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Engineering combination nanomedicines to overcome cancer resistance

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Combination nanomedicine enables the coordinated delivery of multiple therapeutic agents using engineered nanosystems to address tumor heterogeneity, multidrug resistance, and systemic toxicity. Despite extensive preclinical progress, many combination nanomedicine strategies fail to translate clinically due to poor pharmacokinetic coordination, limited predictive models, and manufacturing constraints. This review examines design principles for co-delivery platforms based on liposomal, polymeric, inorganic, hybrid, and biomimetic carriers, with attention to pharmacokinetics, biodistribution, endosomal escape, and interactions with the tumor microenvironment. Strategies integrating chemotherapy, immunotherapy, gene- and RNA-based therapies, photodynamic and photothermal modalities, and selected natural compounds are summarized to achieve synergistic therapeutic effects. Stimuli-responsive and actively targeted systems are highlighted for precise release and improved tumor accumulation. Translational progress from preclinical studies to clinical experience, including opportunities and constraints related to manufacturing reproducibility, quality control, immunogenicity, and long-term fate were discussed. Overall, combination nanomedicine shows promise for improving efficacy and safety in cancer therapy, and future work should prioritize modular, clinically scalable platforms, standardized characterization, clinically relevant models, and pathways for scalable production and regulatory evaluation.

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1. Introduction

Cancer is a heterogeneous disease characterized by uncontrolled cell growth driven by genetic, epigenetic, and microenvironmental changes.[1,2] Based on Global Cancer Observatory projections, global cancer incidence has already surpassed 20 million new cases annually in the mid-2020s and is projected to rise substantially, reaching ~32.6 million cases by 2045. A substantial fraction of this burden is attributable to modifiable risk factors, including obesity, chronic infections, ultraviolet radiation exposure, and alcohol consumption, underscoring the need for more effective and less toxic therapeutic strategies.[1,2] Standard treatments such as chemotherapy, radiotherapy, immunotherapy, and targeted therapies often face limitations, which include low tumor specificity, systemic toxicity, poor penetration into solid tumors, and the ability of cancer cells to adapt through efflux pumps, signaling changes, and altered metabolism.[3,4] In addition, the tumor microenvironment (TME) creates physical and biological barriers that restrict drug entry and promote immunosuppressive conditions, further contributing to therapeutic resistance. Combination therapy, where multiple drugs act on different cancer pathways, has been developed to overcome these barriers (https://link.springer.com/article/10.1186/s12951-024-02815-8). By targeting processes such as proliferation, angiogenesis, immune evasion, and resistance to apoptosis, combination therapy can improve tumor control, delay the onset of resistance, and achieve better patient outcomes. However, its success is often limited by differences in drug pharmacokinetics, toxicity from high systemic

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exposure, and unwanted interactions between drugs. Thus, the clinical success is often limited by mismatched drug pharmacokinetics, cumulative systemic toxicity, and unfavorable drug–drug interactions.

Nanomedicine offers solutions by providing carriers that can deliver several drugs together in a controlled and tumor specific way. Nanoparticles (NPs) such as liposomes, dendrimers, micelles, inorganic systems, and biomimetic carriers improve drug solubility, circulation time, and selective accumulation at tumor sites through the enhanced permeability and retention effect (EPR).[5,6] Despite these advances, challenges remain, including batch-to-batch variability and immune responses to surface modifications. These trade-offs have driven the development of hybrid nanoplatforms that combine polymeric biocompatibility with the functional properties of inorganic materials. Newer generations of nanocarriers are being engineered to respond to tumor-specific stimuli, modulate immune activity, and integrate therapeutic and imaging functions for real-time monitoring. Co-delivery strategies involving checkpoint inhibitors, cytokines, and tumor antigens are under active investigation to enhance antitumor immune responses. Biomimetic carriers, including exosome-like vesicles and cell membrane-coated NPs, can evade immune clearance and extend circulation time (Medical importance and pharmacokinetics of gold nanoparticles in the human body: https://link.springer.com/article/10.1186/s12943-025-02418-3). Nucleic acid-based and gene therapy approaches delivered *via* NPs are also emerging as complementary strategies to reprogram resistant tumors. In parallel, advances in patient-derived organoids and single-cell omics are enabling the design of nanomedicines that better account for tumor heterogeneity and resistance mechanisms.[7,8]

This review focuses on engineering combination nanomedicines to overcome cancer resistance, emphasizing co-delivery strategies and the integration of chemotherapy, immunotherapy, gene therapy, and phototherapy.[9] It further examines progress toward clinical translation, including representative case studies, challenges, and the role of predictive experimental platforms such as organoid models in accelerating personalized nanomedicine. By linking resistance biology with nanoplatform design, this review highlights how rationally engineered combination strategies can address current therapeutic limitations and improve cancer treatment outcomes.

2. Rationale for advanced cancer therapeutics

Drug resistance remains one of the foremost challenges in cancer, significantly limiting the success of chemotherapy, targeted therapy, and immunotherapy. Cancer cells develop adaptive mechanisms to evade cell death, continue proliferating, and metastasize. Overcoming resistance is therefore central to improving long-term therapeutic outcomes. These mechanisms include genetic alterations, signaling pathway adaptations, drug efflux, metabolic rewiring, and microenvironmental influences, each of which is explored in the following sections.[10]

2.1 Genetic and oncogenic mechanisms driving chemoresistance

Genetic mutations are central to cancer development and a major cause of resistance to various therapies. These alterations, either spontaneous or therapy induced, can promote oncogenic signaling, suppress apoptotic pathways, and reprogram cellular metabolism. Understanding these mutations has directly informed the development of targeted and combination therapies designed to delay or overcome resistance.

One of the most well characterized examples is mutations in the epidermal growth factor receptor (EGFR) gene, particularly in non-small cell lung cancer (NSCLC). Activating mutations like exon 19 deletions or L858R enhance EGFR signaling, promoting uncontrolled proliferation and survival.[11–13] While patients often respond to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, resistance commonly develops due to secondary mutations like T790M or through compensatory activation of pathways such as MET or HER2. These insights have led to next generation inhibitors such as osimertinib and combination strategies aimed at suppressing bypass signaling.[14,15]

Another key oncogene is BRAF. The V600E mutation, especially prevalent in melanoma, leads to constitutive activation of the MAPK/ERK signaling pathway.[16] Targeted therapies such as vemurafenib, or the combination of dabrafenib and trametinib, have shown substantial initial responses. However, resistance often emerges through BRAF amplification or reactivation of downstream effectors. Consequently, multi target approaches are under investigation to improve durability of response.[17,18]

KRAS, one of the most frequently mutated oncogenes in colorectal, pancreatic, and lung cancers, activates the RAS/RAF/MEK/ERK axis and contributes to resistance against therapies including EGFR inhibitors. Due to high GTP affinity and structural constraints, KRAS was long considered undruggable. Recent work shows that co mutations such as KRAS with TP53, common in pancreatic and colorectal cancers, aggravate resistance by combining defects in apoptosis with metabolic rewiring. New generation KRAS inhibitors that target G12D and G12V are entering clinical evaluation, and KRAS G12C inhibitors such as sotorasib provide proof of concept, highlighting the need for multi agent strategies that counter adaptive escape.[19–21] Given the coexistence of multiple oncogenic drivers, single target therapy is often insufficient, and combination approaches are required.

TP53, which encodes the tumor suppressor p53, is mutated in more than half of human cancers. Wild type p53 orchestrates apoptosis, DNA repair, and cell cycle arrest.[22] Mutations in TP53 disable these protective mechanisms and may impart gain of function properties that promote tumor progression and therapeutic resistance. Efforts to restore p53 function, including small molecules such as APR 246 and gene therapy vectors, or to exploit p53 deficiency *via* synthetic lethality with targets such as WEE1 or CHK1, are active areas of research.[23] Collectively, genetic alterations initiate resistance but interact with dynamic signaling and cellular adaptations, reinforcing treatment failure and motivating rational combination approaches.

2.2 Adaptive signaling and efflux pathways in chemoresistance

Beyond genetic alterations, aberrant signaling networks and cellular transport mechanisms contribute to chemoresistance. Cancer cells hijack survival pathways, compensate through feedback activation, and remodel signal transduction to evade therapy induced cytotoxicity. In parallel, drug efflux systems reduce intracellular drug concentrations.

One of the most critical pathways is the MAPK/ERK cascade, which regulates proliferation, differentiation, and survival.[24] Activated by receptor tyrosine kinases (RTKs) and G protein coupled receptors (GPCRs), this pathway is frequently dysregulated in cancer.[25] Resistance arises through secondary mutations, pathway amplification, and feedback reactivation of upstream signals, which can maintain downstream proliferative and anti-apoptotic programs despite upstream inhibition (Fig. 1).[26,27]

Similarly, the PI3K/AKT/mTOR pathway is a key survival axis. Upon ligand binding to RTKs or GPCRs, PI3K generates phosphatidylinositol 3,4,5 trisphosphate (PIP3), recruiting AKT for phosphorylation. AKT modulates effectors such as mTOR, GSK3, and FOXO transcription factors to regulate metabolism, survival, and angiogenesis.[28] Resistance mechanisms include PIK3CA mutations, PTEN loss, and compensatory receptor activation. Crosstalk with MAPK signaling further complicates inhibition.[29,30]

The Wnt/β catenin pathway supports stemness and tumorigenesis. Aberrant activation through Frizzled and LRP receptors stabilizes β catenin, which translocates to the nucleus to drive genes involved in proliferation, epithelial mesenchymal transition, and drug resistance.[31,32] Wnt activation contributes to resistance to agents such as cisplatin, doxorubicin (DOX), EGFR inhibitors, and BRAF inhibitors in colorectal and melanoma models.[33] Synergy between Wnt, PI3K/AKT, and MAPK signaling promotes cancer stem like phenotypes and therapy failure.[34,35] Emerging evidence also implicates the nuclear export receptor XPO1 in resistance by exporting tumor suppressors such as p53 and FOXO3; inhibitors such as selinexor are under evaluation in several malignancies.

In addition to signaling plasticity, cancer cells use ATP-binding cassette (ABC) transporters to export drugs. Key transporters include P-glycoprotein (P-gp, ABCB1), multidrug resistance-associated protein 1 (MRP1, ABCC1), and breast cancer resistance protein (BCRP, ABCG2), each linked to poor clinical outcomes and multidrug resistance.[36,37] These transporters can be upregulated by chemotherapy, creating a feedback loop that reduces intracellular drug accumulation and therapeutic efficacy. Although inhibitors such as verapamil and cyclosporine can block efflux, their clinical use is limited by systemic toxicity (Fig. 2).[38,39] Nanoparticle-based delivery strategies can partially bypass or overwhelm efflux mechanisms through enhanced cellular uptake and controlled drug release

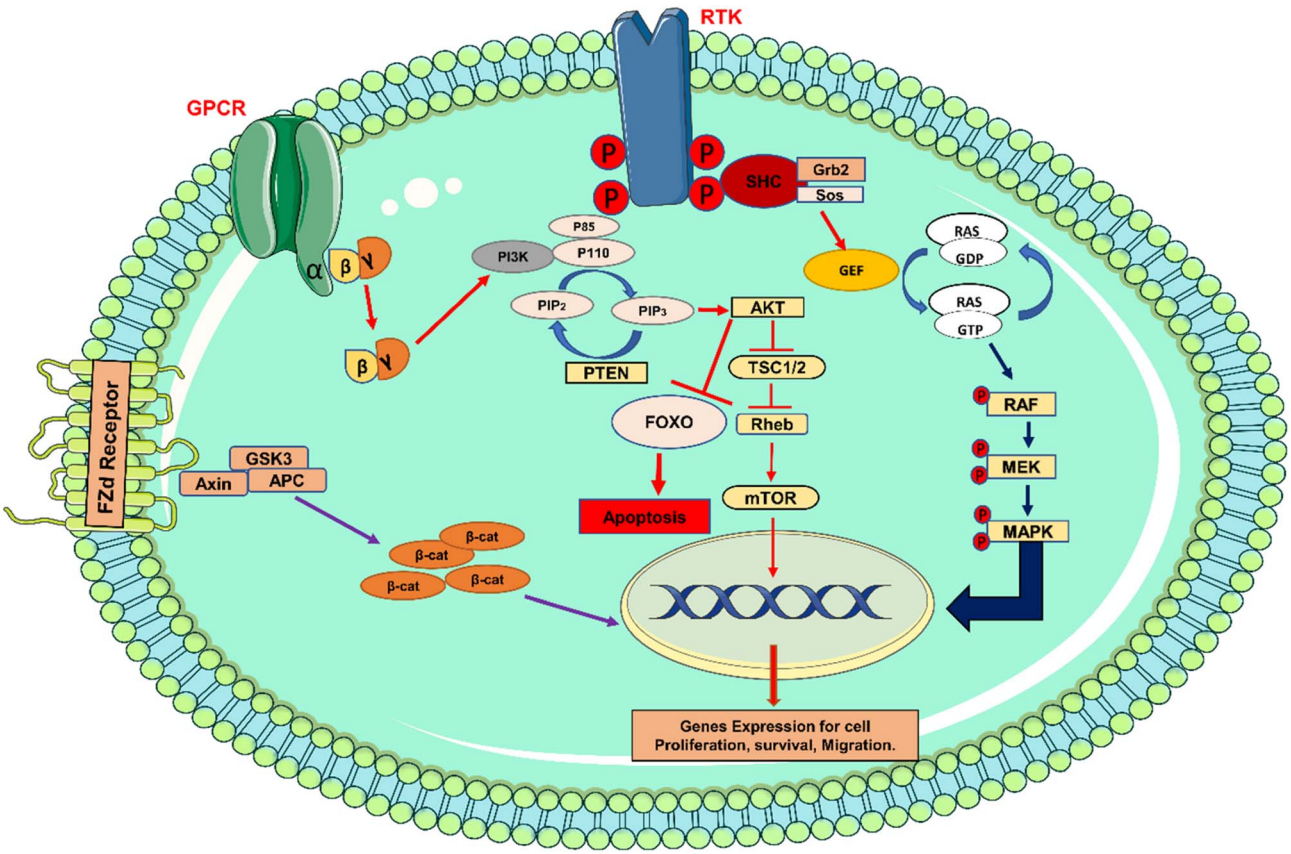

Fig. 1 Wnt/β-catenin, PI3K/AKT/mTOR, and MAPK/ERK signaling pathways involved in cancer chemoresistance.

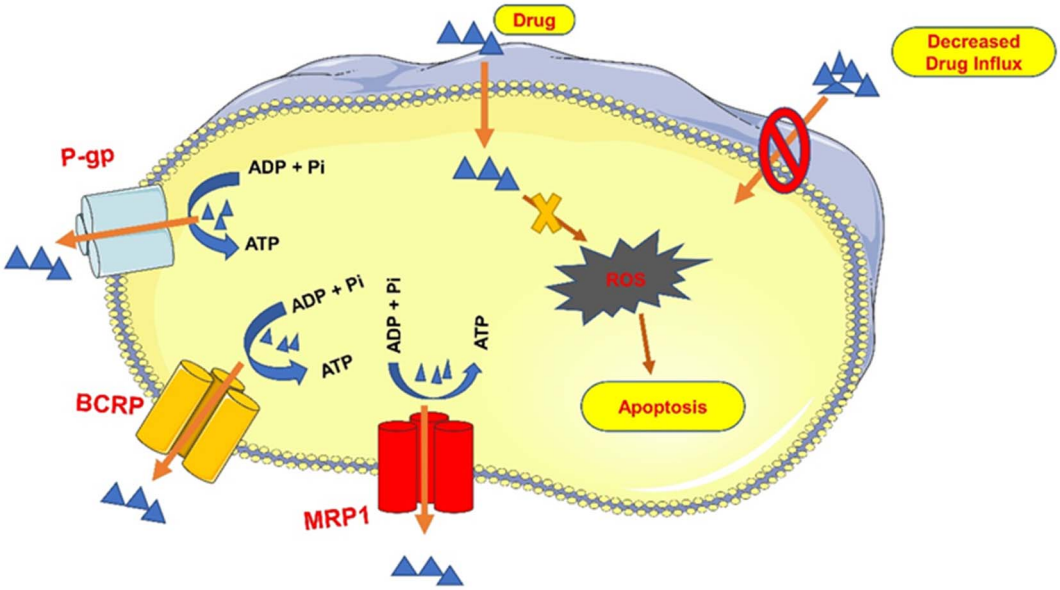

Fig. 2 ABC transporter-mediated drug efflux as a mechanism of multidrug resistance in cancer cells.

within the TME.[7,40] Overall, pathway redundancy and transporter overexpression enable cancer cell survival under therapeutic stress and necessitate rational combination strategies that co-target signaling pathways and drug efflux mechanisms.

2.3 TME and its role in chemoresistance

TME consists of cancer associated fibroblasts (CAFs), immune cells, endothelial cells, and extracellular matrix (ECM) components that interact with tumor cells to influence proliferation, survival, invasion, and therapeutic response.[41] Among these, CAFs are major contributors to chemoresistance. They secrete cytokines, chemokines, and growth factors that enhance survival and epithelial mesenchymal transition, and they release matrix metalloproteinases (MMPs) and other proteases that degrade the ECM, impede drug penetration, and facilitate invasion.[42] MMP 2 and MMP 9 are frequently upregulated and promote ECM remodeling, angiogenesis, and metastasis.[43] This remodeling interferes with drug retention and delivery. MMPs also modulate growth factor bioavailability, including TGF β and VEGF, by releasing matrix bound forms that enhance angiogenesis and survival signaling.[44,45]

Disintegrin and metalloproteinases (ADAMs) reshape the microenvironment and modulate receptor signaling. ADAM mediated shedding of EGFR ligands such as TGF α can activate EGFR signaling under chemotherapeutic stress. ADAM17 is implicated in proliferation and survival in this context.[46,47] Collectively, the microenvironment provides a protective niche that promotes resistance through structural barriers, paracrine signaling, and immune suppression. Targeting CAFs, MMPs, and ADAMs can improve delivery and sensitize tumors to therapy.

TME also mediates immune evasion. Immunosuppressive cells including regulatory T cells, tumor associated macrophages, and myeloid derived suppressor cells are recruited by stromal and tumor derived chemokines and suppress cytotoxic T cells. Upregulation of checkpoint ligands such as PD L1, including on exosomes and under hypoxia mediated HIF 1α stabilization, promotes T cell exhaustion and resistance to PD 1 and PD L1 inhibitors. This is particularly evident in tumors with dense stroma such as pancreatic cancer and in subsets of NSCLC.

2.4 Dysregulation of cell death pathways in chemoresistance

One of the core hallmarks of chemoresistance is the cancer cell's ability to evade programmed cell death. Two critical cellular processes, apoptosis and autophagy, are intimately involved in determining tumor response to chemotherapy. In resistant tumors, these pathways are often dysregulated, enabling cancer cells to survive under cytotoxic stress and continue proliferating.

