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TARGETED LIPOSOMAL DRUG DELIVERY SYSTEMS FOR ENHANCED CANCER THERAPY: FORMULATION, MECHANISMS, AND THERAPEUTIC POTENTIAL

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ABSTRACT

Cancer therapy faces major limitations due to systemic toxicity, low selectivity, and multidrug resistance of chemotherapeutic agents. Liposomal drug delivery systems (LDDS) are nanoscale vesicles capable of encapsulating hydrophilic and hydrophobic drugs, improving solubility, stability, pharmacokinetics, and biodistribution. Targeted liposomes modified with ligands such as folic acid, antibodies, transferrin, or peptides enhance tumor-specific drug accumulation via passive and active targeting. This review provides a detailed discussion on formulation strategies, targeting mechanisms, physicochemical characterization, preclinical and clinical outcomes, therapeutic applications, advantages, limitations, and future perspectives of targeted liposomes for cancer therapy. Special emphasis is given to PEGylation, stimuli-responsive release, co-delivery of drugs, and overcoming multidrug resistance. Recent studies demonstrate improved tumor inhibition, reduced systemic toxicity, and prolonged circulation times, highlighting the clinical promise of targeted liposomal systems.

KEYWORDS: Targeted liposomes, Cancer therapy, Passive targeting, Active targeting, PEGylation, Stimuli-responsive liposomes, Multidrug resistance, Nanocarriers, Therapeutic applications.

INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with over 10 million deaths reported in 2020 (WHO, 2020). Conventional chemotherapy, despite being the mainstay of cancer treatment, is limited by several challenges. Poor tumor selectivity leads to cytotoxicity in healthy tissues such as bone marrow, heart, liver, and gastrointestinal tract, resulting in side effects like myelosuppression, cardiotoxicity, hepatotoxicity, and gastrointestinal complications. Rapid clearance of chemotherapeutic agents from the circulation further reduces drug exposure at the tumor site, necessitating higher or more frequent doses that often exacerbate systemic toxicity. Additionally, multidrug resistance (MDR), caused by mechanisms such as overexpression of efflux pumps (e.g., P-glycoprotein), alterations in apoptotic pathways, and enhanced DNA repair, significantly diminishes the therapeutic efficacy of conventional chemotherapies. Non-specific biodistribution further limits the therapeutic index, as drugs fail to accumulate preferentially in tumor tissue, resulting in dose-limiting systemic side effects.

Liposomal drug delivery systems (LDDS) have emerged as a promising strategy to overcome these limitations. These nanosized vesicles, typically 50–200 nm in diameter, consist of phospholipid bilayers encapsulating an aqueous core. Hydrophilic drugs can be loaded into the core, while hydrophobic drugs are incorporated into the lipid bilayer, allowing for versatile drug delivery. LDDS improve therapeutic outcomes through multiple mechanisms. They protect labile drugs such as doxorubicin or paclitaxel from enzymatic degradation, enhancing drug stability and circulation time. Hydrophobic drugs, including paclitaxel, docetaxel, and curcumin, demonstrate improved solubility without the need for toxic solvents. PEGylation, or the attachment of polyethylene glycol chains, prolongs systemic circulation; for example, PEGylated liposomal doxorubicin exhibits a plasma half-life of approximately 55 hours, compared to only 20 minutes for the free drug. Furthermore, LDDS reduce systemic toxicity, exemplified by lower cardiotoxicity of liposomal doxorubicin and decreased nephrotoxicity in liposomal cisplatin formulations, while enabling sustained and controlled drug release to maintain therapeutic plasma concentrations and minimize peak-related adverse effects.

Targeted liposomes offer an additional layer of specificity by surface modification with ligands such as folic acid, transferrin, peptides (e.g., RGD sequences), or monoclonal antibodies (e.g., anti-HER2). These modifications facilitate active targeting, promoting selective uptake by tumor cells via receptor-mediated endocytosis. Clinical and preclinical studies highlight their efficacy. PEGylated liposomal doxorubicin (Doxil®) has demonstrated reduced cardiotoxicity alongside improved tumor accumulation through both passive (enhanced permeability and retention, EPR effect) and active targeting. Folate-targeted liposomes have shown approximately threefold higher cytotoxicity in folate receptor-positive ovarian cancer cell lines compared to non-targeted liposomes. Anti-HER2 immunoliposomes enhance doxorubicin delivery to HER2-positive breast cancer cells, increasing intracellular drug concentrations by two- to fourfold while sparing normal tissue. Transferrin-conjugated liposomes exhibit improved uptake in rapidly dividing leukemia cells due to overexpression of transferrin receptors.

