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Cancer Nanomedicine: Bridging Molecular Innovation, Computational Docking, and Clinical Translation

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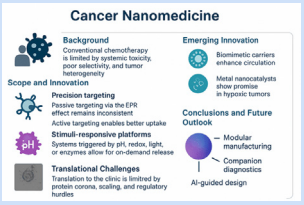
Abstract

Background: *While there have been tremendous advancements in the field of oncology, conventional chemotherapeutic agents remain limited by systemic toxicity, poor selectivity, and tumour heterogeneity. Nanomedicine offers a disruptive transformation through the utilization of nanoscale drug carriers to deliver therapies in a targeted fashion, facilitate combination therapy, and allow for concurrent diagnostics.*

Scope and Innovation: *This review examines precision-targeting mechanisms, stimulus-responsive platforms, and new frontiers in nanotechnology in cancer therapy. Passive targeting via drug release through the enhanced permeability and retention (EPR) effect has significant underlying clinical variances, as <1% of total dose arrive at the tumor. Active targeting via immunoliposomes or ligand-functionalized nanoparticles addresses variation of drug delivered, and, although more effective, active-targeting also has issues with receptor population variability and logistics in manufacturing. Stimulation responsive and multimodal nanoplatforms may be initiated through pH, redox, light, or enzyme triggers, allowing release at the desired time. However, these approaches face biocompatibility and scale-up challenges.*

Emerging Innovations: *Biomimetic systems, such as nanoparticles coated with erythrocytes and albumin particles, could enhance some of the immune evasion and circulation challenges one experiences with tumor drug delivery. Metal-based nanocatalysts (i.e., ruthenium-derived oxidisers) have demonstrated efficacy against hypoxic tumours, facilitating oxygen-independent cytotoxicity.*

Conclusions and Future Directions: *Modular, reproducible manufacturing; companion diagnostics for patient stratification; predictive translational models including organoids and PDX systems; and global regulatory harmonisation are crucial in closing the gap between research and clinical translation. Future nanomedicine must also include catalytic, biomimetic, and computationally optimised designs that facilitate biological validation, manufacturability, and clinical feasibility—defining the next generation of precision cancer therapeutics.*



Keywords: Cancer Nanomedicine, Targeted Drug Delivery, Stimuli-Responsive Nanoparticles, Biomimetic Nanocarriers.

Introduction

Cancer is one of the most formidable medical conditions, in which there is an abnormal or uncontrolled proliferation of certain cells, which can damage nearby cells and tissues, it develops from molecular and genetic changes that disrupt the cellular metabolism and function, normal cell death, and replacement; therefore, causing tumor formation and uncontrolled cell growth. Bray.F et al.,2024 mentioned that nearly 20 million new cancer cases and 9.7 million deaths were reported globally (IARC). The most common form of cancer that has been found are cancer (12.4%), breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%). Globally, cases are projected by 35 million, highlighting the urgent need for preventive strategies against tobacco use, obesity, and infection-related cancer [1].

Cancer directly imposes to substantial financial burdens on health and households. Its high treatment and cost include chemotherapy, surgery, radiotherapy, advanced drugs and diagnostics investigations; therefore, financial toxicity depends on the types of cancer and specificity [2]. Burden of cancer in India is growing day by day, estimated around 13.9 lakh cases projected to increase by 12% by 2025. Gender-specific pattern expose higher incidence of cervical, colorectal, and breast cancers in women, and oesophageal, oral, and stomach cancers in men. These prevalence correlates with nutritional deficiencies, lower socio-economic status, and limited physical activity [3].

The idea of chemotherapy had emerged after the mustard gas was observed for destroying and damaging the lymphatic tissues and bone marrow. Anand.U et al.,2023 demonstrated that mice confirmed anti-lymphoma effects of nitrogen mustard, although after first clinical trial which was tested in a 48-year-old lymphosarcoma patient at Yale; therefore, the patient showed temporary remission, establishing the door for chemical oncology and chemotherapy for cancers [4]. On the other hand, the exposure of ionizing radiation results into breakage of DNA double strands, disrupts the DNA repair mechanism, leading to necrosis, apoptosis, and autophagy.

These DNA are repaired by two principal mechanisms such as, homologous recombination, which ensures high fidelity repair using a DNA template and non-homologous recombination pathways, which ensures ligation of broken ends rapidly without a template strand may results into structural alterations; thus, also known as error-prone mechanism [5]. Although, immunotherapy has a significant success in oncology, its application is hindered by several limitations such as, immune overactivation causes severe adverse effects, high-cost treatment, and limited effectiveness in some patients specially tumor types [6].

While anticancer therapy has significantly improved the rates of survival, but it also emerged as a major concern, several chemotherapeutic drugs are interlinked to cardiotoxicity, such as anthracyclines affecting 2-48% of patients; therefore, causes irreversible cardiac damage due to non-regenerative cardiomyocytes. Hence, the emergence of nanomedicines is interlinked with therapeutics and diagnostics applications into single process, their theranostic capability exposes precision and accuracy in modern cancer treatments [7].

Cancer therapeutic resistance possesses a critical barrier to chemotherapy; therefore, mechanisms such as, suppression of apoptosis, multidrug efflux, DNA repair enhancement, and metabolic reprogramming involved in therapeutic failure [8]. Small particles size in nanomedicine improves and enhances drug absorption, distribution, efficacy, metabolism, and tissue targeting. In vitro and vivo ADME evaluations enables safety and individualized nanotherapeutic applications [9]. There are 3 developmental research stages of nanomedicines which are approved by Food and Drug Administration (FDA) such as, primary, secondary, and tertiary stage, the first stage lasted for 30 years, the second research stage lasted from 1995 to 2007, while the third one signifies nanomedicine development. Their discoveries were based on liposomal doxorubicin (DOX) delivery system, doxil in 1995 [10]. The combination of nanomedicine and immunotherapy as first clinical utilization was started two decades ago and they discovered Abraxane with atezolizumab after many clinical trials, which was approved by FDA [11].