2.4.1 Apoptotic signaling. Apoptosis, or programmed cell death, is a tightly regulated mechanism responsible for eliminating damaged or abnormal cells to maintain tissue homeostasis. Its impairment is a hallmark of many malignancies and a common cause of therapy failure.[48] A central regulatory axis of apoptosis is the BCL 2 protein family, which includes both pro apoptotic (*e.g.*, BAX, BAK, BID, BIM) and anti-apoptotic members (*e.g.*, BCL 2, BCL xL, MCL 1). Upon activation, BAX and BAK mediate mitochondrial outer membrane permeabilization, leading to the release of cytochrome *c* and formation of the apoptosome, which activates caspase 9 and downstream executioner caspases 3 and 7.[49] Overexpression of anti-apoptotic proteins or loss of pro apoptotic proteins reduces apoptotic priming and promotes resistance.[50,51]

In addition to the intrinsic pathway, defects in the extrinsic pathway mediated by death receptors such as Fas and TRAIL receptors, and regulators such as caspase 8 and c FLIP, also contribute to chemoresistance. Additionally, mutations or

alterations in caspase genes, as well as suppression of cytochrome *c* release, further block apoptosis initiation. Mitochondrial dynamics, particularly imbalances in fission and fusion proteins such as DRP1 and mitofusins MFN1 and MFN2, modulate apoptosis sensitivity. Upregulation of fusion proteins correlates with enhanced chemotherapy sensitivity, whereas dysregulated fission contributes to resistance.[52,53] PUMA and NOXA, BH3 only proteins transcriptionally regulated by p53, play essential roles in linking DNA damage and stress to apoptosis. These proteins either inhibit anti apoptotic BCL 2 family members or directly activate BAX and BAK. Loss of p53 function or reduced expression of PUMA and NOXA has been linked to poor response to chemotherapy and reduced apoptotic priming in many cancers.[54,55]

2.4.2 Autophagy signaling pathway. Autophagy is a catabolic process that enables cells to degrade and recycle damaged organelles and macromolecules, thereby maintaining cellular homeostasis. In cancer, autophagy plays a dual role, promoting survival under stress or facilitating cell death depending on context.[56] Key regulators of autophagy include LC3, Beclin 1, and the ATG protein complexes. During autophagosome formation, LC3 is lipidated to LC3 II, which localizes to the autophagosomal membrane. This maturation process is facilitated by the ATG12 ATG5 ATG16L1 complex and eventually leads to fusion with lysosomes to form autolysosomes, where degradation occurs.[57,58] Beclin 1, as part of the class III PI3K complex with VPS34, VPS15, and ATG14L, governs autophagy initiation *via* production of phosphatidylinositol 3 phosphate and recruitment of downstream machinery.[59] Impaired Beclin 1 function has been associated with tumor progression and chemoresistance, whereas its reactivation is being explored for sensitizing tumors to therapy.[60]

In many settings, autophagy acts as a pro survival mechanism, especially under conditions of hypoxia, nutrient deprivation, or chemotherapy induced stress all of which are prevalent in the TME. By degrading damaged organelles and detoxifying ROS, autophagy protects cells from therapy induced damage. Additionally, autophagy may facilitate the efflux or sequestration of chemotherapeutic agents, reducing their cytotoxicity.[61] Crosstalk between autophagy and apoptosis is mediated in part by Beclin 1 binding to BCL 2 family proteins, which can suppress autophagy and shift fate decisions under treatment. However, in other contexts, autophagy can amplify stress induced cell death, especially when apoptosis is suppressed. Therapeutic strategies are being explored to modulate autophagy using inhibitors such as chloroquine and bafilomycin A1 or inducers, depending on whether the cancer type exploits or suppresses autophagic flux.

In addition to classical cell death mechanisms, recent attention has turned to ferroptosis, a non-apoptotic, iron dependent form of regulated cell death driven by lipid peroxidation. Unlike apoptosis, ferroptosis is triggered by the accumulation of reactive oxygen species (ROS) within phospholipid membranes. Ferroptosis inducing compounds such as erastin, RSL3, and FIN56 are being investigated for their ability to overcome drug resistance, particularly in tumors with elevated intracellular iron and lipid ROS. Additionally, inhibitors of ferroptosis such as iFSP1 are being explored for context specific modulation, especially in tumors where ferroptosis contributes to immune escape or paradoxical survival. Resistance to ferroptosis, mediated by upregulation of key regulators such as GPX4, SLC7A11, or ferritin, has been observed in several malignancies including glioblastoma, pancreatic cancer, and triple negative breast cancer. Links between ferroptosis and autophagy, including ferritinophagy through NCOA4, further influence sensitivity to therapy. Targeting ferroptosis regulatory pathways may offer therapeutic leverage, either as monotherapy or in combination with chemotherapy or immunotherapy, to sensitize resistant tumors.

The clinical implications of these resistance mechanisms are profound. For instance, EGFR mutant NSCLC patients initially benefit from first generation TKIs such as gefitinib but develop resistance within 12 to 18 months, commonly due to T790M mutations or MET amplification. Similarly, BRAF V600E mutant melanoma treated with vemurafenib frequently relapses due to ERK reactivation or pathway bypass. In triple negative breast cancer, the combination of TP53 mutations, enhanced glycolysis, and immune evasion contributes to high relapse rates despite aggressive chemotherapy. These examples highlight the need for personalized, multi target regimens that simultaneously address genetic, metabolic, and immune based resistance mechanisms.

2.5 Metabolic reprogramming in chemoresistance

One of the most significant mechanisms underlying chemoresistance in cancer cells is metabolic reprogramming. These metabolic alterations allow tumor cells to adapt to the selective pressures of chemotherapeutic agents by reshaping bioenergetic pathways, stress responses, and biosynthetic demands. Major metabolic shifts contributing to resistance include enhanced glycolysis, mitochondrial flexibility, lipid biosynthesis, and antioxidant defenses, each functioning either independently or in a coordinated manner.

Cancer cells frequently display elevated aerobic glycolysis, known as the Warburg effect, wherein they convert glucose to lactate even under normoxic conditions.[62] This metabolic adaptation not only supplies ATP but also feeds anabolic pathways essential for rapid proliferation and stress resistance.[63] ATP generated *via* glycolysis fuels ABC transporters such as P glycoprotein (P gp), which actively efflux chemotherapeutic agents from cancer cells, lowering intracellular drug accumulation and contributing to resistance.[64] Additionally, glycolytic intermediates are diverted into the pentose phosphate pathway (PPP), generating NADPH and ribose 5 phosphate. NADPH neutralizes ROS, mitigating oxidative damage induced by chemotherapy, while ribose 5 phosphate supports nucleic acid synthesis.[65] Intermediates such as glyceraldehyde 3 phosphate also support serine biosynthesis and one carbon metabolism. Sustained glycolytic flux reinforces survival through PI3K AKT mTOR signaling and increased expression of anti-apoptotic proteins such as BCL 2.[66] Hypoxia inducible factor 1α (HIF 1α), stabilized under hypoxic conditions, induces the expression of glycolytic enzymes, glucose transporters like

GLUT1, and angiogenic factors such as VEGF.[67] In addition, the accumulation of lactate contributes to extracellular acidification, which impairs drug uptake and efficacy. This acidic microenvironment can also select for more aggressive and drug-resistant cancer cell clones, exacerbating chemoresistance.[68]

Mitochondrial metabolism also contributes to resistance. Many tumors toggle between glycolysis and oxidative phosphorylation depending on nutrient status and therapeutic stress.[69,70] Mitochondria control intrinsic apoptosis *via* cytochrome *c* release and apoptosome formation. Overexpression of BCL 2 family proteins can block this process.[71,72] BCL xL supports survival under therapy and can enhance HIF 1 and VEGF signaling.[73,74] DRP1 mediated fission and mitophagy influence drug sensitivity.[75,76] Tricarboxylic acid cycle intermediates such as succinate and fumarate inhibit prolyl hydroxylase enzymes, stabilize HIF 1α, and promote a resistant phenotype.[77–80] High mitochondrial membrane potential can sequester cationic drugs and reduce efficacy.[75]

Reprogrammed lipid metabolism supports resistance through fatty acid synthase driven membrane biogenesis, energy storage, and signaling. FASN overexpression has been consistently linked to poor response, and its inhibition can sensitize tumors.[76,81] The composition of lipid rafts enriched in cholesterol and sphingolipids modulates transporter localization and function, enhancing efflux.[82] Glutamine and acetate can feed lipid synthesis under therapy, and adipocyte derived fatty acids support tumor growth in lipid rich microenvironments such as breast tissue.[83]

Bioactive lipid mediators such as prostaglandin E2 activate EP receptors and PI3K AKT signaling, promoting immune evasion and survival.[84–86] COX 2 inhibitors can restore chemosensitivity in preclinical models.[87] Extracellular vesicles and exosomes enriched in lipids and PD L1 transport resistance signals, suppress T cell activation, and contribute to failure of immune checkpoint blockade.[88,89]

Finally, redox balance is central to resistance. Many chemotherapies induce ROS, and cancer cells counteract this by activating antioxidant programs. NRF2, released from KEAP1, induces GSTs, HO 1, and NQO1 and enhances glutathione synthesis (Fig. 3).[82,90] Mutations in NRF2 or KEAP1 that prevent NRF2 degradation result in constitutive activation and poor prognosis.[91] Sestrin 2 contributes to redox homeostasis by activating AMPK and suppressing mTORC1, and its overexpression has been associated with cisplatin resistance in lung cancer.[84–86,92] Autophagic degradation of KEAP1 results in the release of NRF2 and its translocation into the nucleus, activating the antioxidant response element. Moreover, FOXO3, activated by oxidative stress, translocates to the nucleus to induce SOD, catalase, and glutathione peroxidase and also regulates DNA repair and cell cycle arrest; its role in chemoresistance is context-specific.[93] Altogether, metabolic reprogramming forms a multi layered defense system that sustains growth, avoids apoptosis, and shields oxidative and chemotherapeutic stress. Targeting these metabolic adaptations through glycolysis and glutaminolysis inhibitors, mitochondrial disruptors, lipid metabolism blockers, or redox

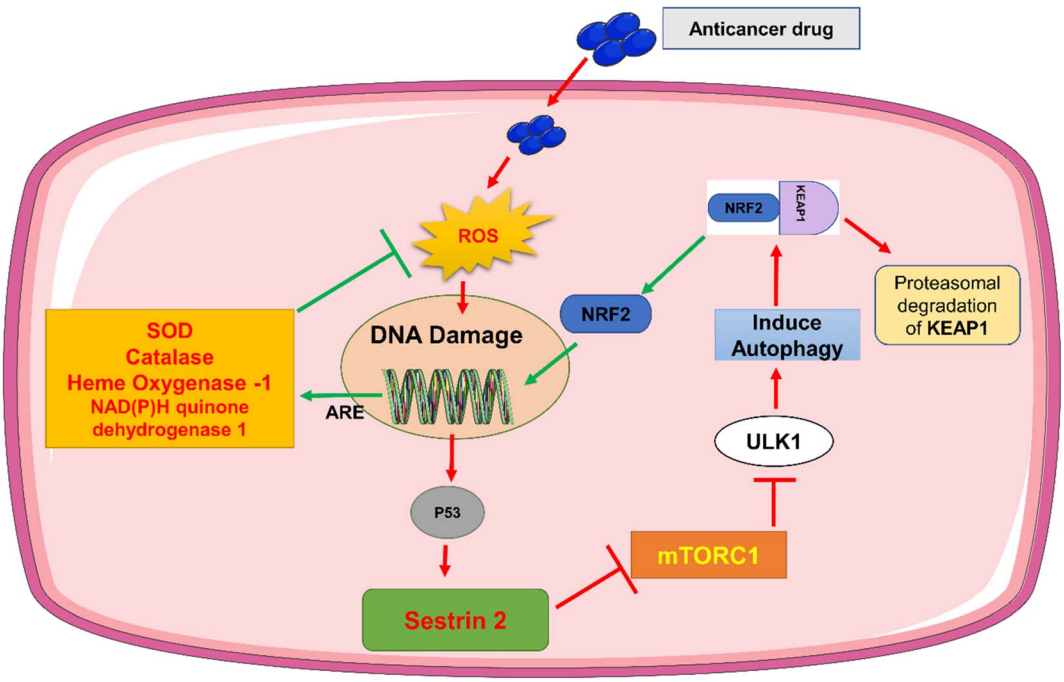

Fig. 3 Schematic illustration of redox-regulated drug resistance mechanisms in cancer cells. Anticancer drug-induced oxidative stress activates NRF2 signaling through KEAP1 degradation, leading to transcription of antioxidant response element (ARE)-driven genes including SOD, catalase, HO-1, and NQO1, which collectively reduce intracellular ROS levels. NRF2 activation also induces autophagy *via* modulation of the mTORC1–ULK1 axis, promoting cellular survival under therapeutic stress. In parallel, p53–Sestrin 2 signaling suppresses mTORC1 activity, further regulating autophagy and redox balance. Together, these interconnected pathways attenuate apoptosis, enhance stress tolerance, and contribute to chemoresistance.

modulators represents a promising direction for overcoming therapeutic resistance and improving treatment efficacy. Patient derived organoids and 3D co culture systems enable high throughput screening of nanoparticle combinations under realistic microenvironment and genotype settings, improving translational relevance (https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2025.1670328/full).

2.6 Influence of the TME on nanocarrier accumulation and efficacy

TME plays a decisive role in regulating nanocarrier accumulation, penetration, and therapeutic efficacy. Abnormal tumor vasculature, elevated interstitial fluid pressure, hypoxia, and dense ECM deposition collectively limits nanoparticle extravasation and deep tumor penetration. In hypoxic tumors, stabilization of hypoxia-inducible factors (HIFs) alters vascular permeability, cellular metabolism, and redox balance, thereby influencing nanoparticle uptake and intracellular trafficking. These features have motivated the development of hypoxia-responsive, pH-sensitive, and redox-activated nanocarriers that selectively release payloads within hypoxic tumor regions, improving spatial precision and therapeutic index. Hypoxia-responsive mesoporous silica nanoparticles (MSNs) offer a promising strategy for selective drug delivery in solid tumors. Azobenzene-gated MSNs enable enzyme-triggered release of doxorubicin specifically in hypoxic TME *via* azoreductase-mediated cleavage, reducing premature drug leakage and off-target toxicity. Enhanced cytotoxicity under hypoxic conditions highlights their potential for improving therapeutic efficacy in hypoxia-driven, drug-resistant tumors.[94] Another study, reported that Hypoxia-adaptive tumors exploit enhanced mitophagy to survive under low-oxygen conditions, contributing to therapeutic resistance. Hypoxia-responsive supramolecular albumin nanoparticles co-delivering hydroxychloroquine and a mitochondria-targeting photosensitizer enable cascade-amplified oxidative stress by simultaneously blocking mitophagy and inducing oxygen-independent mitochondrial damage. This dual spatiotemporal regulation of mitophagy effectively drives tumor cell death in hypoxic tumor models.[95] Desmoplastic tumors, such as pancreatic and certain colorectal cancers, present additional barriers due to excessive collagen deposition, cancer-associated fibroblast (CAF) activity, and ECM stiffening, which restrict nanoparticle diffusion and promote heterogeneous drug distribution. To address these challenges, nanoplatforms incorporating size optimization, ECM-degrading enzyme responsiveness (*e.g.*, collagen degradation), and stromal-modulating strategies have been explored to enhance intratumoral penetration. For example, the ECM of solid tumors constitutes a significant physical barrier to drug penetration and therapeutic efficacy. Three-dimensional breast tumor spheroid models with endogenous collagen I demonstrate that ECM complexity limits doxorubicin access. In contrast, collagenase-mediated ECM degradation significantly enhances intratumoral penetration and cytotoxicity.[96] Similarly, in pancreatic ductal adenocarcinoma (PDAC), collagenase-loaded liposomal systems ("collagozomes") effectively remodel the dense fibrotic stroma, markedly improving paclitaxel penetration and therapeutic response without promoting metastasis, underscoring ECM-targeting strategies as a promising approach for overcoming drug resistance in stroma-rich tumors .[97] Collectively, these findings underscore that effective nanocarrier design must account for TME-driven heterogeneity, particularly in hypoxic and desmoplastic tumors, to achieve consistent drug delivery and therapeutic efficacy.

3. Nanoplatform design for overcoming resistance mechanisms

Nanomedicine has emerged as a transformative approach in oncology, enabling the co-delivery of multiple therapeutic agents through engineered nanoparticle-based platforms. These nanocarriers offer several advantages, including controlled release, extended circulation time, targeted delivery, and reduced systemic toxicity. In the context of chemoresistant cancers, multi-agent loaded NPs are particularly attractive, as they allow simultaneous targeting of diverse resistance pathways while minimizing off-target damage.[98,99] The clinical use of nanomedicine monotherapies is still restricted due to significant regulatory and technical challenges. Because NPs share properties of both drugs and medical devices, they are subject to rigorous requirements for safety, pharmacokinetics, and toxicity, which slows the approval process and raises costs. Scaling up production also poses difficulties, as achieving consistent control over size, charge, and surface modifications during industrial manufacturing is highly complex and resource-intensive. Moreover, safety issues remain unresolved: NPs may accumulate in clearance organs like the liver, spleen, or kidneys, creating risks of long-term toxicity or immune-related complications. Together, these obstacles limit the transition of nanomedicine monotherapies into clinical practice, even though preclinical data have been promising. To overcome these limitations, researchers are increasingly focusing on combination nanomedicine, which appears more practical for clinical translation. One prominent success is CPX-351 (Vyxeos®), a liposomal formulation that co-delivers cytarabine and daunorubicin, already approved for acute myeloid leukemia and shown to extend survival patients. Clinical trials are expanding this approach by combining CPX-351 with agents such as venetoclax and midostaurin, while other NPs systems are designed to simultaneously deliver chemotherapy with siRNA or immune-modulating adjuvants. Beyond hematologic cancers, promising strategies include nab-PTX with cisplatin in biliary tract cancers, CRLX101 with chemoradiotherapy for head and neck tumors, and gold nanoshell-assisted photothermal ablation for prostate cancer. These advances, supported by innovations such as theranostic NPs, stimuli responsive carriers, and cell membrane coated nanoplatforms, demonstrate a clear shift toward multifunctional designs that can improve targeting, enhance circulation, and reduce toxicity, thereby bringing nanomedicine closer to clinical reality.