Recent advancements have expanded the therapeutic potential of liposomes. Co-delivery systems, such as liposomes carrying both doxorubicin and siRNA targeting P-glycoprotein, have successfully overcome multidrug resistance, achieving up to 80% tumor growth inhibition in murine models. Liposomes are also being explored for multifunctional theranostic applications, enabling simultaneous imaging and drug delivery for real-time tumor monitoring. Emerging trends include stimuli-responsive liposomes, designed to release their payload in response to tumor-specific triggers such as acidic pH, elevated enzyme levels, or redox gradients, enhancing intracellular drug availability. Combination therapies using liposomes for chemo-gene delivery are showing promise in improving efficacy against resistant tumors. Clinical translation has extended to cancers of the breast, ovary, lung, liver, and brain, demonstrating the versatility and potential of targeted liposomes for personalized oncology.

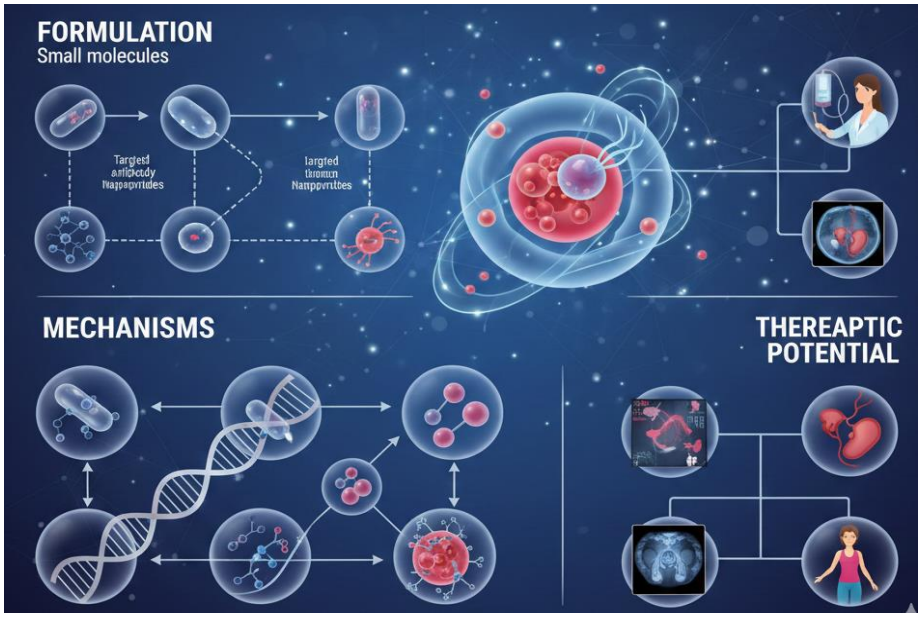

Figure I: Cancer Therapy.

MECHANISMS OF TARGETING

Targeted liposomal drug delivery improves tumor specificity and therapeutic efficacy by exploiting unique physiological and biochemical features of tumors. The main mechanisms can be classified into passive targeting, active targeting, and stimuli-responsive targeting. Each approach leverages distinct principles to enhance drug accumulation at the tumor site while minimizing systemic toxicity.

1. Passive Targeting (Enhanced Permeability and Retention Effect)

Passive targeting utilizes the enhanced permeability and retention (EPR) effect, a hallmark of tumor biology. Tumor vasculature is highly irregular and leaky, with fenestrations ranging from 100 to 800 nm, and tumor tissues often exhibit poor lymphatic drainage. These features allow nanoparticles, including liposomes, to extravasate from the bloodstream and accumulate preferentially in tumor tissue, while being retained longer than in healthy tissues. Liposome size plays a critical role in passive targeting; particles between 50–200 nm demonstrate optimal tumor accumulation without rapid clearance by the reticuloendothelial system (RES). Clinically, PEGylated liposomal doxorubicin (Doxil®) exhibits approximately 10-fold higher tumor accumulation than free doxorubicin, resulting in enhanced efficacy and reduced cardiotoxicity. Passive targeting is particularly advantageous for poorly vascularized tumors, where traditional chemotherapeutics show limited penetration.