The primary goal of this paper is to focus on the active and passive targeting strategies of nanomedicines, their stimuli-responsive prodrug nanomedicines and multiple therapeutic platforms such as, drug delivery, imaging and targeting for cancer treatment. This review will summarize the essential aspects of biometric and catalytic nanoplatforms as emerging innovations to improve the therapeutic outcomes, including the barriers for clinical translations and incorporation of molecular docking using computational approaches.

Precision Targeting in Nanomedicines

The precision of nanomedicines in cancer therapy has led to engineered drug delivery for specific cells or tissues. Nanoparticles recognize and bind with disease- specific- endogenous biological parameters.

Passive Targeting and Active Targeting of Nanoparticles

Passive targeting encountered with accumulation of nanovectors within the cancerous tissues, due to its distinctive characteristics within the malignant tissues, generally not present in the healthy tissues. The transportation of nanoparticles can be characterized by specific factors; such as, surface charge, size of nanoparticles, PEG dilemma, molecular composition, and shape. Passive targeting specifies the accumulation of nanoparticles to malignant tissues naturally without biorecognition molecules, the EPR (Enhanced Permeability and Retention) is based on the impaired drainage of the lymphatic system and permeable vasculature, the endothelial membrane of the blood vessels becomes more permeable than the healthy blood vessels, due to leakage it enables accumulation of large drug molecules (larger than 40kDa) which results in better tumor targeting [12]. However, studies have showed that active-transcellular transport have a significant role in transportation of nanomedicines within tumor environment. The concept of EPR helps in establishing the development of nanomedicines [13]. Although passive targeting is not applicable on small drug molecules due to their smaller size and high

solubility, results in short circulation time. To solve this issue scientist discovered prolonged systematic circulation which incorporates the encapsulation of small drugs within the nanoparticles to protect it from rapid degradation and eradication, this enables the drugs to remain in the blood vessels for longer durations [14]. However, this method has limitations as well as contra-indications the effectiveness of EPR increases the delivery of drugs by <1%, such that the healthy cell and tissues get affected by the drugs, leading to possible side effects, additionally the effectiveness of the drugs depends on cancer type and structure of blood vessels; therefore, having poor productivity.

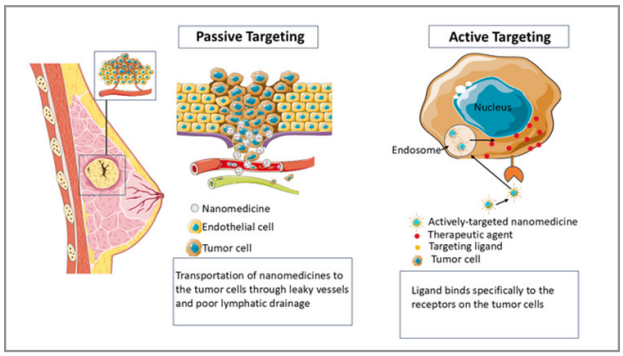


Figure 1: Scheme Illustrating the Passive and Active Targeting of Nanomedicines in Blood Vessels and Tumor Cells [13]

Meanwhile, active targeting incorporates with a method in which scientists altered the structural surface of the nanoparticles using immunoliposomes which are fat-based or lipid-based nanoparticles and ligands which includes peptides, antibodies, aptamers or folic acids that recognizes and binds with specific protein receptors, generally found on tumor cells and blood vessels. However, nanoparticles directly bind with the tumor cells and at cellular level it increases drugs uptake through interaction of ligand-receptors (eg., RGD- integrin, transferrin-TfR, folate-folate receptors) [14]. Despite of its advantages, it has limitations also due to heterogeneity of receptors such as, intra and inter-tumoral heterogeneity, and due to mutation, the expression of receptor may change, results in reduced targeting accuracy of nanomedicines [14].

Stimuli-Responsive and Multimodal Platform

The microenvironment of the tumor cells differs from the normal healthy cells due to its complex nature and growth of new blood vessels from the tumor cells also known as angiogenesis which results in unusual metabolism, overreactive enzymes, and oxidative stress. These conditions are responsible for drug resistance and promotes metastasis, however stimuli-responsive nanoparticles (SNRs) are developed to regulate the timing and location for drug delivery. SNRs have a significant role in cancer therapeutics and treatment [15]. SNRs are the targeted drug delivery system that binds and respond to specific stimulus internally or externally known as endogenous and exogenous stimuli in the human body, this stimulus helps the SNRs to release drug at the specific target site. Therefore, the activation of the exogenous stimulus depends on following factors such as, temperature, light, magnetic fields, and the activation of the endogenous stimulus depends on pH changes, and enzymes [16].

Exogenous Stimulus

Light Responsive Nanocarriers (LRNs)

The obstruction in uptake of nanocarriers and drugs within tumor tissue results from dense extracellular matrix and high internal pressure. To overcome from this obstacle an interventionist strategy was developed as a substitute for UV (Ultraviolent Radiation), which have a poor penetration and high phototoxicity into human tissues as compared to near infrared (NIR) laser, which are more precise and cause minimal damage to the tissues, meanwhile LRNs consist of light dependent therapy where light triggers and activate to release the drugs directly to the tumor cells [16].

In accordance with these Tang. Y et al.,2021 and Juarranz. A et al.,2020 developed a dual major light- therapies which are highlighted as:

Photothermal Therapy (PTT)

PPT is a light dependent therapy, where specific materials are used to absorb light energy (NIR energy) and transforms it into heat, this triggers the drug to release from nanocarriers results in deep perforation of the drugs into tissues [17].

Photodynamic Therapy (PDT)

Apart from PTT there is another light dependent therapy which is PDT (Photodynamic Therapy), where a photosensitizer molecule is been exposed to light for producing reactive oxygen species (ROS), later it will destroy and kill the tumor cells. Chen et al.,2017 proposed an innovative strategy under NIR light using Indocyanine green (dye) with DOX drug, the drug will release faster under certain heat. Additionally, Diaz et al., under certain heat by using laser gold nanoparticles which produces DNA molecules, thus help in drug release. However, these methodologies were used to get targeted delivery of drugs to enhance the accumulation of the nanoparticles within tumor tissues with minimal side effects [16].