3.1 Nanoplatform classes: liposomes, dendrimers, and inorganic NPs

A wide variety of nanoparticle systems have been developed for co-delivery applications, each offering distinct structural and functional attributes. These include liposomes, polymeric NPs (*e.g.*, micelles, dendrimers), metallic and inorganic NPs, and quantum dots, as well as hybrid and stimuli responsive systems.[2,100]

Liposomes are nanoscale lipid bilayer vesicles capable of encapsulating both hydrophilic and hydrophobic drugs (Fig. 4). Their surface can be functionalized with targeting ligands for selective tumor delivery, enhancing therapeutic precision.[101–103] Controlled release, minimal immunogenicity, and biocompatibility make them a clinically successful platform, as demonstrated in several FDA approved liposomal drugs. For example, Doxil® (liposomal DOX) improves pharmacokinetics and reduces cardiotoxicity. Liposomes are also used for co delivering chemotherapeutics and nucleic acids, with ongoing studies exploring combinations to overcome multidrug resistance.[104] However, their clinical scalability, drug loading capacity, and stability remain active areas of optimization.[105,106]

Polymeric NPs, such as those made from PLGA, PEG, and polylactic acid, offer high drug loading efficiency and tunable release profiles. They can co-encapsulate drugs with differing solubilities and release kinetics, improving treatment efficacy.[98,107] These systems protect the therapeutic payload from enzymatic degradation and improve circulation time. Targeting moieties (*e.g.*, folate, antibodies) or stimuli-responsive linkers can be added for site-specific delivery.[108] Polymeric micelles, formed by self-assembly of amphiphilic block copolymers, are widely studied for encapsulating hydrophobic drugs within their core, while maintaining aqueous solubility through their hydrophilic corona.[109,110] Though versatile, challenges remain in enhancing drug loading for hydrophilic compounds and ensuring micellar stability *in vivo*.[111]

Dendrimers are highly branched, monodisperse polymers with precise architecture and tunable surface chemistry. They provide internal cavities for drug encapsulation and surface functional groups for conjugation, enabling co-delivery of multiple agents with tailored pharmacokinetics.[112–114] Their small size, high payload capacity, and ability to be functionalized for targeting or imaging make them a promising platform. Polyamidoamine (PAMAM) dendrimers, for example, have shown utility in co-delivering chemotherapeutics and siRNA to overcome drug resistance.[115]

Micelles and nanogels, though smaller in scale, play vital roles in combination therapy. Micelles improve solubility and stability of hydrophobic drugs and can be tuned for triggered release in response to environmental stimuli. Nanogels, being highly hydrated crosslinked polymer networks, offer controlled release and high biocompatibility. Their deformability enhances penetration into tumor tissues, especially when conjugated with targeting ligands.[111]

Quantum dots (QDs) offer additional functionality through their unique optical and electronic properties. Their tunable fluorescence allows real-time imaging and tracking of drug delivery. QDs can be engineered to co-deliver chemotherapeutics and biological agents while simultaneously serving as diagnostic tools.[112,116] However, concerns about heavy metal content and long-term toxicity have limited their clinical translation, emphasizing the need for more biocompatible alternatives (Fig. 5).[98,112,116]

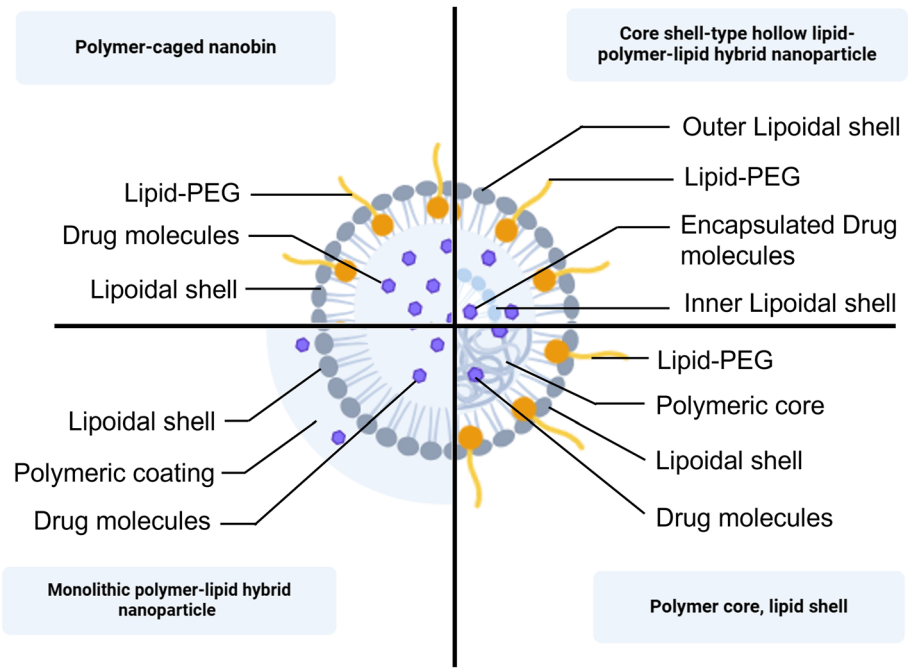

Fig. 4 Schematic representation of lipid–polymer hybrid nanoparticle architectures, including polymer-caged nanobins, monolithic polymer–lipid hybrids, and core–shell lipid–polymer nanoparticles. Key structural features such as polymeric cores, lipoidal shells, lipid–PEG surface modification, and drug encapsulation are illustrated (created by using Biorender).

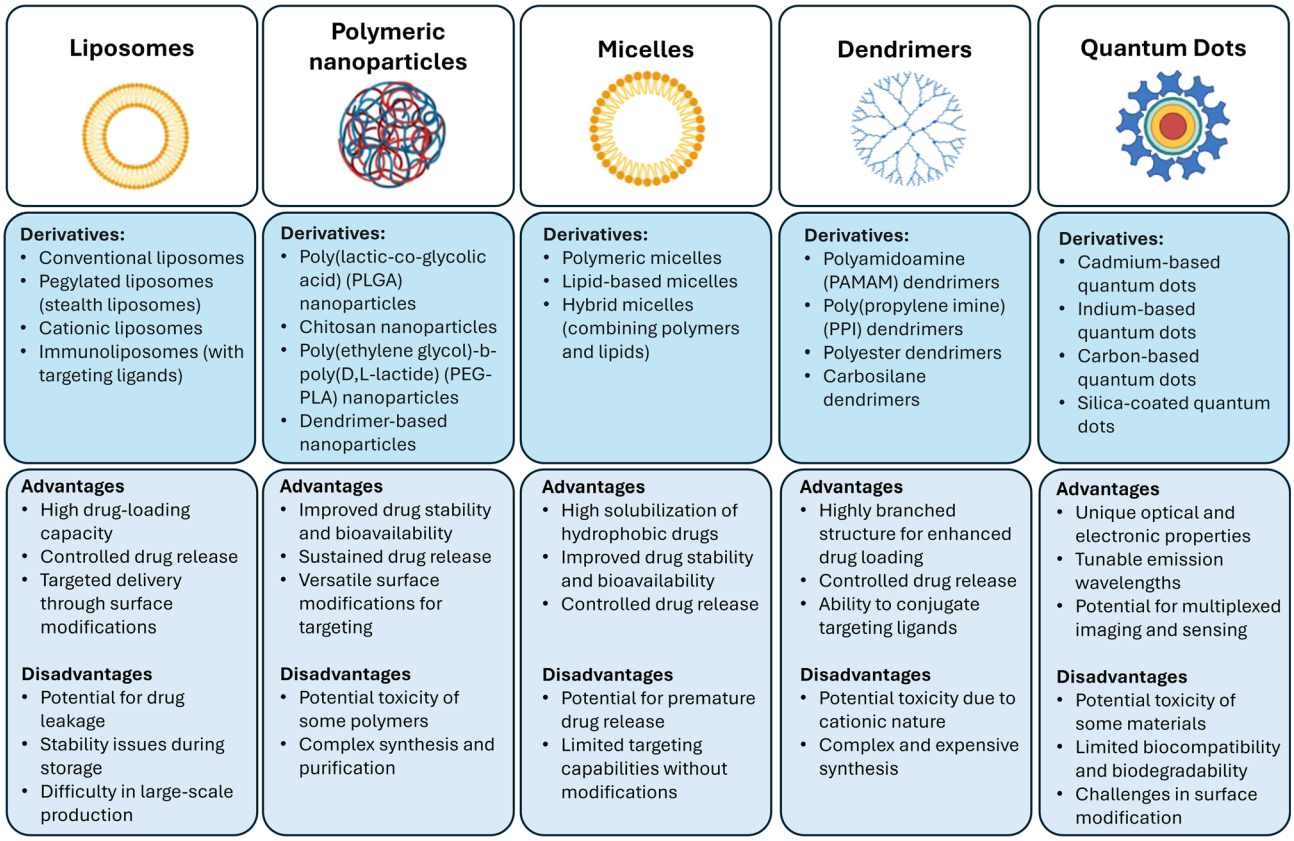

Fig. 5 Schematic overview of major nanoparticle platforms used in nanomedicine including liposomes, polymeric nanoparticles, micelles, dendrimers, and quantum dots summarizing their key variants and general strengths and limitations in drug delivery and biomedical applications (created by using Biorender).

Emerging exosome mimetic NPs, derived from natural cell membranes or engineered to mimic exosomal surfaces, offer enhanced immune evasion, longer circulation, and intrinsic targeting capabilities. These biomimetic systems have shown promise in overcoming the biological barriers of drug delivery and achieving site-specific delivery in aggressive tumor models. Metallic nanoparticles (MNPs), such as gold (AuNPs), silver (AgNPs), iron oxide (Fe_3O_4), and zinc oxide (ZnO), exhibit unique optical and magnetic properties conducive to imaging and therapy (https://advanced.onlinelibrary.wiley.com/doi/full/10.1002/adhm.202403059). AuNPs are biocompatible and easily functionalized, enabling their use in drug delivery, photothermal therapy (PTT), and theranostics.[104] Iron oxide nanoparticles (IONPs) facilitate magnetically guided delivery and are already used in imaging. MNPs also offer external stimuli-responsive release, such as heat, magnetic field, or light-triggered drug release, enhancing spatiotemporal control over treatment. However, concerns about biodegradability and long-term accumulation must be mitigated for clinical safety. Hybrid nanoplatforms that integrate lipid, polymeric, or metallic components offer synergistic benefits in drug loading, targeting, and responsiveness. Lipid–polymer hybrids, for instance, combine the biocompatibility of liposomes with the structural stability of polymeric cores, enabling co-delivery of chemotherapeutics and RNA-based agents with high precision.

3.2 Stimuli-responsive nanocarriers: triggers, specificity, and safety considerations

Smart nanocarriers exploit internal cues such as pH, enzymes, and redox state or external cues such as temperature, light, and magnetic field to enable on demand release at the tumor site.[108] H responsive systems use acid labile linkages for example hydrazone or acetal linkers that hydrolyze in the mildly acidic tumor milieu, enhancing site specificity and reducing systemic exposure.[117] Redox responsive carriers leverage high intracellular glutathione to cleave disulfide bonds and trigger disassembly. Temperature responsive systems based on polymers such as poly N isopropylacrylamide release drugs in hyperthermic regions or under external heating. Light responsive carriers use defined wavelengths to trigger controlled release with spatial and temporal precision.[116] Enzyme responsive systems degrade in the presence of tumor proteases such as MMPs or cathepsins, while magnetic responsive systems incorporate superparamagnetic iron oxide particles to allow guidance and remote release under alternating fields.[118]

These platforms improve precision and have increased efficacy in preclinical models. For example, pH sensitive carriers loaded with DOX showed 40% greater tumor inhibition in acidic breast cancer models than non-responsive controls. In a related model, DOX loaded pH sensitive micelles reduced

tumor volume by up to 80% in MDA MB 231 xenografts over 21 days with lower systemic toxicity. Multifunctional systems that combine pH and redox triggers enable dual stage release with extracellular accumulation followed by intracellular payload delivery and have achieved more than 90% tumor regression in murine colorectal and lung cancer models.

3.3 Engineering strategies for optimization

Nanoparticle engineering tunes release kinetics, biodistribution, and cellular uptake. Methods include nanoprecipitation, emulsification, self-assembly, and layer by layer deposition.[117] Nanoprecipitation, also known as solvent displacement, involves dissolving the polymer and drug in an organic solvent, followed by rapid addition to an aqueous phase under stirring, leading to spontaneous nanoparticle formation through solvent evaporation and polymer precipitation; this method is particularly suitable for hydrophobic drugs and yields NPs with high drug loading and narrow size distribution. Emulsification techniques, such as single or double emulsion solvent evaporation, create oil-in-water emulsions where the polymer-drug solution is emulsified in an aqueous phase, followed by solvent removal to solidify NPs; this is versatile for both hydrophobic and hydrophilic payloads but may require surfactants for stabilization. Emerging microfluidic-based synthesis methods offer better control over nanoparticle uniformity and are increasingly used in preclinical manufacturing pipelines. Microfluidic platforms utilize controlled mixing in microchannels to achieve rapid and homogeneous nucleation, resulting in monodisperse NPs with reproducible size and drug loading; for instance, flow-focusing devices can produce PLGA-NPs with sizes below 100 nm and encapsulation efficiencies exceeding 80%. These methods enable scalable production with minimal batch-to-batch variation, facilitating translation from bench to clinic.

Surface modifications, including PEGylation, not only enhance biocompatibility and prolong circulation but also reduce immune clearance, facilitating higher tumor accumulation.[102,108] PEGylation involves covalently attaching polyethylene glycol chains to the nanoparticle surface, creating a hydrophilic corona that sterically hinders opsonin adsorption and phagocytosis by macrophages, thereby extending circulation half-life up to several hours or days depending on PEG density and molecular weight. Recent research has also demonstrated the utility of zwitterionic coatings and biomimetic membranes (*e.g.*, red blood cell (RBCs) or cancer cell-derived vesicles) to further evade immune detection and prolong systemic circulation. Attaching targeting ligands like transferrin, folate, or antibodies directs NPs to overexpressed receptors on cancer cells, improving specificity and reducing off target effects. Transferrin targets the transferrin receptor (TfR), upregulated in tumors for iron acquisition, facilitating receptor-mediated endocytosis; folate exploits folate receptor alpha overexpression in epithelial cancers; antibodies such as trastuzumab bind HER2 in breast cancer, enabling active targeting with sub-nanomolar affinity.

Incorporation of stimuli-responsive polymers, such as pH-sensitive poly(histidine) or redox-sensitive disulfide bonds, allows for environment-triggered release. Poly(histidine) undergoes protonation below pH 7, transitioning from hydrophobic to hydrophilic and triggering nanoparticle disassembly in acidic endosomes or TME (pH 6.5–6.8). Studies show that PEG-coated nanocarriers achieve up to 30% greater tumor retention by evading macrophage clearance.[115] In preclinical models, PEGylated liposomes demonstrated 2–5 fold higher tumor accumulation *via* EPR compared to non-PEGylated counterparts, with retention persisting up to 72 hours. Similarly, optimizing size (typically 50 150 nm) and zeta potential (~10 to +10 mV) enhances EPR-based tumor penetration and cellular uptake, as smaller particles evade renal clearance while avoiding phagocytosis. Clinically, several nanocarrier systems are advancing through trials. For example, CPX 351, a dual drug liposomal formulation of cytarabine and daunorubicin, has shown improved outcomes in acute myeloid leukemia, highlighting the clinical promise of co-delivery strategies. The ongoing development of HER2- targeted polymeric NPs in HER2+ breast cancer further exemplifies the translational momentum in the field. Trastuzumab-conjugated PLGA NPs loaded with PTX achieved 2.5-fold higher tumor accumulation and 50% greater growth inhibition in HER2+ xenografts *versus* non-targeted controls in phase 1 trials. These advancements highlight polymeric NPs potential in precision oncology, with ongoing trials evaluating safety and efficacy in HER2+ subtypes.

3.4 Endosomal escape mechanisms and translational considerations

Efficient endosomal escape is a critical determinant of intracellular drug and nucleic acid delivery, particularly for co-delivery nanoplatforms targeting resistant and heterogeneous tumors. Different nanocarrier classes employ distinct endosomal escape mechanisms. Polymeric nanocarriers frequently utilize the proton sponge effect, in which buffering polymers such as polyethyleneimine, poly(histidine), or tertiary amine-rich materials induce osmotic swelling and subsequent endosomal membrane rupture under acidic conditions. Liposomal systems primarily rely on membrane fusion or destabilization mediated by pH-sensitive lipids, fusogenic peptides, or ionizable lipid components that undergo conformational changes within endosomes.

Recently, Zhao *et al.* (2026) demonstrated that although mRNA-loaded lipid nanoparticles (LNPs) are effective delivery systems, they suffer from limited endosomal escape. Incorporation of a biodegradable, tertiary amine-based polymer introduced a proton sponge effect, markedly enhancing cellular uptake and improving endosomal escape efficiency from ~20% to ~80% without inducing cytotoxicity.[119] The optimized polymer-modified LNPs achieved approximately 100-fold higher *in vivo* transgene expression while maintaining high mRNA encapsulation efficiency and minimal inflammatory response.

Inorganic and hybrid nanocarriers exploit alternative strategies, including photothermal- or photodynamic-induced

endosomal disruption, magnetic hyperthermia, and reactive oxygen species (ROS)-mediated membrane permeabilization. For example, UHHTN/DOX nanorobots, consisting of gold nanostars, exhibit a photothermal effect that enhances macropinocytosis-mediated endocytosis and facilitates endosomal escape.[120] In another study, stimuli-responsive, tumor-targeted photodynamic nanoparticles demonstrated enhanced tumor penetration and cellular uptake *via* HER2-mediated endocytosis, thereby improving intracellular delivery and therapeutic efficacy.[121]

Biomimetic systems, such as cell membrane-coated nanoparticles and exosome-inspired carriers, leverage natural intracellular trafficking pathways to partially bypass endo-lysosomal degradation, although endosomal escape efficiency remains variable. Recently, Ye *et al.* (2025) demonstrated that neutrophil-derived exosomes, through recognition of inflammatory cues, enable tumor-targeted accumulation and deep tumor penetration (up to 10.2 μm s^{-1}), while coordinating metabolic and immune reprogramming that suppresses tumor progression in preclinical colorectal cancer models.[122] Cell membrane-coated nanoparticles are promising biomimetic nanocarriers, but the integrity and completeness of membrane coating remain incompletely understood. A fluorescence quenching assay revealed that most biomimetic nanoparticles are only partially coated, yet remain capable of homologous targeting and cellular uptake, primarily *via* clathrin-mediated endocytosis.[123] However, the clinical translation of these strategies remains constrained by safety considerations, reliance on external triggers, and challenges in achieving reproducible and controllable endosomal escape *in vivo*.

4. Synergistic combinations in nanomedicine

The integration of diverse therapeutic modalities such as immunotherapy, targeted therapy, gene therapy, chemotherapy, and phototherapies like photodynamic therapy (PDT) and PTT has fundamentally transformed cancer treatment. These combinations allow synergistic interactions that improve therapeutic efficacy and reduce systemic toxicity. Preclinical and clinical studies have demonstrated that exploiting complementary mechanisms of action significantly enhances outcomes. For example, the co-application of PDT and targeted toxins in HER2-positive breast cancer significantly improved cytotoxicity and therapeutic response.[124,125] Many of these nanoplatforms are further engineered to be stimuli-responsive, exploiting tumor-associated triggers such as acidic pH, elevated enzymatic activity, or localized hyperthermia to enable selective drug release, while ongoing design efforts aim to minimize off-target activation under physiological conditions. NPs not only allow for site-specific release but also address tumor heterogeneity and drug resistance key challenges in modern oncology.[126,127] Importantly, the versatility of nanoplatforms facilitates patient-tailored strategies, propelling the field toward precision and personalized medicine.

In this context, synergistic effects refer to combination outcomes that exceed additive therapeutic responses and are supported by mechanistic coupling between treatment modalities. Such synergy arises from complementary biological mechanisms, including chemotherapy-induced immunogenic cell death that enhances immune checkpoint efficacy, nanocarrier-enabled co-delivery that ensures synchronized pharmacokinetics and fixed drug ratios, gene and RNA-based therapies that reprogram resistance pathways, and phototherapies that provide localized ROS or thermal amplification.

4.1 Nanocarrier-enabled combination therapy

As discussed above, nanocarriers, including liposomes, polymeric NPs, and inorganic NPs, offer powerful platforms for delivering multiple therapeutic agents simultaneously and address the limitations of conventional monotherapy by combining agents with different mechanisms of action.[128] Encapsulation protects drugs from degradation and enzymatic breakdown, improves solubility for hydrophobic compounds, and allows controlled, localized release, thereby enhancing the therapeutic index.[102,129] For example, co-delivery of PTX and curcumin in polymeric micelles has demonstrated enhanced efficacy in breast cancer by simultaneously inhibiting mitosis and the NF-κB pathway. Such strategies reduce systemic toxicity and improve pharmacokinetics through extended circulation and sustained release. These synergistic effects are primarily supported by preclinical quantitative data, including enhanced tumor growth inhibition, improved survival rates, and combination index analyses, although standardized synergy metrics remain inconsistently reported across studies. Moreover, surface functionalization *e.g.*, with folate or PEG, enhances tumor specificity and minimizes immune clearance.[129] Recent advances also explore co-delivery of immunomodulators or RNA-based therapies along with chemotherapeutics to synergize cytotoxic and immune-activating effects. Despite their promise, nanocarriers face challenges related to long-term stability, biocompatibility, manufacturing scalability, and regulatory complexity. Continued optimization in drug loading, targeting, and releasing kinetics is necessary to fully harness their potential.[130] Clinically, systems like CPX 351 (cytarabine/daunorubicin liposome) for leukemia and HER2-targeted NPs in breast cancer showcase the translational impact of co-delivery strategies.