2. Active Targeting

Active targeting involves ligand-mediated recognition of overexpressed receptors on tumor cells or tumor vasculature, enabling receptor-specific internalization. Liposomes are functionalized with targeting moieties such as small molecules, peptides, or antibodies, allowing for receptor-mediated endocytosis and intracellular drug delivery.

- Folate-Conjugated Liposomes: Folate receptors are overexpressed in ovarian, breast, and lung cancers. Folate-conjugated liposomes bind these receptors and are internalized via endocytosis. For example, folate-liposome encapsulated paclitaxel reduces the IC50 from 120 nM (free drug) to 35 nM in folate receptor-positive ovarian cancer cells, demonstrating enhanced cytotoxicity.

- Transferrin-Conjugated Liposomes: Rapidly dividing cells, such as leukemia cells, overexpress transferrin receptors to meet their high iron demands. Transferrin-functionalized liposomes exploit this pathway for targeted delivery, increasing intracellular drug concentration and therapeutic response.

- Antibody-Conjugated Liposomes: Monoclonal antibodies, such as anti-HER2, can selectively target HER2-positive breast cancer cells. Anti-HER2 liposomes have shown 2–4 fold higher intracellular accumulation and increased cytotoxicity compared to non-targeted liposomes.

- Peptide-Conjugated Liposomes: Tumor vasculature expresses integrin receptors, which can be targeted by RGD (arginine-glycine-aspartic acid) peptide-modified liposomes. These liposomes improve drug delivery to angiogenic endothelial cells, enhancing tumor penetration and therapeutic outcomes.

Active targeting not only increases intracellular drug delivery but also reduces off-target toxicity by limiting uptake in normal cells. It is particularly useful in tumors with heterogeneous vascular permeability, where passive targeting alone may be insufficient.

3. Stimuli-Responsive Targeting

Stimuli-responsive liposomes are designed to release their therapeutic payload in response to specific tumor microenvironment triggers, providing controlled and site-specific drug delivery.

- pH-Sensitive Liposomes: The slightly acidic tumor microenvironment (pH ~6.5–6.8) or endosomal pH (~5–6) triggers the destabilization of pH-sensitive liposomes, releasing encapsulated drugs selectively at the tumor site. This minimizes systemic exposure and enhances intracellular drug availability.

- Temperature-Sensitive Liposomes: Tumors exposed to hyperthermia (~42°C) can trigger thermosensitive liposomes to release their contents locally, enabling precise spatiotemporal control over drug delivery during hyperthermia-assisted chemotherapy.

- Enzyme-Sensitive Liposomes: Tumor-specific enzymes, such as matrix metalloproteinases (MMPs) or cathepsins, can degrade liposomal components, releasing drugs selectively in tumor tissue. This approach exploits the overexpression of proteases in the tumor microenvironment.

- Redox-Sensitive Liposomes: High intracellular glutathione (GSH) levels in cancer cells can reduce disulfide bonds in redox-sensitive liposomes, destabilizing the vesicle and releasing the drug intracellularly. This ensures enhanced cytoplasmic drug delivery, particularly for chemotherapeutics susceptible to efflux-mediated resistance.

Stimuli-responsive targeting offers temporal and spatial control, allowing liposomes to remain stable during circulation and only release the drug upon encountering tumor-specific conditions. This strategy is particularly effective in minimizing systemic toxicity while overcoming multidrug resistance.

ADVANTAGES OF TARGETED LIPOSOMES

- **Reduced systemic toxicity:** Targeted liposomes significantly lower exposure of healthy tissues to cytotoxic drugs. For example, PEGylated liposomal doxorubicin reduces cardiotoxicity by ~50% compared to free doxorubicin, allowing higher cumulative doses and improved patient safety.

- **Enhanced solubility of poorly water-soluble drugs:** Hydrophobic anticancer agents such as paclitaxel, curcumin, and docetaxel are efficiently incorporated into the lipid bilayer, eliminating the need for toxic solubilizing agents like Cremophor EL and reducing hypersensitivity reactions.