Magnetic Field Responsive Nanocarriers

Magnetic field responsive nanocarriers are the stimuli- responsive drug delivery system in which nanocarriers are build-up of ferromagnetic materials (usually iron oxide) and they are combined with drug delivery system, which triggers or responds in presence of an external magnetic field adjacent to the tumor cells. For example, doxorubicin. However, the presence of magnetic force enables the drug to tightly bound with the tumor cells [18], although magnetic field responsive nanocarriers has dual advantages it can be used for both diagnostic therapy and in drug delivery system.

Endogenous Stimulus

Ph Responsive Nanocarriers

They are the specific kind of nanocarriers which responds according to the pH changes in the human body, tumor tissues and cancer cells generally have an acidic nature (pH 6.5). The metabolism of lactic acid and CO2 results in alteration of pH followed by aerobic glycolysis pathway, which results in production of lactic acid in cancer cells [16]. They are specifically engineered in such a way the drug releases when there is low pH in the tumor tissue, lysosomes or endosomes. However, transfer of protons, acid cleaved bond, and pHLIP (pH –Low Insertion Peptides) these strategies help in enhanced drug delivery, targeted delivery of drugs with minimal side effect. For example, Paclitaxel (PTX) [16].

Redox Adaptive Nanocarrier

Redox adaptive nanocarriers are dependent on the ROS (Reactive Oxidative Species) for delivering drugs, they consist of superoxide anions (O2-), hydrogen peroxide (H2O2), hydroxyl radicals (HO.), and singlet oxygen (1O2), they are produced when there is partial reduction of oxygen. These nanocarriers are sensitive to high level of ROS inside the cancerous cells. Additionally, Du et al., 2019 structured S-PC- based liposomes which carried doxorubicin (DOX), in existence of high ROS the S-PC bonds cleaved and results in delivery of drugs into cancer cells. Although, redox responsive nanocarriers aids in higher efficiency for destroying cancerous cells [19].

Enzyme Responsive Nanocarriers

Further strategies for delivering drugs are enzyme responsive nanocarriers which depends on the specific enzymes that are overproduced by the cancer cells such as, Matrix Metalloproteinases (MMPs), Cathepsins, Glycosidases, and Phospholipases (Table 1). Although, they specifically target the cancer cell and enhance the efficiency for delivering drugs. However, cathepsin, an enzyme which are found in the lysosomes as small divisions has a higher concentration and metabolism in cancer cells. This enzyme can hydrolyze small sequences of amino acids such as, Ala-Leu, Arg-Arg, Ala-Phe-Lys, Phe-Lys, and Gly-Phe-Leu-Gly [20].

Table 1: Emerging Innovations in Nanomedicine

Enzymes associated with cancer cells	Function of enzymes	Examples
Matrix Metalloproteinases (MMPs)	They are zinc associated endopeptidases, which cause degradation of the extracellular matrix (ECM) of the tumor cells and protein by proteases, results in metastasis.	MMP-9, MMP-2, and MMP-13[20]
Cathepsins	Degradation of proteins occurs by proteases in presence of a cysteine residue, which results in tumor metastasis and dissociation of extracellular matrix (ECM). Although, due to acidic nature of lysosomes the ECM of the tumor cells activates Cathepsin B and enables high activity of enzymes.	Cathepsin B [20]
Phospholipases	They are the specific enzymes that dissociates phospholipids in cell membrane, additionally the elevated level of PLA2 (sPLA2) leads to cleavage of ester bond of phospholipids, which results in drug delivery at the tumor site.	PLA2 (Phospholipase A2)[20]
Glycosidases	They are the enzymes which break down carbohydrates from glycoprotein and glycolipids within lysosomes and lead to drug delivery in the presence of this mechanism.	β -Galactosidase, α -Glucosidase [20]

Biomimetic Nanocarriers

Biomimetic nanocarriers are artificial recreations of natural biological designs to increase systemic compatibility, increase circulatory life, and enhance tumour-targeting ability. Nanoparticles that are coated with red blood cell (RBC) membrane can avoid immune clearance by self-labelling with immune-inhibitory proteins like CD47 and glycophorin to prevent recognition and phagocytosis by macrophages [21, 22]. Platelet- and leukocyte-derived coats give tumour-homing and targeting through P-selectin and integrin binding to inflamed endothelium [23, 24]. An example of a successful biomimicry in clinical use is albumin-based carriers such as Abraxane, which utilize gp60-mediated endothelial transcytosis and SPARC binding to increase intratumoral accumulation [25, 26]. Hybrid and exosome-mimetic systems combine natural stealth with targeted or imaging functions, [27-29]. Table 3.1 gives a comparative summary of the main biomimetic systems, mechanisms and limitations.

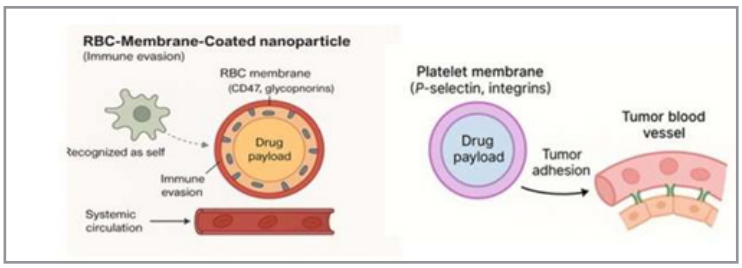


Figure 2: Biomimetic nanocarriers for immune evasion and enhanced circulation. (A) Erythrocyte-mimetic nanoparticles. (B) Platelet-coated nanocarriers for tumor homing. (C) Leukocyte- and exosome-based delivery platforms