4.2 Integration of chemotherapy and immunotherapy *via* nanocarriers

Chemotherapy remains a mainstay in cancer treatment but is often accompanied by immunosuppressive effects that can compromise long-term efficacy. Zitvogel *et al.* (2008) and Galluzzi *et al.* (2015) describe chemotherapy-induced lymphopenia, suppression of dendritic cells, and reduced tumor-infiltrating lymphocytes as key factors limiting immune surveillance.[131,132] Additionally, chemotherapy has been shown to reprogram the tumor immune microenvironment by increasing antigenicity, reducing suppressive myeloid populations, and enhancing interferon signaling, thereby converting immunologically 'cold'

tumors into 'hot' and responsive phenotypes. However, certain chemotherapeutic agents can induce immunogenic cell death (ICD), characterized by calreticulin exposure, ATP release, and HMGB1 signaling, which promotes antigen presentation and primes cytotoxic T lymphocytes. Studies by Casares *et al.* (2005) and Green *et al.* (2009) underscore the potential of ICD to convert tumors into *in situ* vaccines.[133,134]

Combining chemotherapy with immunotherapy including immune checkpoint inhibitors (*e.g.*, anti PD 1, anti CTLA 4) and cancer vaccines can harness the immune stimulatory effects of ICD while mitigating immune evasion.[135,136] This combination strategy enhances antitumor immunity and may overcome mechanisms of tumor resistance and relapse. Gene therapy adds another layer of therapeutic sophistication by enabling correction of oncogenic mutations at the molecular level. Nanoparticle based vectors (lipidic or polymeric) can encapsulate DNA, siRNA, or mRNA and deliver them into tumor cells, where they modulate gene expression and enhance susceptibility to other treatments (Fig. 6). Recent years have marked significant strides in gene therapy and RNA-based nanomedicine, though their representation in the broader nanomedicine discourse lags behind that of phototherapy and immunotherapy, which remain dominant across preclinical and clinical studies. Breakthroughs such as lipid NPs for mRNA cancer vaccines, polymeric carriers for siRNA co-delivery, and self-amplifying RNA systems highlight the transformative capacity of nucleic acid-based approaches to enhance therapeutic efficacy and broaden treatment options. These platforms not only safeguard inherently unstable RNA molecules but also enable targeted delivery, gene regulation, and immune modulation, laying the groundwork for precision medicine. Despite regulatory milestones, including the approval of patisiran, and an expanding clinical pipeline focused on oncology and immunological disorders, gene and RNA-based nanotherapeutics are still comparatively underrepresented, reflecting the need for greater emphasis in both research and translational efforts.

In parallel, phototherapy, immunotherapy, and natural compound-based nanotechnologies continue to demonstrate compelling therapeutic promise, particularly through synergistic combinations. Photothermal and photodynamic therapies, when integrated with chemotherapy or checkpoint inhibitors, have consistently yielded enhanced immune responses and tumor suppression. Nanoparticle-enabled immunotherapies, by delivering adjuvants, cytokines, and antibodies directly to the TME, reduce systemic side effects while amplifying antitumor immunity. Likewise, natural bioactive compounds such as curcumin and resveratrol have been successfully reformulated into nanocarriers to overcome limitations of solubility and bioavailability, strengthening their clinical relevance. Collectively, these advances illustrate the breadth of nanomedicine innovations; however, achieving a more balanced focus that elevates gene and RNA-based approaches alongside established modalities is essential for

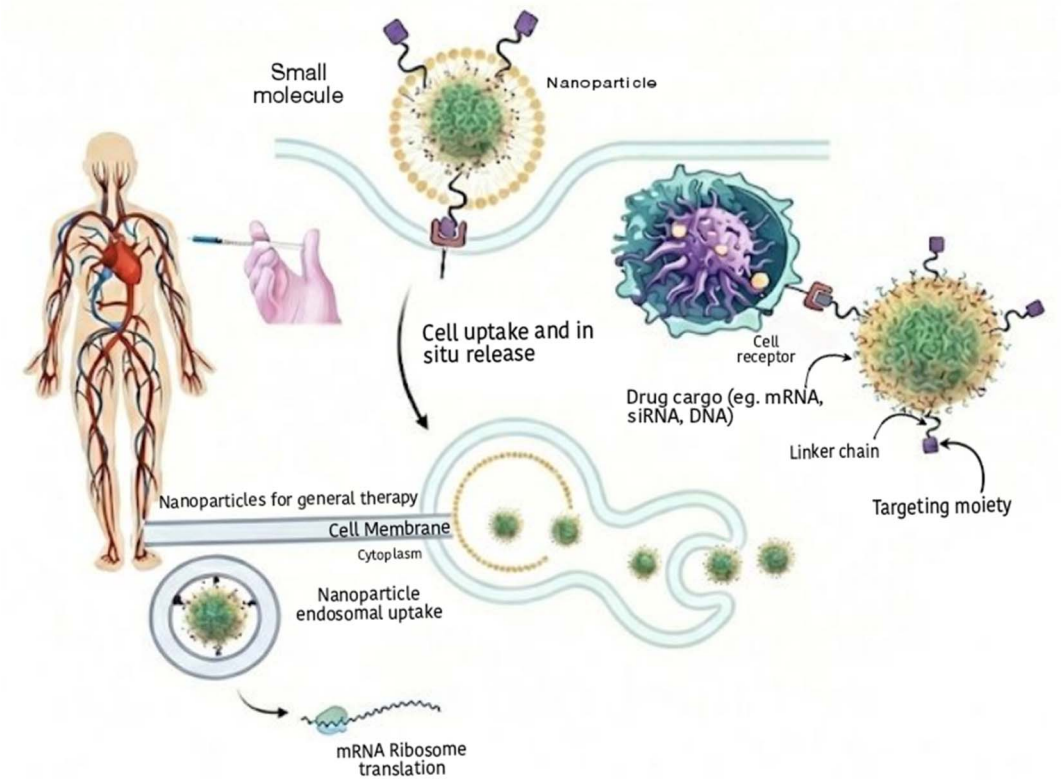

Fig. 6 Nanoparticle-based gene delivery systems for cancer therapy. The figure illustrates spherical nanoparticles encapsulating nucleic acid cargos (DNA, mRNA, or siRNA), surface functionalization with targeting moieties, cellular uptake *via* receptor-mediated endocytosis, endosomal release, and subsequent intracellular gene expression or silencing (draw by using Biorender).

shaping the next generation of combinatorial cancer therapies. This precision approach is particularly useful when combined with immunotherapy, enabling patient-specific treatment regimens based on tumor genetics.[137]

A compelling case of multimodal synergy is the combination of gemcitabine (a nucleoside analog that inhibits DNA synthesis) and rapamycin (an mTOR pathway inhibitor), which has shown therapeutic benefit in medulloblastoma. This combination not only reduces tumor proliferation but also sensitizes tumors to immunotherapy. Rechberger *et al.* (2023) and Lasky *et al.* (2022) highlight that incorporating PI3K/mTOR inhibitors and agents like Mithramycin alongside immune checkpoint blockade can effectively overcome tumor heterogeneity and resistance.[137,138]

4.3 Targeted therapy combined with phototherapy (PDT/PTT)

Phototherapy, encompassing PDT and PTT, has gained significant traction as a minimally invasive strategy to eradicate tumors with high precision. NPs offer the dual advantage of acting as delivery vehicles and energy converters converting light into cytotoxic ROS or hyperthermia. Gold nanorods exhibit exceptional photothermal conversion efficiency for PTT, while copper sulfide and IONPs contribute to both ROS generation and magnetic targeting.[139] For instance, Vines *et al.* (2019) demonstrate the role of AuNPs in PTT induced tumor necrosis and apoptosis.[140] Szwed *et al.* (2024) show that magnetic nanoparticles (MNPs) can induce local hyperthermia when subjected to alternating magnetic fields, especially in combination with chemotherapy and radiotherapy.[141] Reda *et al.* (2022) and Estelrich *et al.* (2018) confirm that these platforms improve tumor selectivity and therapeutic outcomes when co administered with immunotherapy.[142] Estelrich *et al.* (2018) emphasize IONPs, which serve as both magnetic and photothermal agents.[143–145]

Embedding photosensitizers such as indocyanine green (ICG) or zinc phthalocyanine into NPs enables combination PDT–PTT therapy. For example, IONPs coated with silane and loaded with ICG have shown robust antimicrobial activity against Gram negative bacteria, while simultaneously allowing imaging and thermal therapy (Fig. 7).[136,143,146] These nanoconjugates improve solubility, reduce systemic toxicity, and allow spatiotemporal control of drug release and therapeutic activation.[147,148] Synergistic outcomes in PDT/PTT-based combinations are quantitatively supported by increased apoptosis indices, tumor volume reduction, and immune activation markers in animal models; however, comparable quantitative validation in clinical settings remains limited.

Photochemical internalization (PCI), based on photo induced endosomal rupture, significantly enhances intracellular delivery of large biomolecules and chemotherapeutics. PCI is currently being explored in combination with PDT, magnetic hyperthermia, chemotherapy, cold atmospheric plasma (CAP), and sonodynamic therapy (SDT) to extend phototherapy's therapeutic reach. Notably, CAP has emerged as a promising adjunct to PDT for antibacterial therapy, especially for wound associated infections. Combined CAP–PDT approaches have demonstrated potent efficacy against antibiotic resistant pathogens, indicating translational potential for broader clinical applications. Furthermore, PDT integrated with chemotherapy, immunotherapy, or radiotherapy can generate synergistic antitumor responses by engaging both local cytotoxicity and systemic immune activation.

4.4 Role of natural compounds

Natural products, including alkaloids, terpenoids, polyphenols, flavonoids, saponins, and essential oils, are gaining renewed interest in oncology due to their multitargeted mechanisms of action and generally favorable toxicity profiles. Huang *et al.* (2021) reported that these compounds induce apoptosis, suppress angiogenesis, and sensitize tumors to conventional treatments.[20,149] Yuan *et al.* (2022) demonstrated that co-administration of phytochemicals with chemotherapeutic agents can enhance therapeutic efficacy while reducing dose-related toxicity, thereby improving patient tolerability.[150] Talib *et al.* (2022) further suggested that certain bioactive compounds block drug efflux pumps and inhibit resistance-associated pathways such as NF-κB, PI3K/AKT, and STAT3.[151] These multitargeted actions position natural compounds as valuable co-adjuvants in cancer therapy. Asma *et al.* (2022) emphasized the synergistic potential of combining dietary phytochemicals with chemotherapeutics to reduce adverse effects while retaining cytotoxic potency.[152]

Many plant-derived compounds, such as curcumin, resveratrol, quercetin, and genistein, have demonstrated the ability to modulate epigenetic regulation, apoptosis, and inflammatory signaling in preclinical models. Additionally, phytochemical-loaded nanocarriers have shown improved bioavailability, tumor accumulation, and therapeutic index in various *in vivo* studies. As research progresses, the development of phytochemical-loaded nanocarriers is paving the way for enhanced delivery, reduced off-target effects, and improved pharmacokinetics. The incorporation of natural products into multimodal nanotherapeutic strategies holds the potential to strengthen integrative cancer therapy, particularly by targeting resistant and heterogeneous tumors while also supporting safer and more personalized treatment regimens.[144,153] For example, a pH-sensitive hybrid nanocarrier composed of gelatin, agarose, and iron oxide (G-Aga-Fe_2O_3) was developed for controlled quercetin delivery, exhibiting high encapsulation efficiency and tumor-responsive release. This nanoplatform showed enhanced quercetin release under acidic tumor-mimicking conditions, improved cytotoxicity against MCF-7 breast cancer cells, and excellent biocompatibility in normal cells. These findings highlight the potential of hybrid nanocarriers to improve the therapeutic efficacy of natural compounds while minimizing systemic toxicity.[154] Quercetin has also been shown to suppress Wnt16 expression in cisplatin-activated tumor-associated fibroblasts, thereby alleviating stromal-mediated chemoresistance. A targeted quercetin phosphate nanoparticle formulation enhanced quercetin bioavailability, remodeled the tumor microenvironment (TME), and synergized with cisplatin

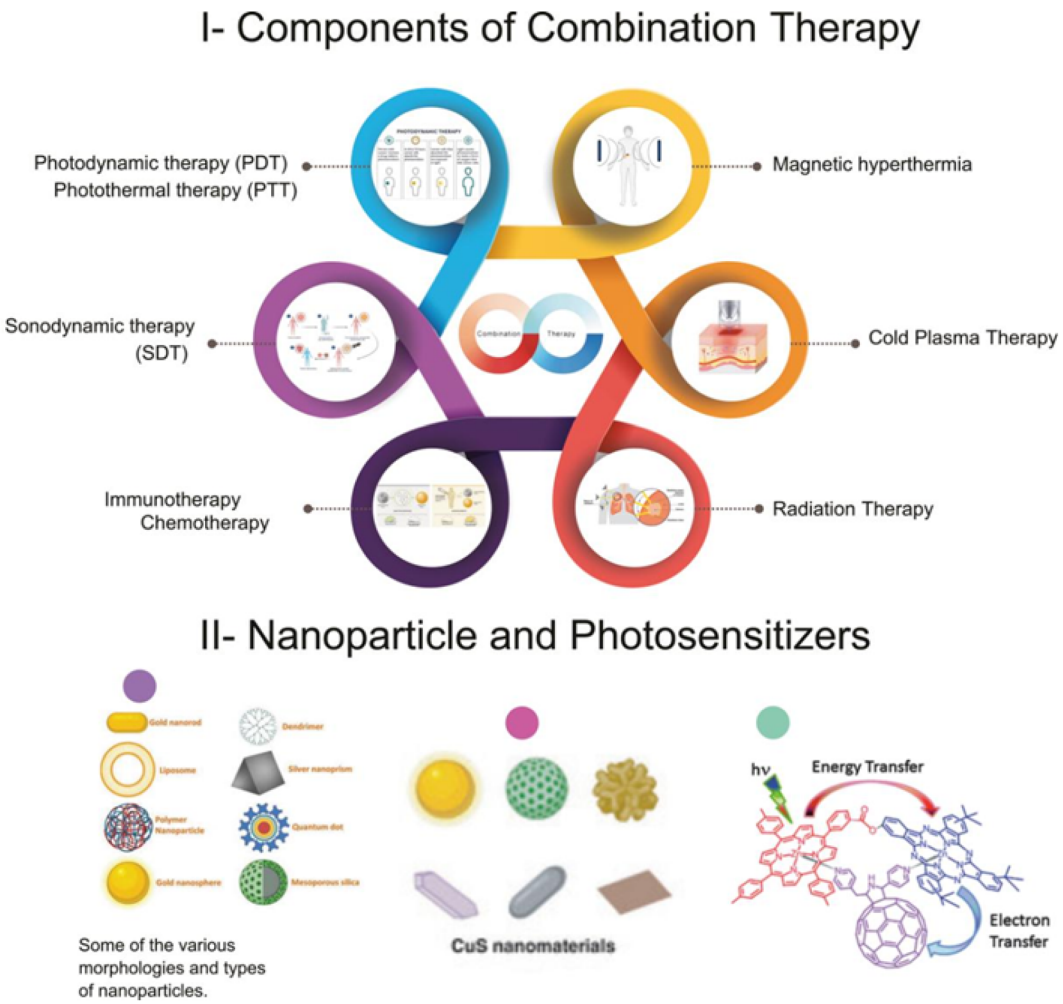

Fig. 7 Overview of combination cancer therapy modalities and representative nanoparticle platforms. Panel I illustrates major therapeutic components, including chemo-, immuno-, photothermal, photodynamic, sonodynamic, magnetic hyperthermia, cold plasma, and radiation therapies. Panel II highlights representative nanoparticle morphologies and photosensitizers used to enable synergistic combination treatments (created by using Biorender).

nanoparticles, resulting in improved drug penetration and antitumor efficacy in desmoplastic bladder cancer models.[155]

Phenylboronic acid – conjugated ZnO nanoparticles were developed for targeted and pH-responsive delivery of quercetin to sialic acid – overexpressing cancer cells, improving tumor specificity and bioavailability. The quercetin-loaded PBA–ZnO nanohybrids induced apoptosis through oxidative stress and mitochondrial damage, effectively suppressed tumor growth *in vivo*, and reduced systemic toxicity. This combinatorial nanoplatform highlights the potential of integrating natural bioactives with inorganic nanocarriers for safe and effective cancer therapy.[156] Tumor-associated fibroblasts (TAFs) drive desmoplasia, drug resistance, and immunosuppression in solid tumors, and their deactivation represents an alternative to direct cytotoxic stromal targeting. A puerarin nanoemulsion (nanoPue) effectively reduced ROS-mediated TAF activation, remodeled the TME, enhanced chemotherapy and PD–L1 checkpoint blockade efficacy, and increased cytotoxic T-cell infiltration in desmoplastic triple-negative breast cancer models. This scalable nanoPue platform highlights a promising stromal-modulating strategy for combination chemo-immunotherapy in desmoplastic tumors.[157] In another study, an enzyme-responsive and acid-sensitive nanoscale micellar system was developed for the co-delivery of berberine and baicalin to enhance breast cancer therapy. These intelligent micelles exhibited high encapsulation efficiency, controlled drug release, effective tumor targeting and penetration, and significantly inhibited tumor proliferation, invasion, and migration while inducing apoptosis both *in vitro* and *in vivo*.[158]

Considering the diverse therapeutic strategies discussed from smart drug delivery systems to multimodal combinations including immunotherapy, phototherapy, and natural product-based interventions, a consolidated overview of current engineering strategies and therapeutic integrations is provided in Table 1. Although the synergistic effects of phytochemical-based combinations are supported by quantitative reductions in IC_{50} values and enhanced chemosensitivity in preclinical studies, clinical validation remains largely correlative rather than quantitative. Overall, the synergistic benefits of multimodal nanomedicine-based combination therapies are

underpinned by strong mechanistic insights across chemotherapy, immunotherapy, gene therapy, and phototherapy. Quantitative evidence robustly supports these synergies at the *in vitro* and *in vivo* levels; however, systematic clinical quantification of synergy remains limited, underscoring the need for standardized metrics and biomarker-driven clinical trials.