➢ **Prolonged circulation time:** PEGylation decreases opsonization and RES uptake, extending drug half-life from ~20 minutes (free drug) to ~55 hours (PEGylated liposomal doxorubicin), thereby improving tumor accumulation via the EPR effect.

➢ **Improved tumor targeting and intracellular delivery:** Surface modification with ligands (folate, transferrin, peptides, antibodies) enhances receptor-mediated endocytosis, resulting in 2–4 fold higher intracellular drug concentration in receptor-positive tumor cells.

➢ **Controlled and sustained drug release:** Liposomes provide prolonged and controlled release, maintaining therapeutic plasma levels, minimizing peak-related toxicity, and improving the therapeutic index.

➢ **Co-delivery of multiple therapeutic agents:** Targeted liposomes can simultaneously deliver chemotherapeutic drugs, siRNA, miRNA, or chemosensitizers, enabling synergistic therapy and improved treatment outcomes.

➢ **Overcoming multidrug resistance (MDR):** Co-delivery systems (e.g., doxorubicin + P-gp inhibitor or siRNA) inhibit efflux pumps, leading to enhanced intracellular drug retention and up to 80% tumor growth inhibition in resistant cancer models.

➢ **Theranostic potential:** Liposomes can carry both drugs and imaging agents (fluorescent dyes, MRI contrast agents, radionuclides), enabling simultaneous therapy and real-time tumor imaging.

➢ V**ersatility across cancer types:** Targeted liposomes have shown efficacy in breast, ovarian, lung, liver, leukemia, and brain cancers, demonstrating broad clinical applicability.

LIMITATIONS OF TARGETED LIPOSOMES

➢ **High production cost:** Use of purified lipids, PEGylation, ligand conjugation, and advanced manufacturing techniques increases formulation and commercialization costs.

➢ **Formulation complexity:** Precise control of lipid composition, particle size, surface charge, PEG density, and ligand orientation is technically demanding.

➢ **Immune clearance by RES:** Despite PEGylation, liposomes may still be captured by the liver and spleen; repeated dosing can induce the **accelerated blood clearance (ABC) phenomenon**, reducing efficacy.

- **Limited drug loading capacity:** Hydrophobic drug loading is generally restricted to **~5–15% (w/w)**, which may require administration of higher lipid quantities.
- **PEG dilemma:** PEGylation enhances circulation time but may reduce cellular uptake and intracellular drug release due to steric hindrance.
- **Scale-up challenges:** Maintaining batch-to-batch reproducibility, uniform particle size, drug entrapment efficiency, and ligand density is difficult at industrial scale.
- **Stability issues:** Liposomes are prone to lipid oxidation, drug leakage, aggregation, and hydrolysis during storage, affecting shelf life.
- **Regulatory hurdles:** Complex characterization, quality control, and long-term safety evaluation can delay regulatory approval.

CLASSIFICATION OF TARGETED LIPOSOMES

Table I: Classification of Targeted Liposomes.

TYPE	DESCRIPTION	EXAMPLES
Conventional Liposomes	Simple phospholipid vesicles	Liposomal doxorubicin (non-PEG)
PEGylated (Stealth) Liposomes	PEG coating to evade RES	Doxil®, Lipodox®
Ligand-Targeted Liposomes	Surface ligands for active targeting	Folate-liposomes, anti-HER2 liposomes
Stimuli-Responsive Liposomes	Triggered drug release	pH-sensitive, thermosensitive, enzyme-sensitive liposomes
Multifunctional Liposomes	Combine targeting, therapy, imaging	Liposomes with fluorescent dye + drug + antibody

FORMULATION STRATEGIES

Components

- **Phospholipids:** Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine
- **Cholesterol:** Stabilizes lipid bilayer
- **PEG-lipids:** DSPE-PEG2000 prolongs circulation
- **Targeting ligands:** Antibodies, folate, transferrin, peptides
- **Therapeutics:** Hydrophilic drugs in aqueous core; hydrophobic in bilayer.

Preparation Methods

- **Thin-Film Hydration:** Evaporation of lipids → hydration with drug solution Encapsulation efficiency: 60–85% for doxorubicin
- **Reverse-Phase Evaporation:** High encapsulation (~90%) for hydrophilic drugs
- **Ethanol Injection:** Rapid formation for hydrophobic drugs

- **Microfluidics:** Monodisperse liposomes, PDI <0.1, size 80–150 nm.