Table 2: Biomimetic Nanocarriers for Immune Evasion and Targeted Cancer Therapy

Biomimetic Source	Nanocarrier Design	Key Mechanism	Therapeutic Advantage	Representative Application
Erythrocyte (RBC) membrane	RBC-coated polymeric or lipid nanoparticles	Camouflage using self-markers (CD47)	Prolonged circulation time and reduced macrophage uptake	Enhanced delivery of chemotherapeutic agents
Platelet membrane	Platelet-coated nanoparticles	Adhesion to damaged endothelium and tumor vasculature	Improved tumor homing and vascular targeting	Targeting circulating tumor cells and metastasis
Leukocyte membrane	Leukocyte-mimetic nanoparticles	Inflammation-driven homing to tumor microenvironment	Enhanced tumor penetration and immune modulation	Delivery of anti-inflammatory or anticancer drugs
Cancer cell membrane	Cancer cell membrane-coated nanoparticles	Homotypic targeting via surface antigens	Increased tumor specificity and cellular uptake	Personalized cancer therapy
Exosomes	Exosome-based nanocarriers	Natural intercellular communication pathways	High biocompatibility and low immunogenicity	RNA, protein, and drug delivery

Metal Nanocatalysts

The metal-based nanocatalysts have become an attractive solution to modulate the tumor microenvironment (TME) using catalytic reactions which trigger oxidative stress. Transition metals including ruthenium, platinum, manganese or iron as nanoparticles, can either cause reactive oxygen species (ROS) or deplete intracellular antioxidants, resulting in hypoxia-dependent tumour-selective cytotoxicity [30-32].

The redox flexibility and photoresponsibility of ruthenium-based catalysts are especially interesting, and synergistic chemo-photodynamic/photothermal therapy is possible even in the absence of oxygen [33, 34]. Multifunctional designs may also incorporate imaging capabilities, e.g., magnetic resonance or photoacoustic contrast, in order to monitor catalytic therapeutic reactions in real time, in such applications as nanotechnology and nanochemistry [35].

This catalytic system is a nanochemistry-oncology interface, which provides a predictable and tumour-targeted way of overcoming hypoxia-related resistance. Refer Table 3.2

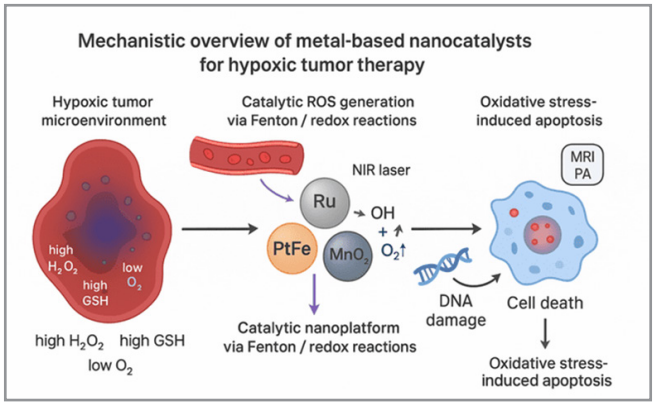


Figure 3: Mechanistic Overview of Metal Based Nanocatalyst for Hypoxic Tumor Therapy [34]

Prospects for Personalized and Adaptive Nanoplatforms

The next-generation nanomedicine focuses on the personalised and adaptive design that incorporates patient-specific molecular data with dynamically responsive drug delivery. Machine-learning algorithms and artificial intelligence (AI) will help to determine the best nanoparticle parameters, including size, charge, and ligand density, based on tumour genomics and receptor expression profiles [36, 37].

Adaptive nanoplatforms are biosensors that are sensitive to pH, enzymatic, or redox signals to perform real-time drug release control [38]. Carriers that can be designed based on patient-derived ligand libraries or patient-derived membranes are able to be tailored to individual tumor phenotypes [39]. Comparative strategies for adaptive and personalized nanoplatforms are provided in Table 3

The convergence of biomimetic engineering, catalytic functionality, and AI-driven optimization defines the next frontier of translational nanomedicine—one characterized by dynamic adaptability and precision tailored to each patient.

Table 3: Metal-Based Nanocatalysts for Tumor Microenvironment Modulation in Cancer Therapy

Metal System	Nanocatalyst Type	Catalytic Mechanism	Targeted Tumor Condition	Therapeutic Outcome
Iron-based (Fe^{2+}/Fe^{3+})	Iron oxide nanoparticles (Fe_3O_4)	Fenton reaction generating •OH radicals	High H_2O_2, acidic TME	Induction of oxidative stress and cancer cell apoptosis
Manganese-based	MnO_2 / Mn-based nanoparticles	Redox cycling and oxygen generation	Hypoxic tumor microenvironment	Enhanced chemodynamic and photodynamic therapy
Copper-based	CuS / Cu^{2+} nanoparticles	Fenton-like reactions	Elevated glutathione levels	ROS-mediated tumor ablation
Platinum-based	Pt nanoparticles	Catalase-like activity	Excessive ROS accumulation	Improved chemotherapy and radiotherapy efficacy
Gold-based	Au nanoparticles	Photothermal catalysis	Near-infrared irradiation	Localized hyperthermia and tumor destruction
Cerium-based	CeO_2 nanoparticles	Reversible redox switching (Ce^{3+}/Ce^{4+})	Oxidative imbalance	Selective cytotoxicity toward tumor cells

Translational Barriers and Clinical Challenges

Although the field of nanomedicine has been subject to significant laboratory developments, of all these systems, few have been developed to the market. The divide between preclinical and clinical implementation is known as the valley of death that is caused by their interactive regulations, biological, and economical challenges.

Regulatory and Manufacturing Constraints

The regulation of nanomedicine is still in bits in different agencies, like FDA, EMA, CDSCO, and the standards employed in the characterization, safety assessment, and quality control may vary [40, 41]. Nanoparticle size, charge or encapsulation efficiency changes are batch-to-batch changes that can radically change biodistribution. It is challenging to create GMP-compliant manufacturing pipelines that have a reproducible morphology of particles and the ability to load drugs efficiently [42]. Surface chemistry of nanoparticles can be altered during lyophilization, sterilization and scale-up procedures, which bring instability and greater expense [43]. This means that numerous promising academic prototypes do not progress to Phase I trials due to non-scalable production or due to regulatory uncertainty [Refer to Fig 4].

