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Updates and current states on liposomal vehicles for tumor targeting: precision therapy in the spotlight

Niloufar Rahiman[1,2*]

*Correspondence:
rahimann2@mums.ac.ir;
niloufarrh66@gmail.com

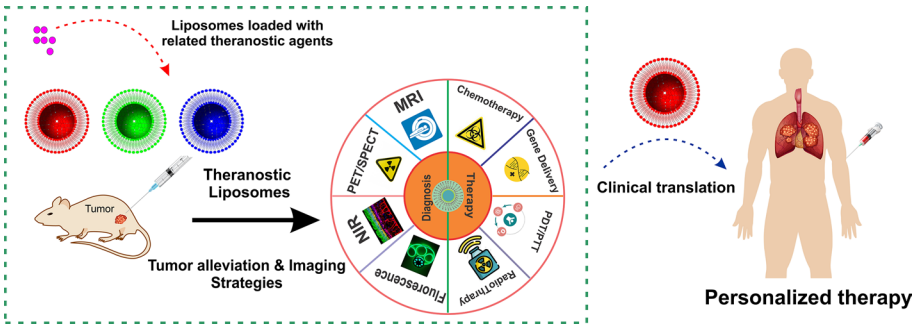
[1] Nanotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Department of Pharmaceutical Nanotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Precision medicine, through theranostics, can identify various tumors and metastatic tumors for diagnostic purposes using a radioactive drug combined with a therapeutic agent. This novel approach combines diagnostic and therapeutic agents to simultaneously image and treat cancer, providing a safe and optimal way to improve cancer prognosis. Through theranostics and precision therapy, real-time monitoring of disease progression and treatment response while delivering targeted therapy to the tumor site would be possible. The synthesis and design of these agents are noteworthy as they must be biocompatible, detectable by imaging, tumor-specific, and therapeutically effective. Nanocarriers, such as liposomes, have been one of the most successful nano-biomimetic systems in drug delivery to date. Recent innovations for liposomes include the introduction of imaging probes for optical imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT) in vivo, and new agents for photodynamic and photothermal therapies. Liposomes can encapsulate a range of diagnostic and therapeutic agents and have received much attention as nanocarriers for theranostic applications in the diagnosis and treatment of diseases, particularly cancer. They are one of the most promising nanocarriers in cancer theranostics for precision therapy. In this review, the use of liposomes as theranostic agents in the treatment, imaging, and diagnosis of cancer has been reviewed and some approaches have been suggested to direct them toward precision medicine.

Keywords: Cancer, Imaging, Liposome, Personalized nanomedicine, Precision medicine, Theranostics

Graphical Abstract



Introduction

Theranostics, which combines diagnostics and therapeutics, has emerged as a promising approach to personalized medicine in cancer treatment (Shrivastava et al. 2019; d'Angelo et al. 2020). It offers a cost-effective and time-efficient solution that considerably reduces the side effects of drugs used in cancer therapy while producing improved outcomes for patients. Moreover, theranostic agents present highly efficient nanocarriers for the simultaneous loading of imaging and therapeutic agents (d'Angelo et al. 2020; de Morais et al. 2023). Liposomes' advantages, including their resemblance to cell membrane structure, biocompatibility, low immunogenicity, high drug loading capacity, and site-specific properties, make them superior to other nanocarriers (Tila et al. 2015; Lopes et al. 2023).

Theranostic liposomes have been proven as promising platforms for propelling medicine into the personalized field (Kelkar and Reineke 2011). As liposomes are considered biomimetic systems of nanomedicine, they can be well applied as personalized vehicles to achieve precise theranostics in cancer therapy (Su et al. 2022). Early and precise cancer detection is considered a key item for the successful treatment of tumors which could be realized by theranostic–nanomedicine strategies (Hosseini et al. 2023).

Cancer remains one of the most significant challenges worldwide, with millions of new cases and deaths reported annually (Piñeros et al. 2022). Surgery, radiotherapy, and chemotherapy are the main strategies for cancer treatment, but they often lead to adverse side effects due to their non-specific targeting of healthy tissues. Furthermore, resistance to these treatments frequently develops, leading to postoperative recurrence and metastasis (Avramescu et al. 2020; Debela et al. 2021). Thus, the need for early detection and effective therapies has become increasingly noteworthy (Zhang et al. 2020). Nanotechnology has opened new horizons in cancer diagnosis and treatment, enabling the development of imaging-based diagnostic and therapeutic agents (Abolhasani Zadeh et al. 2022; Mosleh-Shirazi et al. 2022).