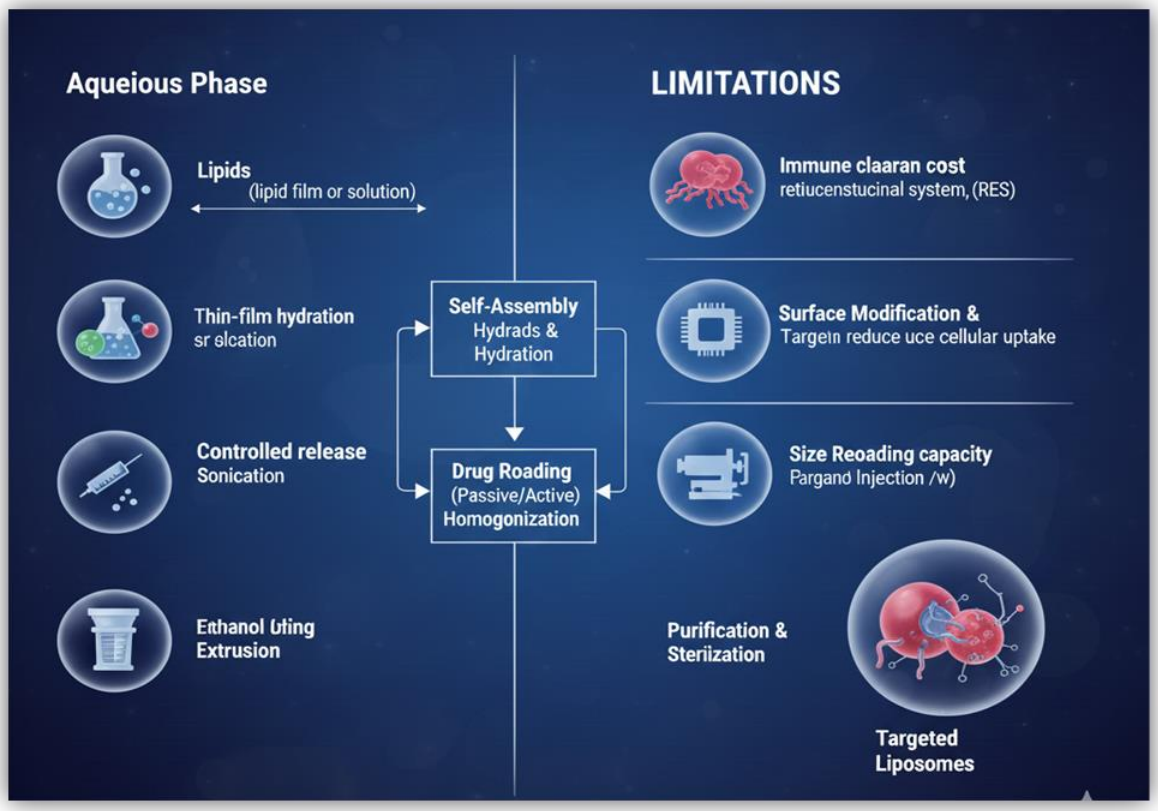

Fig II: Preparation Methods of Targeted Liposomes.

FACTORS AFFECTING FORMULATION

- Lipid composition and cholesterol ratio → affects membrane rigidity and drug leakage
- PEG density → affects circulation time and RES uptake
- Ligand density → affects active targeting efficiency
- Particle size → <200 nm for tumor penetration; <50 nm may get renal clearance
- Zeta potential → ±20–30 mV for stability
- Drug-lipid interactions → affects encapsulation efficiency.

CHARACTERIZATION PARAMETERS

Table II: Characterization Parameters.