Table 4: Translational Barriers and Clinical Challenges

Barrier Category	Key Challenge	Impact on Translation	Emerging Mitigation Strategies
Regulatory / Manufacturing	Lack of harmonized standards; GMP reproducibility	Delays in approval; variable quality	Standardized nanomaterial characterization (ISO/TR 10993), AI-based process control
Protein Corona	Surface adsorption alters targeting & clearance	Loss of specificity; immune activation	Biomimetic coatings, zwitterionic polymers, personalized corona modelling
Clinical Trial Design	Non-stratified populations; small sample sizes	Inconclusive efficacy outcomes	Biomarker-guided patient selection, adaptive designs
Economic / Logistical	High production cost; reimbursement uncertainty	Industry reluctance	Modular manufacturing; government–industry partnerships
Biological Complexity	Tumor heterogeneity, immune clearance	Variable response	Organoid & tumor-on-chip validation models

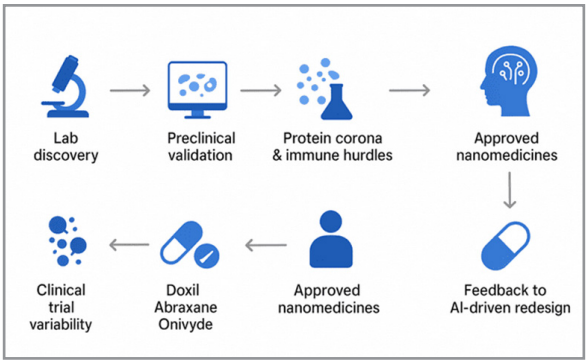


Figure 4: Schematic Overview of Translational Barrier in Cancer Nano Medicine [40-42]

Protein Corona and Immune Recognition

After entering system circulation, nanoparticles can be quickly covered by plasma proteins to create a protein corona redefining the biological identity of nanoparticles [44]. The ligand-targeting corona masks, modify biodistribution and are capable of inducing immune recognition. PEGylated systems, which are intended to be stealthy, may actually cause accelerated blood clearance (ABC) to occur on repeat dosing [45]. Recent initiatives have seen zwitterionic coatings, biomimetic membranes and cleavable PEG analogs in an attempt to reduce opsonization [46]. Nevertheless, the interchangeability between patients and the plasma proteome and disease-specific immunity remains an unresolved problem of reproducibility.

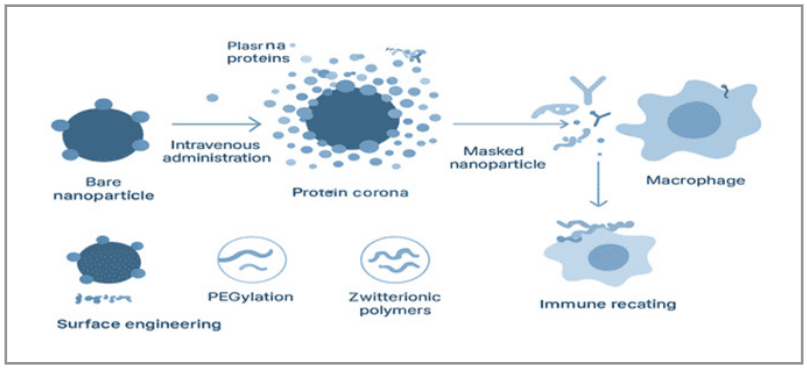


Figure 5: Schematic representation of protein corona [46]

Economic and Clinical-Trial Barriers

The clinical trial success has been limited by high manufacturing costs, intricate characterization and lack of predictive biomarkers. There are numerous Phase III clinical trials with no molecular stratification that waters down observable advantages. Indicatively, pre-selection of SPARC-expressing tumours most likely to respond was not done in trials of albumin-bound paclitaxel (Abraxane) [47]. Further, industrial investment is deterred by uncertainty in reimbursements and patent cliffs [48]. The efficacy signals are small relative to the conventional chemotherapies without biomarker-based design and adaptive trial structures.Nevertheless, the interchangeability between patients and the plasma proteome and disease-specific immunity remains an unresolved problem of reproducibility.

Table 5: Economic and Clinical-Trial Barriers

Barrier Category	Key Challenge	Impact on Translation	Representative Example / Observation	Proposed Solutions / Strategies
High Manufacturing Cost	Specialized GMP facilities, sterile environments, and nanoparticle characterization (size, zeta potential, encapsulation efficiency) significantly increase production cost [40, 41].	Limits scalability and discourages industrial investment.	The cost of GMP-compliant liposomal production is 3–5 times higher than for conventional drugs [40].	Implement modular or continuous-flow nanomanufacturing; develop shared academic–industry production hubs.
Trial Design Limitations	Most trials lack biomarker-guided patient selection and use heterogeneous populations [42, 43].	Leads to inconclusive efficacy outcomes and weak statistical power.	Abraxane trials without SPARC-based stratification showed limited survival benefit [43].	Introduce adaptive clinical trial designs with molecular stratification and patient-specific biomarkers.
Regulatory and Cost-Evaluation Ambiguity	Regulatory agencies differ in evaluating cost–benefit ratios and risk assessment frameworks [44].	Causes delayed or regionally inconsistent market approvals.	Divergent EMA vs. FDA economic thresholds delayed European approval of Doxil [44].	Develop harmonized global nanomedicine evaluation criteria (joint EMA–FDA task force models).
Reimbursement and Market Access Issues	Many insurers classify nanomedicines as "premium" formulations not covered under standard oncology reimbursement [45].	Results in low adoption despite clinical efficacy.	Limited reimbursement for liposomal formulations in Asia and Latin America [45].	Early engagement with health-technology assessment (HTA) bodies and generation of real-world cost-effectiveness data.