5. Preclinical and clinical translation of combination nanomedicine

5.1 Preclinical and clinical insights into synergy

From a clinical translation perspective, it is important to compare emerging nanocarriers with established platforms such as liposomes and polymeric nanoparticles. Traditional formulations benefit from well-characterized pharmacokinetics, scalable manufacturing, regulatory familiarity, and multiple clinical approvals (*e.g.*, liposomal doxorubicin, CPX-351, nab-paclitaxel). Their limitations include restricted payload diversity, moderate control over spatiotemporal release, and limited adaptability to tumor heterogeneity. The emphasis on synergy has shifted therapeutic paradigms from single agents to multi agent combinations particularly in oncology, where tumorigenesis involves intricate molecular reprogramming. Standard therapies like surgery, radiation, chemotherapy, and immunotherapy, although effective, come with substantial risks including toxicity, recurrence, chemoresistance, and reduced quality of life. Multimodal strategies aim to overcome these challenges by combining treatment modalities to augment efficacy and reduce side effects.[179,180] For example, Mahalingam *et al.* (2020) reported a Phase 1b trial in pancreatic adenocarcinoma combining pembrolizumab, pelareorep (an oncolytic virus), and chemotherapy which enhanced tumor control *via* both oncolysis and immune activation.[181] Similarly, the CUSP9v3 protocol for glioblastoma designed by Halatsch *et al.* integrates nine repurposed non cytotoxic agents with continuous low dose temozolomide to disrupt tumor survival mechanisms. A Phase Ib/IIa study showed that this regimen could be safely administered with close monitoring.[182]

Furthermore, novel platforms such as high throughput organoid screening and single cell omics are revolutionizing the evaluation of these complex therapeutic combinations. For example, techniques like single cell RNA sequencing (scRNA seq) and CyTOF are identifying resistant tumor subpopulations and characterizing treatment responses with unprecedented resolution. These techniques have enabled researchers to delineate how certain cell types such as granulocytes or monocytes respond to nanoparticle exposure, identifying pathways

Table 1 Unified overview of smart nanomedicine strategies, engineering features, and combinatorial therapeutic applications summarizing key characteristics of smart nanocarriers (*e.g.*, stimuli responsiveness), surface modifications for targeting and immune evasion, integration with combinatorial treatments (PDT, PTT, immunotherapy), and recent advances in phytochemical-based nanoformulations, with each entry illustrating a representative mechanism, application, and example system

Category	Application	Strategy	Function	References
Smart nanocarriers	Stimuli-responsive mechanisms	General nanoparticle platforms	Targeted, on-demand release triggered by internal or external stimuli	102, 108, 117, and 159
	pH-responsive	Acidic TME sensitive carriers	Selective release in TME	102, and 117
	Temperature-responsive	Thermo sensitive polymers	Release drugs in response to local temperature changes, such as hyperthermic regions	108, and 117
	Light-responsive	Photosensitive linkers/ nanomaterials	Controlled drug release *via* light activation	115, and 117
	Enzyme-responsive	Protease sensitive nanocarriers	Site-specific degradation and drug release in the tumor milieu	116, and 118
	Magnetic-responsive	Magnetic field controlled nanocarriers	Remote activation and targeting	104, and 115
Surface modification	Ligand conjugation	Folate/Antibody functionalized carriers	Tumor specific receptor targeting	99, and 105
	PEGylation	Polyethylene glycol (PEG) coatings	Enhanced circulation and immune evasion	100, and 159
	Electrostatic modulation	Charge tuning	Improved cellular uptake	105, and 160
Combination therapies	Anticancer	Photofrin, zinc phthalocyanine, quinoline derivatives	Photosensitizer capped metal nanoconjugates for cancer	161, and 162
	Antibacterial	Porphyrins, silver/gold NPs	Photosensitizer antibacterial strategies	163
	Chemotherapy	DOX/chlorin e6/methylene blue	Photosensitizer + chemotherapeutic agents	164–166
	Photochemical internalization	Aluminum phthalocyanine/ bleomycin	Photo-induced endosomal escape	167, and 168
	Photothermal therapy	IONPs/ICG, zinc phthalocyanine	Light triggered hyperthermia & drug delivery	169
	Cold plasma therapy	5 ALA + methylene blue PDT + CAP	Enhanced antibacterial or anticancer synergy	170–172
	Sonodynamic therapy	Curcumin, chlorin e6, Rose Bengal	ROS-mediated cytotoxicity *via* ultrasound	173, and 174
	Immunotherapy	Hematoporphyrin + R837, MOF Abs	Immune stimulation with targeted nanoplatforms	175, and 176
	Radiotherapy	Rose Bengal + oxygen microbubbles	Radiation enhanced tumor targeting	177, and 178

linked to either cytotoxicity or immune tolerance.[144,183] Incorporating these technologies into preclinical models offers better insight into tumor heterogeneity, allowing researchers to test combinational therapies with enhanced precision. As a result, human PDOs are being integrated into combinational nanomedicine workflows, offering clinically translatable platforms to model individual responses to multi agent therapies and reduce the reliance on animal models.

In contrast, novel nanocarriers such as covalent organic frameworks (COFs) and biomimetic nanoparticles offer enhanced structural tunability, high surface area for multi-drug loading, and improved responsiveness to TME cues. COFs enable precise control over pore size and functionalization, supporting high drug-loading capacity and programmable release, but face translational challenges related to long-term biodegradability, *in vivo* stability, and regulatory uncertainty. A nanoscale covalent organic framework (nTG-DFP-COF) was developed to enhance fluorescence-guided cryosurgery by exhibiting temperature-dependent luminescence with increased emission under cryogenic conditions. This biocompatible and cancer-specific nanoplatform enables precise differentiation between malignant and healthy tissues during cryoablation, improving surgical accuracy and safety. The integration of diagnostic and therapeutic functions highlights its potential for advancing image-guided treatment of resistant tumors.[184] An iodine-decorated porphyrin-based covalent organic framework (pCOF-I) was developed as a multifunctional theranostic nanoplatform for melanoma treatment, enabling doxorubicin delivery, photodynamic therapy (PDT), and CT imaging. AS1411 aptamer functionalization enhanced tumor targeting and cellular uptake, resulting in synergistic chemo-PDT efficacy and practical imaging guidance in preclinical melanoma models. This work highlights the potential of COF-based nanocarriers for integrated multimodal cancer therapy and diagnosis.[185]

Biomimetic nanoparticles, including cell membrane-coated and exosome-inspired systems,[122] demonstrate superior immune evasion, prolonged circulation, and active tumor homing; however, their clinical deployment is constrained by complex manufacturing, batch-to-batch variability, and scalability concerns.

Despite encouraging evidence of synergistic efficacy, the clinical translation of multimodal nanomedicine faces significant challenges related to dosing, timing, and therapeutic sequencing. In combinations involving phototherapy and gene delivery, optimal sequencing is critical, as premature photothermal or photodynamic activation may compromise nucleic acid integrity or cellular uptake, whereas delayed activation may reduce synergistic benefits. Similarly, dose balancing remains complex, since phototherapy relies on localized energy thresholds while gene therapies require sustained intracellular expression for efficacy. Temporal coordination of light exposure, gene expression kinetics, and immune activation is therefore essential but remains insufficiently standardized. Current preclinical studies often optimize these parameters empirically, underscoring the need for predictive models, real-time imaging, and adaptive dosing strategies to guide clinical implementation.

5.2 Long-term safety considerations and risk mitigation strategies

While nanomedicines offer clear therapeutic advantages, long-term safety remains a critical consideration for clinical translation. Clinical and post-marketing data from approved nanoplatforms, such as liposomal doxorubicin (Doxil®), nab-paclitaxel, and iron oxide nanoparticles, indicate that chronic toxicities may include hepatosplenic accumulation, transient hepatotoxicity, renal clearance-related nephrotoxicity, and immune-related effects such as complement activation and antibody formation. For example, repeated administration of PEGylated nanocarriers has been associated with accelerated blood clearance and anti-PEG antibody production in some patients, potentially altering pharmacokinetics and therapeutic efficacy.[186]

Emerging nanocarriers, including inorganic nanoparticles and COFs, raise additional concerns related to long-term biodegradability, persistence in clearance organs, and chronic inflammatory responses, particularly in the liver, spleen, and kidneys. Preclinical studies have shown that non-biodegradable nanomaterials may remain detectable for months, underscoring the need for extended toxicological evaluation beyond acute dosing windows.[187] To mitigate long-term risks, several design strategies are being adopted, including the use of biodegradable or metabolizable materials, ultrasmall platinum nanozymes as an antioxidant for theranostics in acute kidney injury,[188] zwitterionic or biomimetic surface coatings to reduce immune activation, and controlled dosing schedules to minimize organ burden. Incorporation of stimulus-responsive degradation, "on-demand" clearance mechanisms, and real-time imaging to monitor biodistribution are also emerging as practical approaches to improve long-term safety. Collectively, integrating systematic chronic toxicity studies with rational nanocarrier design will be essential for advancing nanomedicines toward safe and sustainable clinical use.

5.3 Case studies on synergistic cytotoxicity and tumor regression

The integration of nanomaterials into therapeutic regimens has ushered in a new era of precision oncology. One compelling example is the use of cytotoxic cationic silica nanoparticles (CSiNPs) co administered with molecular adjuvants like c-di-GMP, which amplify cytotoxicity and immune activation. These platforms leverage previously discussed resistance pathways such as mitochondrial dysfunction and immune escape to trigger synergistic tumor regression.[149]

Soluble inorganic NPs such as ZnO, copper oxide (CuO), and AgNPs also show promise in targeted cancer therapy due to their unique redox activity, ion release, and TME modulating capabilities (https://www.sciencedirect.com/science/article/pii/S2590006424000565). For instance, dextran coated IONPs have been shown to activate macrophages toward a pro inflammatory phenotype, thereby suppressing tumor

progression.[189] These properties allow for both cytotoxic and immunomodulatory effects, offering multi-pronged strategies against tumor growth.

Despite their promise, challenges remain fully elucidating the long-term fate and toxicity profiles of NPs, especially with materials like AuNPs. Current research focuses on modifying surface chemistry and doping strategies to improve selectivity, reduce systemic toxicity, and achieve sustained therapeutic effects. Coating or functionalizing these NPs with targeting ligands or polymers not only enhances biocompatibility but also fine tunes their release kinetics and interaction with cancer cells.[190] Notably, artificial intelligence (AI) and machine learning (ML) are increasingly integrated into nanoparticle design pipelines to accelerate optimization and predict biological responses. For example, AI driven drug screening using organoid models and omics datasets enables rapid evaluation of synergistic nanoparticle based regimens targeting apoptosis, angiogenesis, and DNA repair pathways.[191]

Recent developments also showcase how NPs can directly address chemoresistance. Through tailored delivery, NPs can bypass efflux pumps and deliver agents intracellularly, effectively overcoming both intrinsic and acquired resistance mechanisms. A key example is nanoparticle facilitated delivery of PTX and curcumin co encapsulated in polymeric micelles, which showed improved efficacy in resistant breast cancer models by simultaneously disrupting mitosis and NF κB signaling pathways. Beyond curcumin and resveratrol, several other natural bioactives have demonstrated synergistic potential when integrated into nanocarrier systems. Quercetin, a flavonoid with strong antioxidant and pro-apoptotic activity, has been shown to sensitize tumor cells to chemotherapy by inhibiting PI3K/AKT signaling and downregulating heat shock proteins, thereby enhancing nanoparticle-mediated drug retention. Genistein, an isoflavone, exerts epigenetic modulation and tyrosine kinase inhibition, and when nanoformulated, it synergizes with chemotherapeutics by suppressing angiogenesis and reversing multidrug resistance. Berberine, an isoquinoline alkaloid, disrupts mitochondrial function and activates AMPK signaling, leading to metabolic stress in cancer cells; its encapsulation within nanocarriers improves bioavailability and enables synergistic ROS-mediated cytotoxicity when combined with inorganic or polymeric nanoparticles.

Other studies have shown how doped NPs such as zinc doped CuO-NPs can enhance ROS generation and mitochondrial dysfunction selectively in cancer cells, leading to apoptosis without damaging healthy tissues. Moreover, organoid based adverse outcome pathway (AOP) models are being used to study the systemic effects of these NPs, addressing both efficacy and biosafety.[192] Finally, in brain cancers, the co-administration of gemcitabine and rapamycin *via* NPs has been effective in sensitizing medulloblastoma cells to immune checkpoint inhibitors. This approach disrupts both DNA synthesis and mTOR signaling pathways, providing a dual mechanism of tumor control and enhancing immune responsiveness.[193] Together, these studies highlight that while synergistic efficacy is well supported preclinically, successful clinical translation will depend on rational optimization of modality sequencing, dose synchronization, and patient-specific tumor biology.

6. Advanced strategies for overcoming the challenges of monotherapy

To address all the challenges outlined in above sections, the synthesis of smart NPs with tunable properties such as size, shape, surface functionalization, and morphology has been adopted to improve penetration, targeting precision, circulation time, and clearance is necessary.

6.1 Overcoming biological barriers

For nanomaterials to effectively reach their target sites, they must traverse complex physiological environments composed of mechanical, enzymatic, and cellular barriers, including epithelium, endothelium, and intracellular membranes (Fig. 8). Effective targeting requires maintaining structural stability while crossing barriers such as the blood–brain barrier (BBB), evading immune clearance by the mononuclear phagocyte system (MPS) and the reticuloendothelial system (RES), and accumulating at tumor sites *via* leaky vasculature.

Parameters like NPs size, surface chemistry, and biocompatibility are essential in reducing off target effects. However, internalization alone is insufficient. NPs must also ensure endosomal escape and subcellular delivery. Metallic NPs, due to their small size, cross biological barriers through passive diffusion, receptor mediated transport, or trans synaptic mechanisms (Fig. 9).[194]

For instance, TAT AuNPs loaded with DOX penetrated the BBB and improved survival in glioma models (Fig. 10A–C).[195] Similarly, functionalized multi walled carbon nanotubes accumulated in the brain without disrupting tissue integrity.[196] Recent studies indicate that protein corona composition, determined by nanoparticle surface coatings (*e.g.*, PEG, oleic acid), influences degradation rates and biological fate.[197,198] Polymeric NPs, due to their tunability, can be tailored with stabilizers such as PEG or polysorbate 80 to prolong circulation and enhance BBB permeability.[199] These surface modifications significantly improve the bioavailability, stability, and targeting potential of NPs.

Despite these advances, RES-mediated clearance *via* opsonization remains a bottleneck. To reduce RES uptake, strategies like using smaller sized NPs or PEGylation have been adopted. PEGylated lipid NPs achieved up to 35% siRNA delivery in xenograft models. However, RES blockade using agents like gadolinium chloride or dextran sulfate may reduce nanoparticle clearance but also compromise immune function. More sophisticated approaches such as CD47-derived "don't eat me" peptides incorporated into liposomes (DSLs) have shown promise in enhancing circulation by inhibiting phagocytosis.[200] Additional strategies include co administration of λ-carrageenan with PEG-AuNPs for synergistic RES inhibition and stiffness tunable nanogels that sequentially block RES uptake and deliver chemotherapeutics like DOX (Fig. 11).[201]

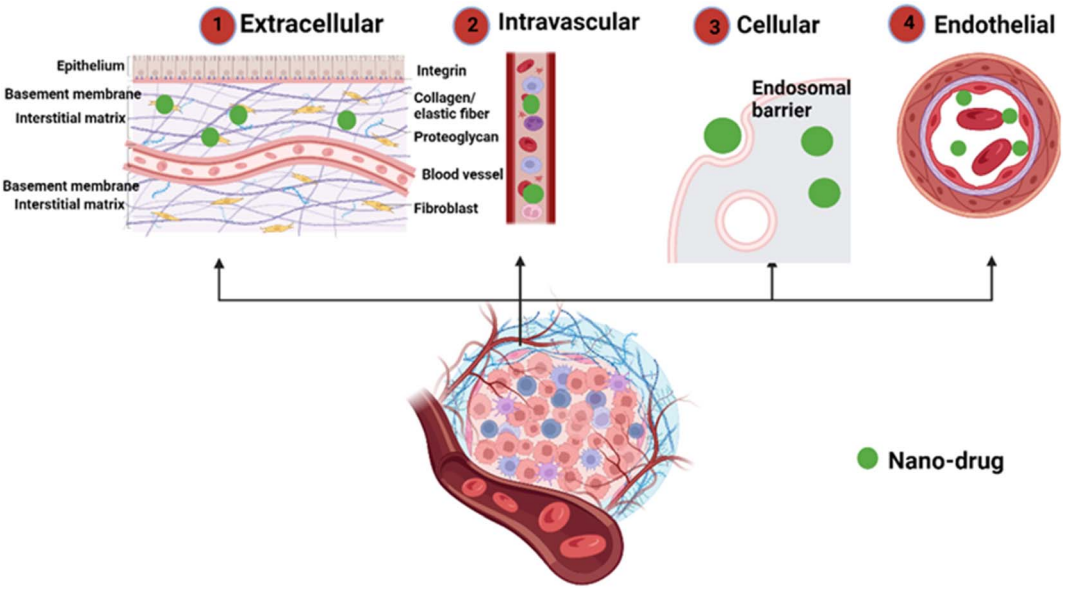

Fig. 8 NPs need to surpass major levels of biological barriers, including (1) extracellular, (2) endothelial, (3) intravascular (4) endothelial, for successful targeting mechanisms. However, depending on the depth of the target region, several biological barriers differ. The higher the depth, the higher the number of barriers (created by using Biorender).

Clearance of NPs is essential for safety and translational viability. The body uses renal and hepatic pathways depending on nanoparticle size (Fig. 12). Small NPs are excreted renally, whereas larger ones accumulate in RES organs.[202] MnO-NPs with PEG chains demonstrated efficient excretion through kidney and liver routes,[203] and ultrasmall AuNCs conjugated with neutravidin improved renal clearance.[204] Biodegradable NPs like PLGA are excreted *via* bile and urine, whereas non-biodegradable materials (*e.g.*, AuNPs) accumulate for extended periods, as shown by persistent liver deposition over six

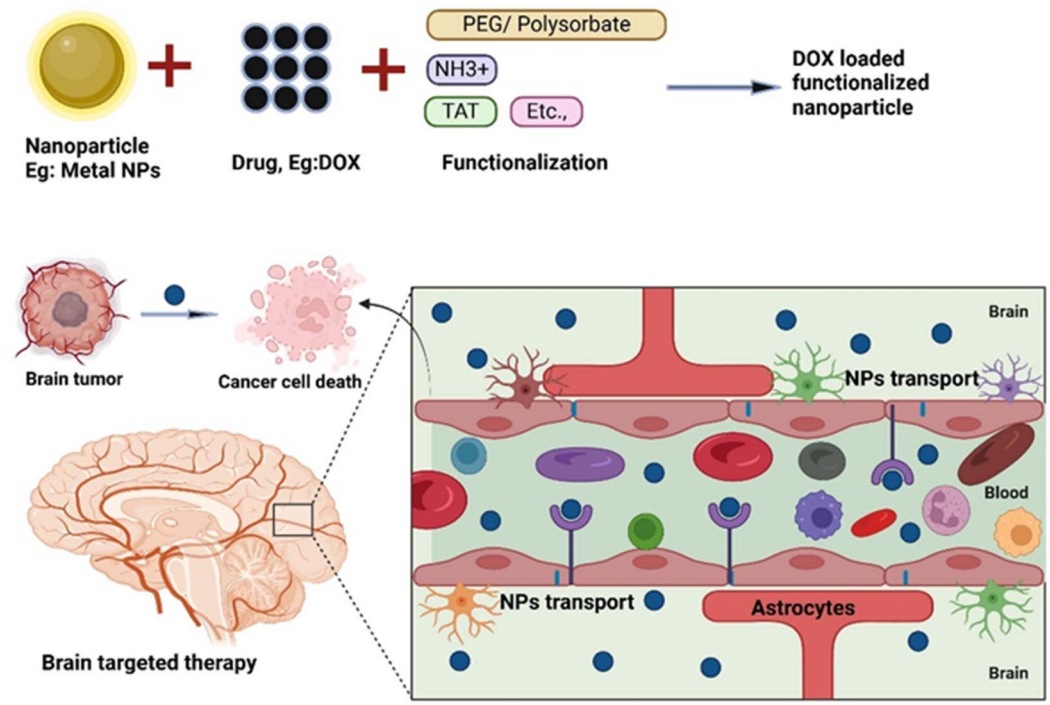

Fig. 9 Illustration of blood–brain barrier (BBB) transport and brain-targeted drug delivery using doxorubicin (DOX)-loaded functionalized nanoparticles. Surface-modified nanoparticles enable BBB traversal, enhanced brain accumulation, and targeted tumor cell killing (created by using Biorender).

