

The rapid expansion of nanotechnology has resulted in an increase in exploration efforts in the realm of nanoparticles; however, only a limited number of these advancements progress to clinical trials. Many of these innovations stall at the in vitro and in vivo stages. While each specific Nano expression encounters unique challenges in clinical restatement, there are overarching obstacles that can be distributed as natural, technological, and study- design related.

Natural challenges encompass issues like the lack of suitable administration routes, difficulties in controlling biodistribution, the capability of nanoparticles to cut natural walls, implicit declination, and enterprises about toxin [174]. Generally, nanoparticles are administered through intravenous injections into the bloodstream, causing them to fleetly disperse down from the target point. Accordingly, high medicine attention is needed, which may not achieve the asked remedial issues [175]. nevertheless, glamorous nanoparticles offer an implicit result by exercising 3D glamorous fields to steer nanoparticles against the blood inflow. still, the safety of glamorous fields, their implicit relations, and the counteraccusations of exercising multitudinous nanoparticles need thorough disquisition. Managing the fate of nanoparticles within natural systems poses considerable challenges. Despite being composed of biocompatible accoutrements and finagled for prolonged retention and half- life, nanoparticles still pose pitfalls of lung, liver, and order damage. Factors like face area, flyspeck size, shape, solubility, and agglomeration govern toxin [176]. Lung deposit of nanoparticles has been observed, leading to inflammation, oxidative stress, and cytotoxic goods [177]. Healthy cells are also susceptible to free revolutionaries generated by nanoparticles [178]. Addressing toxin could involve the use of further biocompatible accoutrements like chitosan or developing accoutrements that disintegrate upon near- infrared light exposure. escaping the" mononuclear phagocytic system [MPS]" is another challenge. Nanoparticles adsorb proteins in natural fluids, leading to the conformation of a protein nimbus that triggers MPS uptake. sheeting nanoparticles with accoutrements that hamper protein nimbus conformation has been explored but yielded limited success. Designing nanoparticles targeting" macrophages" and employing them as new medicine carriers could give a feasible result. Being strategies include precluding macrophage reclamation, depleting and reprogramming tumour- associated macrophages [TAMs], and inhibiting" CD47- SIRPα pathways" [179].

Technological challenges related to the scaling up of Synthesis, harmonious optimization, and precise performance predictions are crucial for the successful clinical implementation of nanoparticles. The majority of nanoparticles utilized in both in vivo and in vitro experiments are produced in small batches, making it unfeasible to create large-scale products due to equipment constraints and other factors. Despite encouraging clinical results validated in animal models, they are often not fully optimized. To address this issue, systematic methods that involve testing different Nano formulations via selective repetitions can lead to a single, optimized formulation [180 – 182]. These discoveries should not be directly transferred to human trials. The complexity of predicting the effectiveness and behaviour of nanoparticles, as well as the challenge of replicating in vivo results in human trials, present significant obstacles. Using computational or theoretical models that mimic physiological tissues and environments can improve predictions. Technologies such as organs-on-chips show promise in enhancing the accuracy of predicting nanoparticle behaviour. Various challenges in study design, including factors like study size, aims, and the timing of nanoparticle treatments during therapy, greatly influence clinical studies. Dependence solely on "cell and animal models" may not always produce results that are applicable to human trials. Exercising a single model is inadequate to replicate the complexity of natural mortal responses. A significant challenge arises from the fact that nanoparticles are infrequently employed as first- line curatives. Despite approved Nano phrasings, they're frequently reserved for secondary treatments in cases of complaint progression during clinical trials. This disposed patient population could compromise the clinical trial results and limit the implicit benefits of nanoparticle treatments for those still amenable to treatment.

Conclusion and unborn Outlook

The objectification of nanotechnology into cancer treatment has fleetly expanded, offering the potential to design and modify parcels that surpass traditional curatives. Nanoparticles crop as the coming generation of cancer treatments, enabling precise delivery of motes for discovery, opinion, and remedy. The various methods focus on the unique characteristics of nanoparticles and are increasingly being adopted for different types of cancer. They improve the effectiveness of drug absorption, compatibility with the body, targeting tumours, and stability when compared to traditional medicines. Nanoparticles also facilitate the use of combination therapies to address resistance to multiple drugs. Current research emphasizes the improved efficiency of drug delivery using various nanoparticles. However, challenges persist, such as replicating conditions within a living organism, addressing immune responses, and managing long-term toxic effects. Despite the pledge of" Nano vaccines" and" artificial antigen- presenting cells," their clinical effectiveness is limited and necessitates safety assessments. The development of" immunomodulatory factor-loaded nanoparticles" has implicit to enhance immunotherapy. As exploration advances in comprehending cancer mechanisms and multidrug resistance, nanoparticle- grounded medicines, although abundant, remain primarily in exploratory stages. Addressing toxin, delivery mechanisms, and remedial impacts is vital for thoughtful design. visioning transformative issues, the confluence of nanotechnology and cancer remedy will reshape approaches grounded on nanoparticles.

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