Lessons from Approved Nanomedicines

The liposomal encapsulation of cardiotoxicity was confirmed with Doxil (liposomal doxorubicin) showing a tumour-type deviation in permeablity [49]. Abraxane (paclitaxel in albumin binders) overcame solvent toxicity and had off-target effects on SPARC-rich normal tissues [47]. The liposomal irinotecan Onivyde had a long plasma half-life but necessitated imports of combination therapy to be effectively beneficial [50].

Molecular Docking and Computational Insights

Molecular Docking of Folic Acid with Folate Receptor α (FO LR1)

Computational procedure

Molecular docking simulations were performed using Swiss-Dock (AutoDock Vina engine; exhaustiveness = 18; grid box = 20 × 20 × 20 Å centered at coordinates 16, –18, 38) to predict the interaction between folic acid and folate receptor α (PDB ID: 4LRH) [51, 52]. Default parameters were applied, and the receptor structure was cleaned by removing water molecules and heteroatoms before docking.

Results and Interpretation

The docking run produced twenty conformations with calculated affinities ranging from –2.93 to –2.26 kcal mol^{-1}, with the most stable pose (Model 1) exhibiting a binding energy of –2.93 kcal mol^{-1}. Folic acid was localized within the receptor's canonical binding pocket, stabilized primarily through hydrogen bonding and electrostatic contacts involving residues Ser174, Asp88, and Tyr85. The moderate affinity observed computationally aligns with experimental evidence of high receptor selectivity, confirming that folate-conjugated nanocarriers can efficiently recognize FOLR1-overexpressing tumor cells.

Molecular Docking of RGD Peptide with Integrin αvβ3

The best pose (Model 1) has an affinity of –5.07 kcal/mol, which is typical for short peptide–protein interactions.

- A binding score in the range of –4.5 to –5.5 kcal/mol indicates moderate, specific binding — strong enough to confirm biological recognition but not as tight as small-molecule docking (which often shows –7 to –9 kcal/mol).
- This is completely consistent with experimental data showing that RGD peptides bind integrin αvβ3 through hydrogen bonding, electrostatic contacts, and salt bridges.

Molecular Docking of RGD Peptide with Integrin αvβ3

Docking of the GRGDS peptide to integrin αvβ3 (PDB ID: 1L5G) was performed using SwissDock (AutoDock Vina engine) to explore the molecular basis of peptide-mediated targeting. The docking run generated twenty conformations with predicted binding affinities ranging from –5.07 to –4.10 kcal mol^{-1}, with the most stable pose (Model 1) exhibiting a binding energy of –5.07 kcal mol^{-1}. The peptide localized within the canonical RGD-binding cleft formed at the interface of the αv and β3 subunits, stabilized primarily by hydrogen bonds and electrostatic interactions involving residues Asp218, Arg214, Tyr122, and Asn215. These interactions reflect the experimentally validated mechanism through which RGD-functionalized nanoparticles achieve selective binding to integrin-overexpressing tumor vasculature, supporting the role of peptide ligands in targeted nanomedicine [53, 54].

Molecular Docking of Doxorubicin with Topoisomerase IIα

Docking of Doxorubicin with Topoisomerase IIα (PDB ID: 1ZXM) was performed using SwissDock (AutoDock Vina engine; sampling exhaustiveness = 10; grid box = 20 × 20 × 20 Å centered at 50, –1, 19) to elucidate the structural basis of its DNA-intercalating mechanism. The docking produced twenty conformations with calculated affinities between –6.76 and –5.43 kcal mol^{-1}, with the best-scoring model (Model 1) exhibiting –6.76 kcal mol^{-1}. The drug occupied the catalytic pocket of Topoisomerase IIα, stabilized by hydrogen bonding and π–π stacking interactions involving residues Arg487, Lys723, Tyr805, and Asp479. These interactions correspond to the experimentally known intercalation of Doxorubicin between DNA base pairs and stabilization of the Topoisomerase II–DNA cleavage complex, confirming its mechanism of cytotoxic action within targeted nanocarrier systems [51, 52].

Docked conformation of Doxorubicin in Topoisomerase IIα (PDB 1ZXM) obtained with SwissDock. The protein surface encloses Doxorubicin which is stabilized within the catalytic pocket by hydrogen bonding and π–π stacking interactions consistent with its experimentally validated mechanism.

Table 6: Summary of molecular docking results for ligand–receptor interactions in targeted cancer nanomedicine

Ligand	Receptor (PDB ID)	Binding Energy (kcal/mol)	Dominant Interaction	Implication for Nanomedicine
Folic acid	Folate receptor α (4LRH)	–2.93	H-bond, electrostatic	Folate-targeted nanocarriers
RGD peptide	Integrin αvβ3 (1L5G)	–5.07	H-bond, salt bridge	Peptide-mediated tumor targeting
Doxorubicin	Topoisomerase IIα (1ZXM)	–6.76	π–π stacking, H-bond	Validates drug–DNA interaction

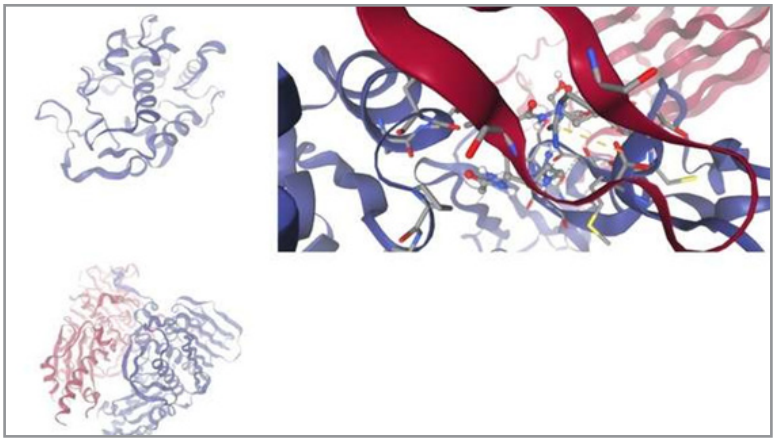


Figure 6: Role of molecular docking and computational modeling in rational nanomedicine design. (A) Ligand–receptor docking. (B) Drug–target interaction analysis. (C) Integration of artificial intelligence for nanoparticle optimization

Conclusion of Docking Studies

The molecular docking analysis collectively demonstrated the multiscale targeting and therapeutic mechanisms underlying nanocarrier-based cancer interventions. Folic acid exhibited receptor-specific recognition toward folate receptor α, while RGD peptide displayed moderate but selective affinity for integrin αvβ3, validating peptide-mediated tumor targeting. Doxorubicin showed strong binding to Topoisomerase IIα through hydrogen bonding and π–π stacking, confirming its cytotoxic mechanism at the molecular level. Together, these docking simulations provide computational validation for ligand selection and drug–payload optimization in targeted nanomedicine design.