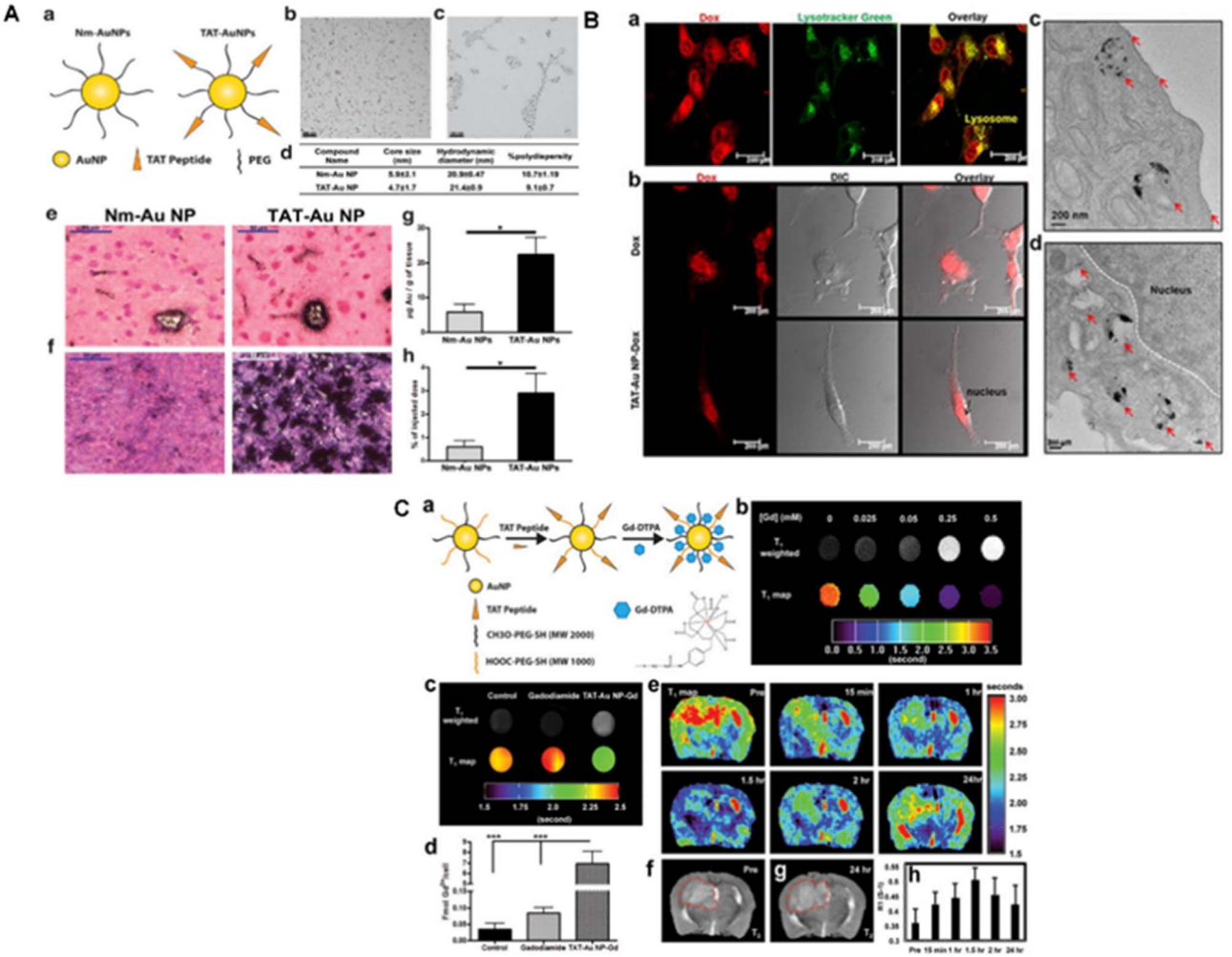

Fig. 10 (A) The BBB penetration and tumor targeting studies of non-modified PEGylated (Nm Au NP) and TAT AuNPs (B) *in vitro* studies of Au NP mediated Dox release in glioma cell lysosomes and cell nuclei, and (C) TAT AuNP Gd conjugates for enhanced malignant glioma imaging. This figure was adapted from ref. 198 with permission 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinhem.

months.[205] AgNPs present an added challenge due to unpredictable degradation behaviors and aggregation under reactive *in vivo* conditions. To enhance clearance and circulation time, polymeric NPs with PEG or polysorbate 80 coatings have proven effective.[199,206] Notably, smaller PEGylated particles exhibited longer circulation times (>12 h) compared to their larger counterparts.[206] Understanding nanoparticle biodistribution, cellular uptake, and clearance mechanisms including exocytosis, endocytosis, and mitotic dilution, is essential for clinical translation. Control over pharmacokinetics and clearance timing can reduce off target effects and long term toxicity.[207]

6.2 Strategies to enhance nanoparticle efficacy and biocompatibility

6.2.1 Deep tumor penetration and immune evasion. NPs, while promising for drug delivery, are inherently vulnerable to the immune system's defense mechanisms. The lymphatic system and the RES can readily recognize and eliminate foreign nanomaterials, reducing therapeutic efficacy. Moreover, the formation of a protein corona around NPs can mask tumor targeting ligands, further hindering their ability to reach diseased tissues. To address these challenges, various surface engineering strategies have been developed to prolong circulation time, minimize immune clearance, and enhance tumor specific penetration.[208]

One widely adopted approach involves surface modification using hydrophilic polymers such as PEG, hyaluronic acid (HA), or polyvinyl pyrrolidone (PVP). PEGylation, in particular, produces "stealth" NPs that are less likely to be detected by immune cells, thereby increasing systemic stability and tumor accumulation.[209] For instance, PEG immunomodulatory NPs have been designed to avoid off target uptake and improve biodistribution in metastatic lung models. In one such study, mesoporous silica NPs (immune MSN) coated with light PEG demonstrated improved uptake by antigen-presenting cells (APCs) 24 hours post-injection, validating their enhanced performance.[210] Beyond PEG, other stealth strategies have been investigated. Incubation of clusterin with polymer-modified nanocarriers, such as PEG or poly(ethyl ethylene phosphate)

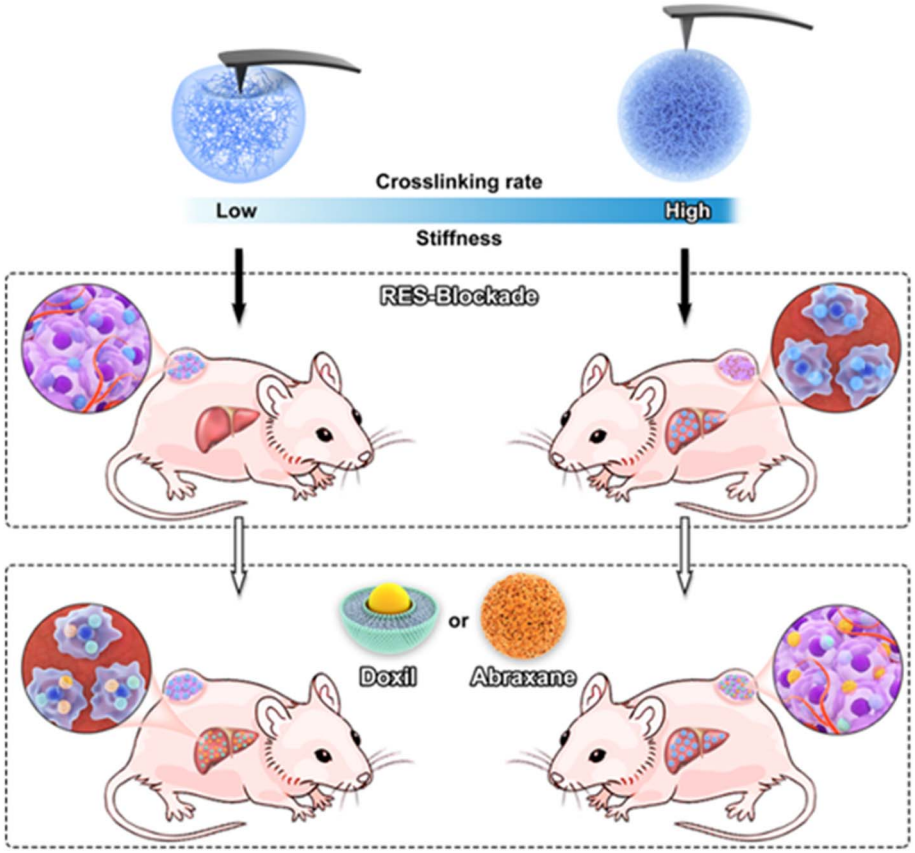

Fig. 11 Nanogels with distinctive stiffness are injected preferentially, and soft nanogels accumulate more in the tumor, while stiff nanogels accumulate more in the liver and temporarily block RES. This figure was adapted from ref. 201 @2023, The authors, and is licensed under a Creative Commons Attribution 4.0.

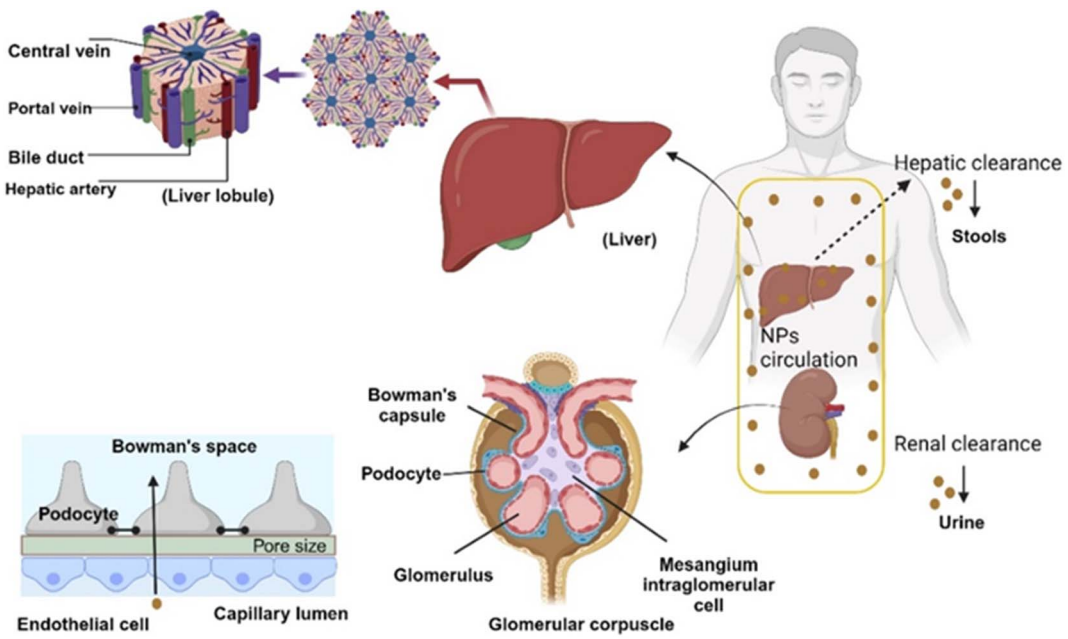

Fig. 12 Overview of hepatic and renal clearance pathways of NPs. The illustration depicts NP circulation, hepatic uptake and biliary excretion, as well as glomerular filtration and renal elimination (created by using Biorender).

(PEEP), has been shown to reduce nonspecific uptake by altering PC composition.[211] However, PEGylation is not without limitations it may induce biofouling and activate the complement system, leading to opsonization. To overcome these drawbacks, alternative coatings such as polyglycerol (PG) have been employed. PG coatings can effectively suppress protein corona formation across a range of nanoparticle sizes and compositions, thereby enhancing stealth behavior and reducing macrophage recognition.[212] Recent advancements in high-dimensional immune profiling tools have enhanced our ability to evaluate nanoparticle immune compatibility. For example, a study using mass cytometry (CyTOF) and single cell RNA sequencing (scRNA seq) analyzed the effects of AgNPs on peripheral blood mononuclear cells (PBMCs). The study demonstrated that AgNPs interacted with monocytes, B cells, and T cells without triggering inflammatory responses, indicating a favorable immunological profile. In contrast, titanium dioxide nanoparticles (TiO_2/E171) elicited a granulocyte mediated inflammatory response in mouse PBMCs, highlighting the material specific immune behavior of NPs and the need for precise safety validation before clinical translation.[213–215]

Zwitterionic polymers offer another promising route for immune evasion. These polymers, characterized by balanced cationic and anionic groups, are highly hydrated and resist nonspecific protein adsorption, thereby extending blood circulation time. A study using a phosphorylcholine based zwitterionic copolymer to coat ZIF 8 nanodrugs (DOX@ZIF 8@P(MPC co C7A)) demonstrated reduced drug leakage and improved delivery efficiency to tumor tissues.[215] Fig. 13 illustrates the extended circulation and tumor penetration achieved through functionalized nanocarriers loaded with agents like PTX or DOX and coated with PEG conjugated immune stimulating silica mesoporous NPs.

Biomimetic strategies also play a critical role in immune evasion. For example, RBCs mimicking NPs have been engineered using a polymeric PTX core enveloped in a hydrophilic RBCs vesicle shell. These constructs extended blood circulation by 5.8-fold, achieving an elimination half-life of 32.8 hours substantially longer than uncoated polymeric NPs (5.6 hours). Moreover, co administration of tumor penetrating peptides like iRGD significantly improved tumor accumulation and penetration.[216] Synthetic RBCs created using a silica cell bio replication method further illustrate the potential of this approach in prolonging systemic persistence. Similarly, hydrogel microparticles (MPs) with tunable elasticity have been used to bypass clearance organs and extend biodistribution profiles.[217] Magnetically guided RBCs mimicking micromotors have also been explored for oxygen and photosensitizer (PS) delivery in PTT.[218,219]

The modulation of the protein corona has also emerged as an effective tactic. Coating NPs with plasma immunoglobulin G (IgG) can form a stable PC that, when reintroduced into circulation, reduces immune recognition and prolongs systemic retention.[220] Precoating liposomes with human plasma proteins has also been shown to reduce immune clearance *in vivo*.[221] Another innovative approach involves the use of "dysopsonic proteins" like apolipoprotein E (ApoE), which when adsorbed onto NPs prior to injection, significantly enhance circulation time and reduce phagocytic uptake.[222]

6.2.2 Enhancing safety and multi drug efficacy. In the pursuit of improving monotherapy outcomes, integrating NPs with biocompatible materials has proven to be a pivotal strategy. These carriers mitigate many limitations associated with conventional chemotherapy such as systemic toxicity, off-target effects, and poor solubility by enabling stable drug encapsulation, prolonged circulation, and controlled release.

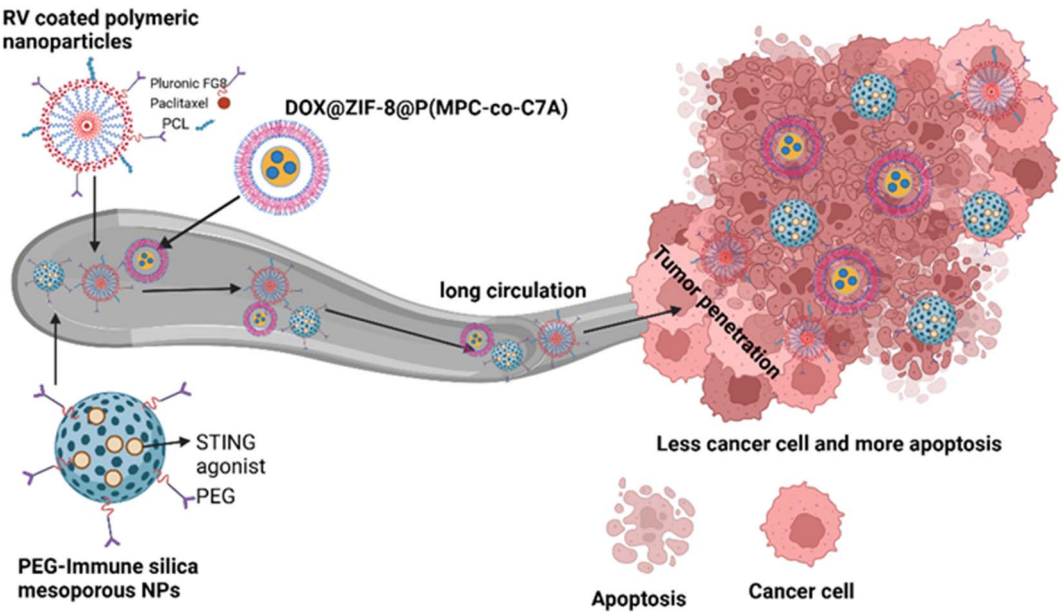

Fig. 13 Schematic representation of selected NPs involved in tumor penetration for targeted cancer therapy. DOX: doxorubicin, RV: RBC mimetic vesicle, PEG, ZIF 8: zeolitic imidazole framework 8 NPs (ZIF 8 NPs), phosphorylcholine-based zwitterionic copolymer coated ZIF 8 nanodrug (DOX@ZIP 8@P(MPC co C7A)) (created by using Biorender).

For example, liposomes like Doxil®, which encapsulates DOX, have achieved clinical success by significantly reducing cardiotoxicity compared to free drug formulations (Fig. 14).[128] Biodegradable polymers such as PLGA and PEG have been widely used to form NPs that not only improve pharmacokinetics but also support multi-drug loading.[108]

Importantly, these polymeric systems can be surface modified with ligands for precise tumor targeting or with stealth coatings such as PEG or polysorbate 80 to avoid rapid clearance by the immune system, enhancing accumulation in the TME. Micelles and dendrimers also offer structural advantages for delivering hydrophobic or charged drugs in a compact and stable form. Nanogels, as crosslinked polymeric networks, also allow high drug loading, tunable swelling, and responsive drug release profiles, particularly useful in combination settings where synchronized or sequential release is beneficial. When functionalized with targeting moieties or responsive linkers such as pH, enzyme, or temperature-sensitive systems, they facilitate site-specific release and minimize systemic exposure an essential requirement for reducing the adverse effects of potent monotherapies. Moreover, quantum dots, though primarily explored for diagnostics, are increasingly incorporated into hybrid drug carriers to enable real-time imaging of drug distribution and release, aligning with the goals of precision medicine.[113,130] By integrating safety, modularity, and multifunctionality, they represent a cornerstone in addressing the clinical limitations of monotherapy and advancing the translational success of nanomedicine-based combination therapies.[110,116,159]

6.2.3 Targeted therapy *via* surface modifications. Challenges such as off-target effects and suboptimal biodistribution necessitate sophisticated surface modification strategies. One pivotal strategy involves ligand conjugation, where targeting moieties such as antibodies or peptides are appended onto the nanoparticle surface.[2,99,104,159] This modification enables specific recognition and binding to overexpressed biomarkers on target cells, enhancing the selectivity and precision of drug delivery. By targeting receptors associated with diseased tissues, ligand conjugated NPs facilitate efficient delivery of therapeutic payloads to the intended site while reducing systemic exposure.