PARAMETER	PURPOSE	TECHNIQUE	TYPICAL VALUE
Particle size	Tumor accumulation	DLS, TEM	50–200 nm
PDI	Homogeneity	DLS	<0.3
Zeta potential	Stability	Electrophoresis	±20–30 mV
Encapsulation efficiency (%)	Drug loading	UV/HPLC	50–95%
Drug release	Controlled release	Dialysis, Franz	24–72 h

profile		cell	
Morphology	Shape, lamellarity	TEM/SEM	Spherical, unilamellar/multilamellar
Stability	Shelf-life	ICH accelerated testing	6–12 months

THERAPEUTIC APPLICATIONS

➢ **Breast Cancer:** Targeted liposomes have been extensively explored in breast cancer therapy, particularly for HER2-positive tumors. Anti-HER2 immunoliposomes encapsulating doxorubicin or paclitaxel selectively bind to HER2 receptors, leading to receptor-mediated endocytosis and higher intracellular drug concentrations. Clinical studies with PEGylated liposomal doxorubicin (Doxil®) demonstrate significant tumor regression with nearly 50% reduction in cardiotoxicity compared to conventional doxorubicin. Liposomal formulations also allow higher cumulative doses without increasing systemic toxicity.

➢ **Ovarian Cancer:** Folate receptor-targeted liposomes are highly effective in ovarian cancer due to overexpression of folate receptors on tumor cells. Folate-conjugated liposomal paclitaxel and cisplatin have shown 3–4 fold increased cellular uptake and significantly lower IC_{50} values compared to non-targeted formulations. Liposomal doxorubicin is clinically approved for recurrent ovarian cancer, offering improved progression-free survival and reduced hematological toxicity.

➢ **Lung Cancer:** In non-small cell lung cancer (NSCLC), transferrin- and peptide-targeted liposomes enhance uptake in rapidly dividing tumor cells. Liposomal formulations of docetaxel and gemcitabine show prolonged circulation, improved tumor penetration, and reduced pulmonary toxicity. pH-sensitive liposomes further enhance intracellular drug release within the acidic tumor microenvironment.

➢ **Liver Cancer (Hepatocellular Carcinoma):** Targeted liposomes modified with galactose or glycyrrhetinic acid exploit asialoglycoprotein receptors on hepatocytes. Liposomal doxorubicin and sorafenib exhibit higher liver tumor accumulation and reduced off-target toxicity. These systems improve therapeutic outcomes while minimizing damage to healthy liver tissue.

➢ **Brain Tumors:** Liposomes improve drug delivery across the blood–brain barrier (BBB) when surface-modified with ligands such as transferrin or apolipoproteins. Liposomal

temozolomide and doxorubicin demonstrate enhanced accumulation in glioblastoma models, leading to 2–3 fold increased survival in preclinical studies compared to free drugs.

- **Leukemia and Hematological Malignancies:** Transferrin-conjugated liposomes are effective in leukemia due to high transferrin receptor expression on malignant cells. Liposomal cytarabine and daunorubicin show sustained plasma levels, improved bone marrow targeting, and reduced systemic toxicity. Co-delivery systems targeting P-glycoprotein have demonstrated reversal of multidrug resistance.

CONCLUSION

Targeted liposomal drug delivery systems represent a highly versatile and advanced platform for achieving enhanced, safe, and precise cancer therapy. By integrating passive targeting through the enhanced permeability and retention (EPR) effect, active targeting using surface-bound ligands, stimuli-responsive drug release, and PEGylation for prolonged circulation, liposomes significantly improve drug accumulation at tumor sites while minimizing exposure to healthy tissues. These combined strategies result in reduced systemic toxicity, improved therapeutic index, and controlled or sustained drug release, thereby enhancing overall treatment efficacy. Looking ahead, the future development of targeted liposomal systems is focused on creating multifunctional liposomes for theranostic applications, which can simultaneously deliver anticancer drugs and diagnostic imaging agents to enable real-time monitoring of tumor response. Another promising direction is the co-delivery of chemotherapy agents with gene therapy or siRNA, allowing simultaneous tumor cell killing and modulation of resistance pathways. Advances in molecular oncology are also paving the way for personalized liposomal formulations, designed based on individual tumor receptor expression, genetic profiles, and microenvironment characteristics, ensuring patient-specific treatment strategies.

Furthermore, the design of stimuli-responsive and environment-sensitive liposomes, capable of releasing drugs in response to pH changes, enzymes, redox conditions, or temperature, is expected to further enhance intracellular drug delivery and therapeutic precision. Overall, targeted liposomal drug delivery systems hold substantial clinical promise and are emerging as a cornerstone of next-generation cancer therapy, with demonstrated and potential benefits in the treatment of breast, ovarian, lung, liver, and multidrug-resistant cancers.

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