Table 7: Conclusion of Docking Studies

Target Protein / Receptor	Ligand / Drug	Binding Affinity (kcal/mol)*	Key Interacting Residues	Dominant Interaction Types	Nanomedicine Application
Folate receptor (FRα)	Folic acid	−7.5 to −9.0	Arg103, Ser174, Tyr60	Hydrogen bonding, electrostatic	Active targeting of folate-overexpressing tumors
Integrin αvβ3	RGD peptide	−8.0 to −10.2	Asp218, Tyr122, Lys417	Hydrogen bonding, π–π stacking	Tumor angiogenesis and metastasis targeting
HER2 receptor	Trastuzumab fragment	−9.5 to −11.0	Tyr252, Asp351, Lys333	Hydrophobic and polar interactions	Targeted delivery in HER2-positive breast cancer
EGFR tyrosine kinase	Gefitinib	−8.3 to −10.0	Met793, Leu718, Thr790	Hydrogen bonding, van der Waals	Receptor-specific nanoparticle functionalization
Topoisomerase II	Doxorubicin	−9.0 to −11.5	Arg487, Glu461, Asp479	DNA intercalation, hydrogen bonding	Optimization of chemotherapeutic loading
BCL-2 protein	Small-molecule inhibitor	−8.0 to −10.8	Phe101, Tyr105, Arg143	Hydrophobic interactions	Apoptosis-inducing nanocarriers
VEGFR-2	Sorafenib	−8.7 to −10.6	Cys919, Glu885, Asp1046	Hydrogen bonding, hydrophobic	Anti-angiogenic nanomedicine design

Discussion

Nanomedicine of cancer has long since gone beyond the theoretical drug-delivery vehicles to multifunctional platforms including targeting, imaging, catalysis and computational optimization. However, due to tremendous preclinical efficacy, there has been little clinical translation of nanomedicine. This review critically synthesizes advances in precision targeting, stimuli-responsive targeting, biomimetic and catalytic nanoplatforms and molecular docking platforms and their therapeutic applicability and translation barriers.

In the past, cancer nanomedicine has relied on passive targeting through the enhanced permeability and retention (EPR) effect. Though accumulation mediated by EPR results in preferential deposition of the nanoparticles in the tumor, more recent results showed less than percent of the dose that is injected gets into tumor and the nanoparticle accumulation is interpatient and intertumor variable. These findings outshine the outdated notion that EPR may be applied only to enable the successful targeting and emphasize the necessity of having complementary policies. Active targeting, ligand-/ antibody-functionalized nanoparticles to enhance cellular uptake by receptor-mediated endocytosis has

been shown to improve cellular uptake but the heterogeneity of targets, dynamic changes in expression and the challenge of making nanoparticles universally applicable plague it. Passive and active targeting therefore should be viewed as complementary rather than complements.

The development of stimuli-reactive nanoplatforms is also significant as they enable the release of drugs in spatial and temporal terms as well as react to endogenous (pH, redox state, enzymes, etc.) or exogenous (light, magnetic field, temperature, etc.) stimuli. These systems increase therapeutic indices as they improve minimization of premature drug leakages and minimization of system toxicity to the body. Nonetheless, they are difficult to translate to clinical practice due to the issue of reproducibility, stability and premature activation in the off-target environment. These limitations indicate the importance of rational design, conventional characterization and predictive in vitro-in vivo correlation frameworks. Nanocarriers Erythrocyte-, platelet-,c leukocyte-, and exosome-coated nanoparticles are biomimetic nanocarriers that address immune clearance and circulation-time barriers of synthetic nanomaterials.

These systems have enhanced immune avoidance and gene-homing on biologic surfaces that are biologic to the immune system. The translationally-realistic biomimetic approaches are endorsed in the clinical approved albumin-based nanocarriers such as Abraxane 125. Still, large-scale clinical use is still curtailed by the issue of membrane isolation, donor variation, and scalability, as well as regulatory permission.

Metal nanocatalysts introduce a fresh outlook of tumor microenvironment control through catalytic generation of reactive oxygen species or intracellular antioxidants deficiency. These systems have the best chances of being effective in hypoxic tumors in which conventional photodynamic therapy is not effective. Despite their therapeutic efficacy, their safety issues of long-term toxicity, biodistribution and clearance need high levels of safety consideration before application in clinical use.

Computational modeling and molecular docking are combined together as a way to provide a mechanistic verification of the ligand selection and drug-target interactions of nanomedicine design. Docking studies show the specificity of receptors and therapeutic applicability of folic acid, RGD peptides, and doxorubicin and are applied to justify the rational design of targeted nanocarriers. Though docking is not an alternative to an experimental validation, it is far more efficient in reducing empirical trial-and-error and making a design more efficient in case of artificial intelligence and machine-learning methods.

Some of the largest obstacles in nanomedicine development are regulatory heterogeneity, manufacturability, the formation of protein corona, and cost constraints. Lack of well coordinated international regulatory systems and scalable manufacturing lines that comply with GMP standards is also a contributing factor that facilitates collapsing of promising nanotherapeutics during the clinical stage. Such problems will require standardized protocols of characterization, design of clinical trials that are biomarker based and early integration of cost efficiency studies.