Stealth coating, often achieved through PEG, provides a protective barrier against immune recognition, thereby prolonging circulation and enhancing tumor accumulation.[8] Additionally, pH responsive coatings leverage the acidic TME to trigger site specific drug release, thus minimizing off target effects.[100] Similarly, stimuli responsive polymers like poly(N isopropyl acrylamide) (PNIPAM) enable temperature triggered release, offering spatiotemporal control over drug delivery.[160] Surface modification with charged polymers or peptides can enhance electrostatic interactions with cellular membranes, promoting internalization and increasing retention within target cells.[105] Such modifications improve intracellular trafficking and drug accumulation at disease sites. The integration of these surface engineering strategies with advanced nanocarrier design is central to achieving controlled pharmacokinetics and effective drug distribution.[99]

Coatings on IONPs significantly influence their degradation and performance in biological environments.[223] For instance, carbon shell-coated IONPs (IONP@C) exhibit exceptional stability and antioxidant properties, with proven biocompatibility *in vitro* and *in vivo*, making them ideal for applications such as lung cancer therapy.[224] This platform promotes ROS generation in the TME through Cu^{2+} release and subsequent Fenton-like reactions, leading to improved anticancer efficacy. Similarly, folic acid (FA), a well-known targeting ligand, is effective in directing NPs to cancers by overexpressing folate

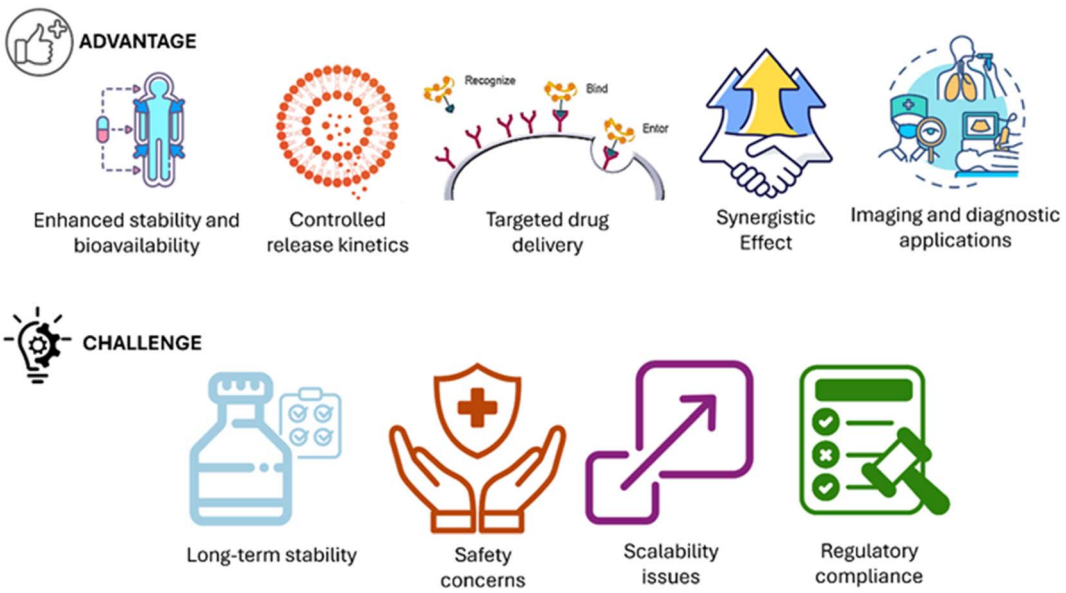

Fig. 14 Advantages and challenges of nanoparticle-based biocompatible material systems for drug delivery and imaging. Key benefits include enhanced stability, controlled release, targeted delivery, synergistic therapeutic effects, and imaging capabilities, while major challenges involve long-term stability, safety, scalability, and regulatory compliance (created by using Biorender).

receptors. Conjugation of FA with chitosan (CS), a cationic polymer that enhances membrane penetration, has been successfully implemented in CS coated CuS nanorods for targeted photothermal ablation therapy (PAT).[225] Another promising approach includes the co-delivery of chemotherapeutics with metal NPs. For example, AgNPs combined with DOX within polymer micelles enhance tumor targeting through improved circulation and passive accumulation *via* the EPR effect.[226] However, upon administration, NPs can interact with blood proteins, forming a protein corona that alters their size, surface properties, and biological fate. Studies have shown that PEG-coated gold/iron NPs are less stable than those coated with oleic acid and polymers, underlining the protective role of polymeric coatings and the PC in nanoparticle degradation.[197,198] It is well known that using shell-enhanced stability with no toxicity effects can prevent the rapid deprivation of IONPs in the biological environment. For instance, IONP@C showed admirable biocompatibility in both *in vitro* and *in vivo* models and thus can be promising in nanomedicine.[224]

In another strategy, AgNPs conjugated with the anti-CD20 antibody Rituximab (AgNPs@Rituximab) showed increased specificity and cytotoxicity against chronic lymphocytic leukemia (CLL) cells, improving selective targeting and reducing systemic exposure.[227] Peptide NP conjugates have also demonstrated efficacy in inducing apoptosis in colon cancer cells.[228] Moreover, AgNPs coated with monomethyl auristatin E (MMAE) and functionalized with the tumor penetrating RPARPAR peptide have shown specific uptake and cytotoxicity in neuropilin 1 (NRP 1) positive prostate cancer cells while sparing NRP 1 negative melanoma cells. When co-cultured, only the prostate cancer cells were targeted and eliminated by the RPARPAR MMAE AgNPs complex (Fig. 15).[229]

Dual drug delivery systems also benefit from advanced surface modification. For instance, floxuridine (FUDR) and carboplatin (CARB) were successfully co-loaded into MOF 808 nanocarriers functionalized with PAAMAM glycopolymer. These systems demonstrated enhanced anticancer activity in HepG2 cells due to synergistic drug effects.[230] Another study utilized DNA-modified hollow mesoporous silica nanoparticles (HMSNs) for chemo-PTT. Constructed using ZIF 8 as a template, these particles enabled pH-sensitive degradation, loading of indocyanine green (ICG) and DOX, and highly effective NIR triggered hyperthermia.[231] Aptamers, synthetic oligonucleotides with high binding affinity for specific targets, have also been integrated into surface-modified NPs for selective cancer therapy.[232] For example, DOX-loaded AuNPs conjugated with PSMA aptamers showed enhanced activity against PSMA-positive LNCaP prostate cancer cells while sparing PSMA negative PC3 cells.[233] Another innovative approach involved pH-selective adsorption of CD340 antibodies and IgG1 onto

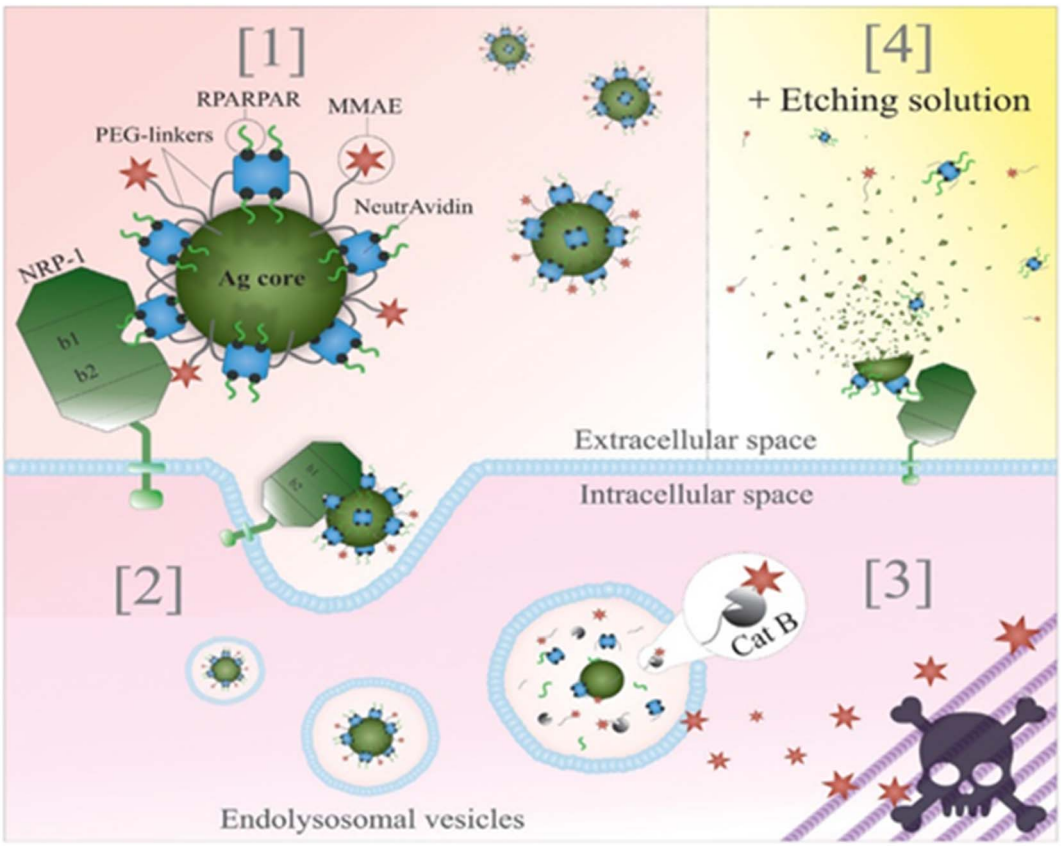

Fig. 15 CendR peptide-guided therapeutic AgNPs. (1) AgNPs functionalized with RPARPAR peptides (green) and MMAE (red) for targeted drug delivery. (2) Binding to NRP 1 triggers endocytosis. (3) Lysosomal degradation releases active MMAE, disrupting tubulin (purple) and inducing cell death. (4) Extracellular AgNPs can be removed with a biocompatible etching solution. This figure has been adapted from ref. 229 under the Creative Commons Attribution (CC BY) license (@2020 The Authors).

carnauba wax NPs to specifically target HER2-positive breast cancer cells.[234] In conclusion, surface modifications such as ligand conjugation, stealth coating, charge-based interactions, and stimuli-responsive elements are pivotal in achieving targeted delivery and maximizing therapeutic efficiency. By combining these features with innovative engineering, nanoparticle-based delivery platforms can be optimized for controlled drug release and precise localization. Continued advancement in these strategies holds immense potential to improve clinical outcomes across various cancer types and enable personalized treatment paradigms in nanomedicine.

6.3 Precision nanomedicine: personalized design strategies

Personalized and precision medicine aims to tailor treatment strategies to an individual's specific genetic, physiological, and disease-related profile. NPs with their tunable physicochemical properties and functional versatility, play a central role in this paradigm by offering site-specific drug delivery, controlled release, and real-time therapeutic monitoring.[115,118,235] Engineering techniques that optimize drug release kinetics and biodistribution are essential to achieving targeted therapeutic action while minimizing systemic toxicity. NPs' small size, large surface area, and functionalization potential enable efficient encapsulation and delivery of therapeutic agents.[236] Through precise engineering, such as stimuli-responsive polymers, targeting ligands, and shape/size control NPs can respond to specific physiological triggers like pH or enzymes, thus enhancing therapeutic efficacy and reducing off-target effects (Fig. 16). Additionally, optimization of nanoparticle biodistribution *via* surface modifications enhances circulation time and facilitates accumulation at desired sites, a critical factor in minimizing systemic toxicity.[109,128,237] These advances improve drug half-life, retention at the disease site, and overall therapeutic index.[117,159] Importantly, integrating patient-specific parameters such as genetic mutations, disease stage, and comorbidities into NPs design can guide therapeutic choices, supporting the goals of individualized therapy.[114] This synergy between nanotechnology and personalized medicine offers a transformative path for cancer therapy and beyond.[8,113]

6.3.1 Role of size, shape, and charge in design. Physicochemical properties, particularly size, shape, and surface charge, greatly influence the ability of NPs to cross biological barriers, circulate effectively, and penetrate tumor tissues. Smaller NPs (<20 nm) show superior tumor penetration but are rapidly cleared from circulation, while larger NPs (100–200 nm) exhibit better accumulation *via* the EPR effect but suffer from limited tissue diffusion.[186,238–240] Studies indicate optimal size ranges vary depending on formulation, *e.g.*, 2–6 nm for ultrasmall AuNPs, 70 nm for PLGA NPs, and ~30 nm for PEG b PLA micelles.[241]

To address the trade-off between penetration and circulation, researchers have developed hybrid NPs combining large and small components. For instance, quantum dots (~10 nm) embedded in gelatin NPs (~100 nm) showed enhanced diffusive transport and extended circulation through size transformation in response to matrix metalloproteinase 2 (MMP 2) activation.[242] Similarly, core@satellite MSN@U/DCNPs underwent size reduction (180 to 20 nm) and charge reversal from negative to positive in acidic TME, improving uptake and deep penetration

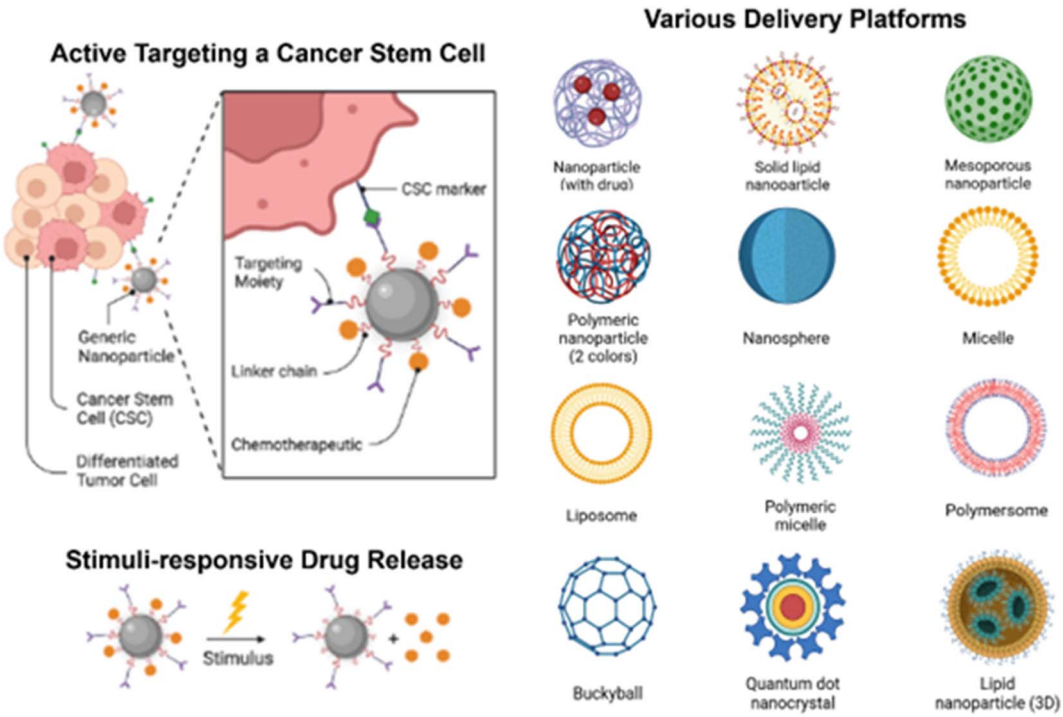

Fig. 16 Illustration of smart nanocarrier systems featuring active targeting of cancer stem cells, diverse nanoparticle delivery platforms, and stimuli-responsive drug release mechanisms (created using BioRender).

(Fig. 17A).[243] Stimuli-responsive platforms, such as PEG b PCL conjugated with platinum prodrugs, enable size shrinkage and payload release specifically in TME (Fig. 17B).[244] Angiopep 2 modified gelatin DOX nanocarriers also demonstrated size reduction and enhanced tumor delivery in triple negative breast cancer (Fig. 17C).[245] Another system, G-AuNPs-DOX-PEG, used gelatin degradation in the TME to release smaller AuNPs for deep tumor penetration (Fig. 17D).[246]

Shape also impacts biological interactions. Spherical NPs are more readily internalized *via* endocytosis, whereas rod or tube-shaped particles are internalized less efficiently but evade phagocytosis longer.[247,248] The ECM and EPR effect, along with vascular permeability, further modulate NPs accumulation and retention. A triblock nanoparticle (BBR PLGVRKLVFF Ce6) exhibited dual shape and charge transformation to enhance circulation, penetration, and apoptotic activity (Fig. 18).[215,249,250]

6.3.2 Biomimetic NPs for better interactions. Biomimetic NPs, cloaked with natural cell membranes such as those derived from RBCs, platelets, white blood cells (WBCs), stem cells, or cancer cells, offer promising advantages in enhancing drug delivery efficacy. These NPs inherit surface markers that facilitate immune evasion, prolonged circulation, and homotypic

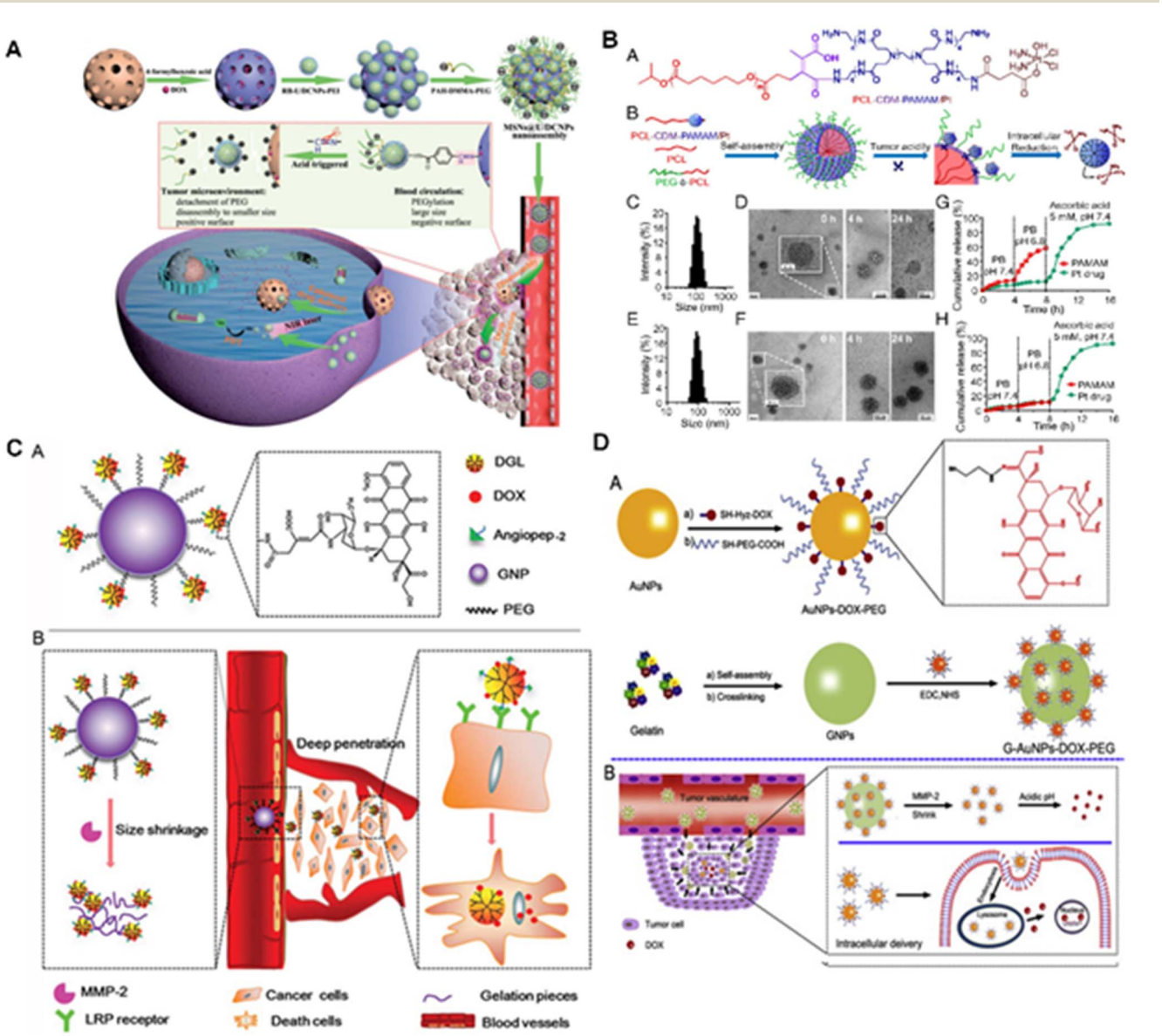

Fig. 17 (A) Schematic illustration of the preparation of core@satellite nanoassemblies and the acidic TME triggered size/charge dual transformability for combined chemo and PDT. This figure has been adapted from ref. 243 with permission under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License (CC BY-NC 3.0). (B) Preparation and physicochemical properties of clustered NPs. This figure has been adapted from ref. 244 under the Creative Commons Attribution-NonCommercial 3.0 Unported License (CC BY-NC 3.0) (@2016, The Authors), with permission. (C) The schematic illustration of the linker between DOX and DGL in the Angio DOX DGL GNP and the delivery of Angio DOX DGL GNP in breast cells was adapted with from ref. 245. @2015 Hu *et al.*, licensed under Creative Commons Attribution (CC BY) license. (D) Schematic design of G AuNPs DOX PEG and its elucidation of intra-tumor delivery procedure of G AuNPs DOX PEG. This figure has been adapted from ref. 246 with permission from Elsevier, copyright ©2015.

targeting while minimizing the need for time-consuming receptor ligand characterization. For instance, RBC membrane coated nanoparticles (RBCm@NPs) demonstrate a 5.8-fold increase in circulation time compared to uncoated NPs, although they lack specific tumor targeting capabilities. Platelet derived NPs provide tumor affinity but pose a risk of thrombosis. WBC derived NPs stimulate immune interactions but may show batch-dependent variability. Cancer cell membrane-based systems offer homotypic targeting yet carry carcinogenic risks, while stem cell membrane-coated NPs, although tumor affinitive, often lack specificity due to broad receptor expression. Bacterial outer membrane vesicles (OMVs), derived from Gram-negative bacteria, present a unique and emerging alternative. These vesicles contain immunogenic proteins and lipopolysaccharides, enabling robust immune activation within TME. OMVs have been successfully explored for cancer immunotherapy and have advanced into clinical trials owing to their immunostimulatory properties and safety profile.[251–254]

To evaluate the safety and therapeutic efficacy of biomimetic NPs in a patient-specific manner, advanced preclinical models are increasingly employed. Organoid-based platforms derived from patient tissues provide a biologically relevant environment that mimics tumor heterogeneity and microenvironmental complexity. Integration of these platforms with AI-driven analytics, high-throughput drug screening, and omics tools such as single cell RNA sequencing and mass cytometry enables precise characterization of nanoparticle behavior, biodistribution, immune response, and off target effects in real time. For instance, organoid platforms combined with AOP frameworks can help map molecular perturbations to toxicity outcomes, improving prediction of long-term safety and therapeutic efficacy.

6.3.3 Covalent organic frameworks (COFs) in cancer therapy. COFs represent a promising class of nanocarriers due to their high crystallinity, tunable porosity, functional versatility, and biocompatibility.[255] COFs can encapsulate therapeutic agents efficiently, prevent premature drug leakage, and facilitate targeted delivery with controlled release. Their integration into monotherapy and combination therapy formats has shown remarkable preclinical success across PDT, PTT, and sonodynamic therapy (SDT). In PDT, traditional photosensitizers (PSs) like porphyrins and BODIPY suffer from poor solubility and non-specificity. Embedding these within COFs (*e.g.*, DPP TFB and EB TFB) improves solubility, mitochondrial targeting, and ROS generation, enhancing PDT efficacy.[256] For PTT,

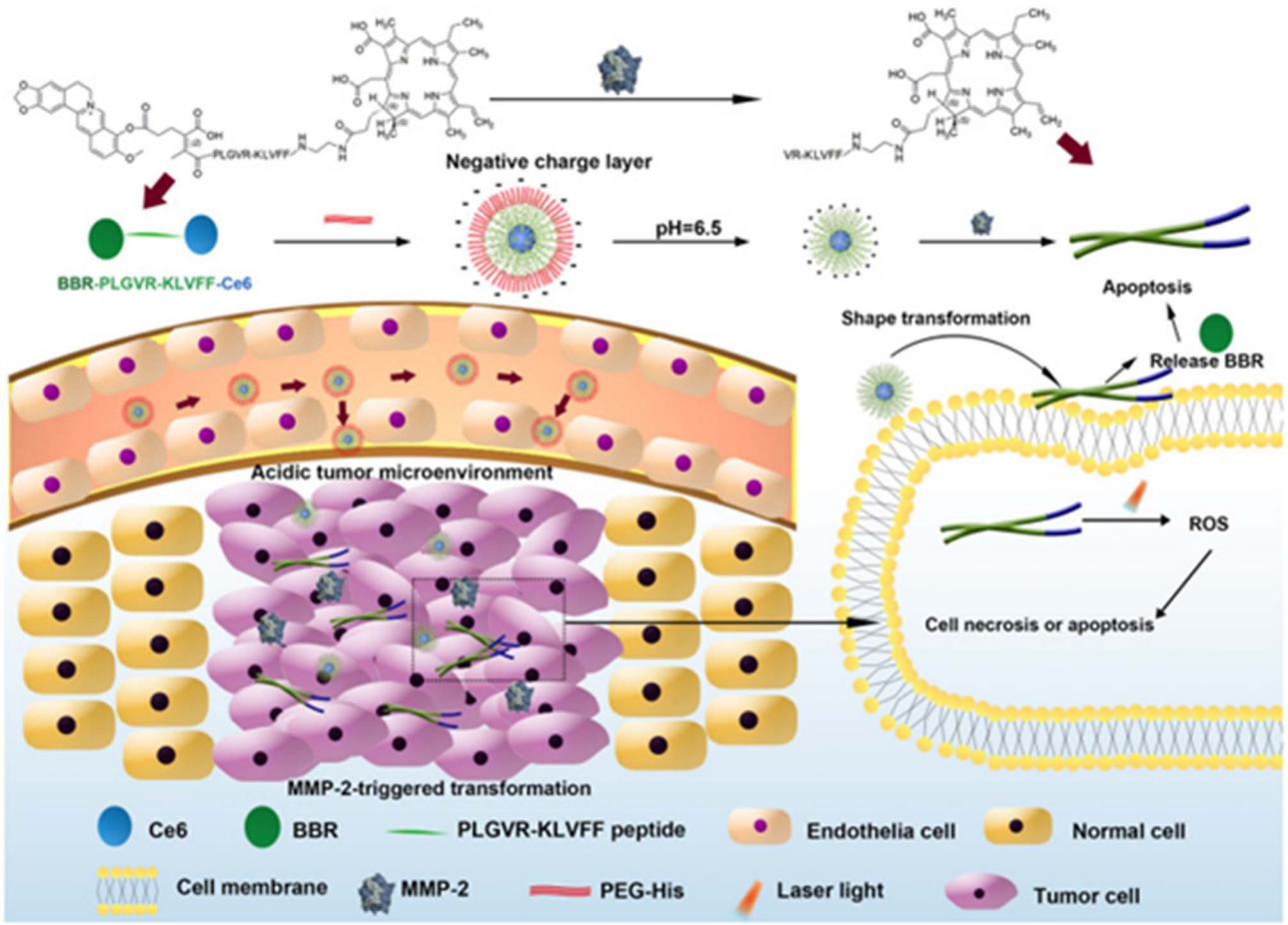

Fig. 18 Scheme illustration of the composition of PEG His@BPC and its therapeutic effect on breast cancer. This figure has been adapted from ref. 250 under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0).

COFs loaded with gambogic acid (GA) an HSP90 inhibitor demonstrated improved tumor suppression under NIR irradiation, with up to 87.76% inhibition *in vitro*. An *in vitro* study suggested that gambogic acid (GA), an HSP90 inhibitor, doesn't have significant anti-tumor effects. However, combining COF GA with laser radiation significantly improved tumor inhibition by up to 87.76%, signifying the synergistic effects of HSP90 inhibitors and COF upon NIR irradiation.[257] For SDT, a unique COF-based nanobowl system (RB@COFs MnOx PEG, RCMP) enhanced ferroptosis-induced tumor killing under ultrasound. RCMP + US achieved 74% inhibition of osteosarcoma, significantly outperforming non-irradiated and control treatments (Fig. 19A).[258] To address drug resistance and poor selectivity, multimodal COF systems have been engineered. One such platform, CuS@COFs BSA FA/DOX, released DOX in acidic TME, promoted H_2O_2 accumulation, and enhanced chemodynamic therapy. Upon irradiation, this system achieved tumor inhibition rates of 81.85%, compared to ≤40% in control groups (Fig. 19B).[258] The use of COFs in drug delivery systems highlights their potential to enhance therapeutic efficacy and minimize adverse effects in cancer treatments.[257]

6.4 Translational and predictive platforms for precision nanomedicine

Although advances in nanoparticle engineering have significantly improved circulation time, targeting efficiency, and therapeutic performance, clinical translation remains constrained by biological complexity and patient heterogeneity. Variations in immune surveillance, tumor architecture, and microenvironmental dynamics limit the predictive value of conventional preclinical models, frequently leading to inconsistent therapeutic outcomes. Addressing these challenges requires integrative platforms that systematically link nanoparticle design parameters with biological responses across cellular, tissue, and organismal levels.

Recent developments in artificial intelligence (AI), multi-omics profiling, and patient-derived experimental systems are beginning to bridge this translational gap. AI-driven frameworks enable integration of high-dimensional datasets encompassing nanoparticle physicochemical properties, biodistribution, immune interactions, and therapeutic responses, allowing identification of non-linear determinants of nanomedicine performance. Machine-learning models facilitate optimization of particle size, surface chemistry, drug loading ratios, and release kinetics while reducing off-target toxicity and enhancing therapeutic index. These capabilities are particularly critical for combination nanomedicine, where precise coordination of synergistic drug interactions is essential.

Patient-derived organoids and tumor-on-chip platforms further strengthen translational relevance by recapitulating tumor heterogeneity, ECM architecture, and immune crosstalk that are not captured in conventional two-dimensional cultures. Integration with single-cell transcriptomics, spatial omics, and high-resolution immune profiling enables patient-specific evaluation of nanoparticle penetration, cellular uptake, immune modulation, and resistance pathways. When combined with adverse outcome pathway-inspired frameworks, these systems provide mechanistic links between early molecular perturbations and downstream therapeutic efficacy and safety.

Despite these advances, challenges related to scalability, reproducibility, and regulatory compatibility remain. Multifunctional nanocarriers often encounter barriers in Good Manufacturing Practice production due to formulation complexity and quality control variability. Emerging solutions such as microfluidic manufacturing, AI-assisted process

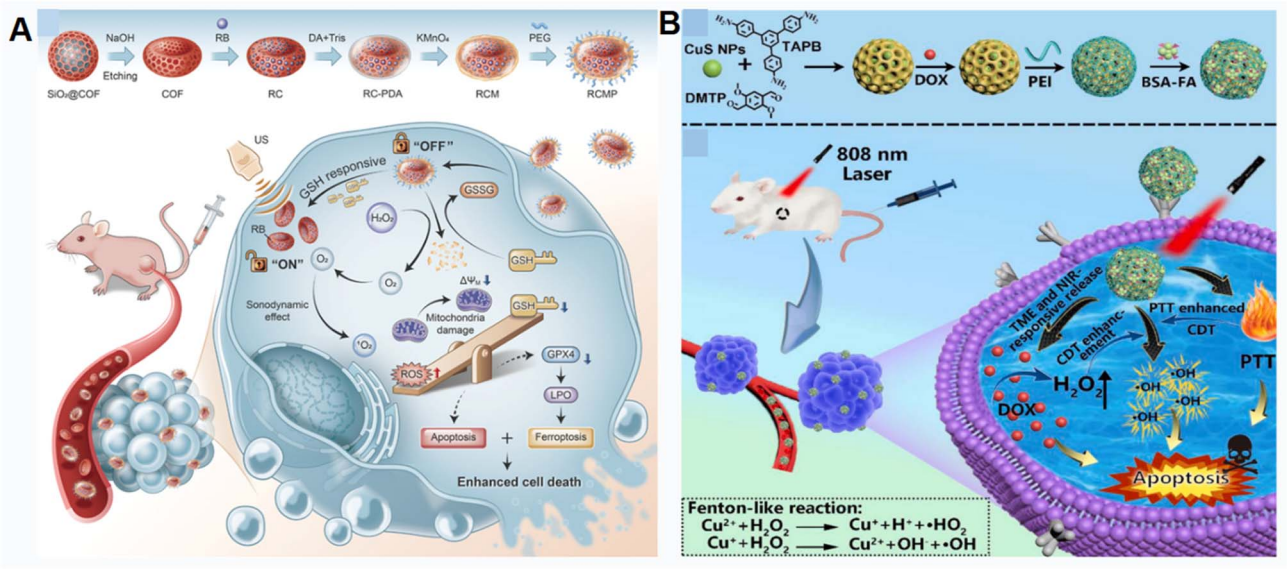

Fig. 19 (A) Schematic illustration for the preparation and therapeutic application of the activatable nanosensitizers RCMP. This figure was adapted from ref. 258 under the terms of the creative commons Attributions License (CC BY 4.0). (B) Schematic illustration of (A) the preparation and (B) therapeutic functions of CuS@COFs BSA FA/DOX. This figure was adapted from Ref. @2022 Elsevier B.V.

optimization, and real-time quality monitoring offer scalable routes while preserving functional integrity. In parallel, regulatory frameworks must evolve to accommodate modular and multi-component nanomedicines rather than single-agent formulations. Collectively, the integration of AI-guided design, patient-relevant experimental models, and systems-level evaluation marks a critical transition toward personalized nanomedicine. These predictive platforms enhance translational reliability and support the rational development of next-generation nanotherapeutics tailored to individual tumor biology and immune context.

7. Limitations of current experimental models in nanomedicine research

Despite substantial progress in nanomedicine development, the predictive power of current experimental models remains limited, representing a major barrier to successful clinical translation. A central challenge lies in the inadequate representation of the TME, which *in vivo* comprises diverse cell populations, complex ECM architecture, dynamic biochemical gradients, and continuous immune surveillance. Conventional *in vitro* models, particularly two-dimensional cultures, oversimplify this complexity and therefore fail to accurately predict nanoparticle behavior, therapeutic efficacy, and resistance mechanisms observed in patients.

Advanced platforms such as organ-on-a-chip systems have emerged to address this gap by enabling the integration of multiple cell types, immune components, and physiologically relevant mechanical and biochemical cues. When combined with immune profiling and real-time monitoring, these platforms provide deeper insights into nanoparticle–immune interactions and therapeutic response dynamics that are not captured by traditional models.[251]

Another major limitation is the frequent absence of functional immune components in experimental systems, despite the immune system playing a decisive role in tumor progression, immune evasion, and treatment response. This lack of immune representation restricts understanding of how nanomedicines interact with immune cells, influence immune checkpoints, or trigger unintended inflammatory pathways. Recent advances incorporating single-cell RNA sequencing, mass cytometry, and multi-omics approaches have begun to address this limitation by revealing the heterogeneity and plasticity of tumor–immune interactions at high resolution.[252] Patient-derived organoids and immune-competent models further improve translational relevance by capturing individualized tumor and immune characteristics.

Tumor heterogeneity presents an additional obstacle to translational success. Many experimental studies rely on homogeneous cancer cell lines that do not reflect the genetic, phenotypic, and functional diversity of patient tumors. This oversimplification can obscure resistance mechanisms and lead to misleading efficacy predictions. Integrating multi-omics data with machine learning has shown promise in linking tumor heterogeneity to therapeutic outcomes, enabling patient-specific response prediction and more rational nanomedicine design.[253]

Equally important are the limitations imposed by static experimental conditions. Most *in vitro* assays do not reproduce dynamic features of the TME, such as fluid flow, mechanical stress, and nutrient gradients, all of which influence nanoparticle transport, cellular uptake, and drug release. Advances in microfluidic systems and multiplexed imaging now allow real-time visualization of nanoparticle distribution and cellular interactions under physiologically relevant conditions, improving mechanistic understanding and predictive accuracy.[254,255]

Long-term safety and patient specificity remain additional unmet needs. Short-term studies often overlook delayed toxicity, nanoparticle persistence, immune adaptation, and resistance evolution. Moreover, variability in materials, synthesis protocols, and analytical methods continues to challenge reproducibility across studies. Addressing these limitations will require integrative, patient-relevant platforms that combine organoids, microfluidics, advanced imaging, multi-omics, and AI-driven analytics to better align preclinical evaluation with the biological complexity of human tumors.

8. Ethical implications

The increasing clinical translation of nanomedicines raises important ethical, regulatory, and societal considerations that extend beyond technical performance. The intrinsic complexity of multifunctional nanotherapeutics can limit patient understanding, underscoring the need for clear, transparent, and accessible communication regarding anticipated benefits, potential risks, and unresolved uncertainties to ensure meaningful informed consent. Uncertainty surrounding long-term biodistribution, nanoparticle persistence, and delayed toxicity further highlights the ethical obligation to pursue extended safety monitoring and transparent post-approval reporting.

Equitable access represents another critical ethical concern. The high cost, technical sophistication, and specialized infrastructure required for many nanomedicine platforms may restrict availability, potentially exacerbating existing healthcare disparities. From a regulatory perspective, conventional evaluation frameworks may struggle to fully accommodate adaptive, multi-agent, and data-intensive nanomedicines, emphasizing the need for flexible, mechanistically informed assessment strategies and robust quality control standards. Addressing these ethical dimensions alongside scientific development is critical to ensuring that advances in nanomedicine translate into clinically effective and socially sustainable outcomes.

9. Conclusion

In summary, nanomedicine has made substantial progress in addressing the limitations of conventional monotherapies through advanced nanoparticle engineering, multifunctional drug delivery systems, and precision design strategies. Innovations in surface modification, biomimetic platforms, stimuli-responsive carriers, and emerging materials have significantly

improved targeting, efficacy, and safety in preclinical studies. Nevertheless, biological complexity, immune interactions, and patient heterogeneity continue to pose formidable challenges to consistent clinical translation. To address these challenges, the integration of artificial intelligence, high-dimensional omics, and patient-derived experimental models has emerged as a critical shift toward predictive and personalized nanomedicine. These approaches enable mechanistically informed design, real-time evaluation, and adaptive optimization of nanotherapeutics, while improving translational relevance and reducing reliance on oversimplified models. At the same time, challenges related to scalability, reproducibility, regulation, and ethics must be addressed to fully realize the clinical potential of these technologies. Ultimately, the future of nanomedicine will be shaped by the convergence of material innovation, systems-level biological understanding, and data-driven analytical frameworks. By prioritizing modular, clinically scalable nanoplatforms evaluated in patient-relevant models, nanomedicine is well positioned to deliver safer, more effective, and truly personalized therapeutic solutions across a broad range of diseases.

Author contributions

Hina Singh and Sri Renukadevi Balusamy conceived and designed the study and led the initial drafting of the manuscript. Priyanka Singh contributed to the overall conceptual framework, supervised and coordinated manuscript development, and carried out critical revisions. Johan Sukweenadhi, Anupama Shrivastav, Muthupandian Saravanan, and Aruchamy Mohanprasanth contributed to literature review, and manuscript writing. Ivan Mijakovic and Priyanka Singh provided critical evaluation and intellectual input to strengthen the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

The authors have declared that no competing interests exist.

Data availability

No new experimental data, software, or code were generated or analysed in this study. This review includes some figures and information reproduced or adapted from previously published works, all of which are properly cited within the text and figure captions. In addition, several original schematic illustrations were created using BioRender to conceptualize mechanisms, designs, and pathways discussed in this article. All sources of republished materials are fully acknowledged, and permissions have been obtained where required.

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