Future Directions

Bridging the current gap between the laboratory innovation and the clinical translation of cancer nanomedicine is the future possibility of these three areas through modular design, integration of biomarkers and digital convergence. This process can be expedited with a number of proactive approaches towards regulatory approval and applications to individual patients.

Modular Simplicity for Manufacturing

Next-generation nanomedicines must adopt modular simplicity to improve reproducibility and mass production.Core, shell, and surface ligand interchangeable modules should be designed to make nanoparticles simpler and more interchangeable. Modular platforms allow a high degree of flexibility in adapting to different drugs without re-optimisation of formulation parameters at scale, decreasing the development time and regulatory burden [52, 53]. It has been demonstrated that continuous-flow microfluidic systems and self-assembly reactors could be used to obtain high-throughput, GMP-scale production of liposomes and polymeric nanoparticles with reproducible physicochemical characteristics [54]. The approach would also reduce expenses and lead to scalability, which should promote industrial translation.

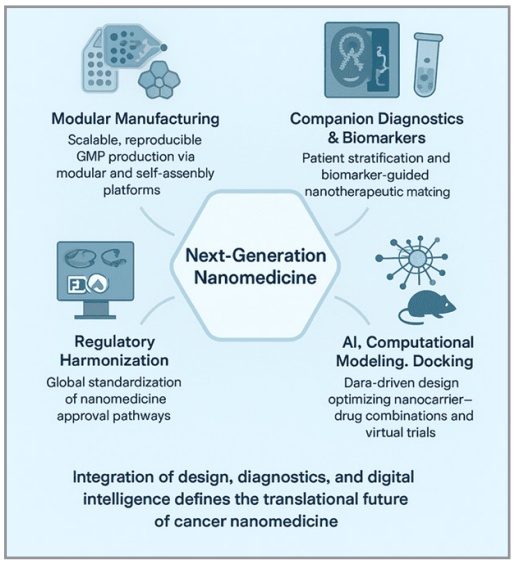


Figure 7: Roadmap of Future Directions in Cancer Nanomedicine [54]

Companion Diagnostics and Biomarker-Based Patient Stratification

Companion diagnostics plays an important role in enhancing the precision of clinical trials and therapeutic efficacy. Stratification of nanomedicine uptake or response can be performed by comparing nanomedicine nanoparticles and carriers with molecular biomarkers components, including SPARC with albumin-based nanoparticles or folate receptors 5 with folate-conjugated nanoparticles, so that patients can obtain the most compatible nanoparticles [55, 56]. The imaging biomarker (e.g. nanoparticle tracers, PET or MRI) can be implemented in early-stage trials to allow real-time monitoring of the biodistribution, directing adaptive dose regimens [57]. Such a precision-medicine strategy guarantees increased response rates, reduced side effects, and is in line with the philosophy of personalized oncology.

Translational Models: 3D Organoids and Patient-Derived Xenografts

This has frequently not translated into human clinical trials because the constraints of the traditional 2D cell cultures and animal models fail to predict the preclinical success of nanomedicines [58]. New 3D tumour organoids and patient-derived xenografts (PDX) better reflect tumour heterogeneity, stromal interactions, and drug penetration [59]. These models enable predictive evaluation of nanocarrier penetration, immune avoidance and off-target impacts erecting clinical evaluation. Further closer to mimicking the dynamic physiological conditions, such as blood flow and immune cell infiltration, the integration of nanomedicine testing pipelines with the organoid-on-a-chip systems can be done [60]. These high-order translational models are necessary to allow the preclinical-clinical gap in the development of nanomedine.

Regulatory Harmonization

The development of nanomedicine still faces uneven regulatory frameworks across regions, despite encouraging results. Criteria for safety assessment, equivalency testing, and nanomaterial characterisation vary amongst the U.S. FDA, EMA, and CDSCO [61]. Clinical approval and market access would be greatly accelerated by regulatory harmonisation, which would be achieved through unified standards for size, charge, and toxicity assessment [62]. Reducing redundant testing and facilitating mutual recognition of safety dossiers could be achieved through the establishment of internationally recognised guidelines (such as ISO/TR 10993 for nanotoxicology) and cooperative data-sharing between agencies [63]. Harmonisation will support sustainable nanotherapeutic pipelines by boosting investor and manufacturer confidence.

Integration of Artificial Intelligence, Computational Modeling, and Molecular Docking

By forecasting the ideal nanoparticle parameters—size, charge, ligand density, and release kinetics—based on tumor omics data, artificial intelligence (AI) and computational models are transforming the design of nanomedicine [63]. In silico screening of ligand-receptor interactions is made possible by AI-assisted molecular docking, which lessens the need for empirical experimentation [64]. To determine the best nanoparticle–drug combinations, machine learning can combine docking data, pharmacokinetic models, and clinical results [65]. Additionally, patient digital twins—computational models that incorporate physiological and genomic information—may enable virtual nanotherapy trials prior to practical implementation [66]. A data-driven era of precision nanomedicine will be defined by the convergence of molecular modeling, computational chemistry, and artificial intelligence.

Conclusion

Cancer nanomedicine has recently moved into a decisive translational phase in which these innovations converge with clinical feasibility, biological validation, manufacturability, and computational complementarity. The next generation of cancer nanomedicines will require not only thoughtfulness of nanoscale engineering but also scalable and reproducible manufacturing pipelines as well as validated models that are biologically relevant to patient complexities. Companion diagnostics and biomarker-based sub-grouping will optimise patient selection. AI-driven modeling and molecular docking will facilitate rapid identification of the optimal nanoparticle–drug–target combinations. Potential for real-world application between the lab and clinic requires regulatory harmonisation and cost-effective GMP frameworks that enforce consistency around benefits seen in the lab into clinical results [67-70].

As nanomedicine matrices move forward along the developmental path towards adaptive, intelligent, patient-centric systems, the material science, computation, and oncology interface will dictate the actual success of this scientific direction. Therefore, the evolution of cancer treatment is here—it simply requires precision-based metrics on a data-driven, sustainable nanoplatform that ultimately commits scientific advances founded in patient-centred application.

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