Nevertheless, designing theranostic-based nanocarriers requires careful consideration of several factors, such as selecting an effective therapeutic agent, a stable carrier, implementing goal-setting and sustainable drug release approaches, and choosing an imaging agent (Chi et al. 2017; Cong et al. 2018; Madamsetty et al. 2019). Liposomes have been extensively studied for delivering therapeutic agents over the past few decades and have become widely recognized as carriers of choice for cancer treatment or

diagnosis. Approved liposomes for cancer treatment include Onivyde ™, Marqibo®, Doxil®, Visudyne®, and Depocyt® (Crommelin et al. 2020). However, to date, there are currently no clinical approved liposomal formulations as the only-diagnosis nano-tool.

Theranostic liposomes, which simultaneously encapsulate both imaging and an anticancer agents, have been shown to be effective in diagnosis and treating cancers at the cellular and molecular levels (Jain et al. 2019; Li et al. 2019; Saraf et al. 2020). Liposomes can also be combined with specific receptor–ligands to target and amplify cancerous cell membrane receptors, further enhancing their effectiveness as the theranostic platforms for highly effective personalized therapy (Nabil et al. 2019; Narendra et al. 2020; Saraf et al. 2020).

Liposomes can serve as in vivo imaging platforms and theranostic substrates utilizing hydrophobic fluorescent dyes, quantum dots, fluorescent nanoparticles, and contrast agents (Huang and Lovell 2017; Shete et al. 2022). Therapeutic radiolabels such as ^{186}Re or ^{99m}Tc (Soundararajan et al. 2009) can be labeled on liposomes for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in vivo, and therapeutic metals such as gold, carbon, iron, gadolinium, silver, platinum, zinc, and titanium (Alwattar et al. 2021) may be used to enhance the therapeutic efficacy of drugs through site-specificity and tracking (Lee et al. 2018; Lee and Im 2019).

This review presents nanotheranostic technology's application in personalized medicine, specifically focusing on theranostic liposomes' role in the treatment and imaging of tumors. The challenges of clinically translating these theranostic liposomal therapeutics are also discussed. By combining diagnostic and therapeutic agents in a single carrier, theranostic liposomes offer promising solutions to personalized cancer therapy.

Nanosized systems and liposomes for personalized nanomedicine

Liposomes are the established and clinically effective nanosystems for the targeted delivery of anticancer agents (Pacheco et al. 2023). They are spherical bilayer vesicles made up of one or more layers of lipids that self-assemble in aqueous solutions (Has and Pan 2021). Liposomes can reach their site of action through the enhanced permeability and retention (EPR) effect, which enables them to extravasate into the interstitial space from within the bloodstream. Stealth (PEGylated) liposomes, in particular, can accumulate passively in solid tumors due to their leaky vasculature and defective lymphatic drainage (Al-Jamal and Kostarelos 2011).

Despite being larger than other conventional nanoparticles, liposomes (90–150 nm) have unique features that make them a valuable platform for biomedical nanotechnology research (Chatterjee and Kumar 2022; Setia et al. 2023).

Liposomes can be actively or passively targeted to specific tissues. For active targeting, liposomes can be modified with ligands that bind to receptors on the surface of target cells (Al-Jamal and Kostarelos 2007; Sajja et al. 2009; Kilcoyne et al. 2016; Børresen et al. 2018). Moreover, liposomes can be labeled with imaging agents such as quantum dots (Das et al. 2022) or chelated with agents like Gd and Mn, radionuclides like Tc-99, In-111, and Ga-67, or iodine-based agents, making them amenable to the evaluation of therapeutic efficacy in individual patients (Petersen et al. 2012; Phillips et al. 2013). For passive targeting, the EPR effect is involved to gain benefit from the intrinsic features of

solid tumors for more accumulation of the liposomes either theranostic or conventional (Subhan et al. 2021).

Radionuclides could be applied in clinical diagnostic PET imaging or internal tumor radiotherapy through PEGylated or conventional ^{64}Cu-liposomes and PEGylated ^{177}Lu-liposomes, respectively. They could also be used for predicting responses to cancer nanomedicines as well as the characterization of drug delivery to tumors (Petersen et al. 2016; Lee et al. 2018).

^{186}Re-labeled liposomes (named ^{186}Re-obisbemeda), have completed Phase I clinical trials for recurrent glioblastoma and are now in Phase II trials. In addition, other types of tumors including ovarian cancer, colorectal cancer, and head and neck cancer are also treated and monitored by ^{186}Re-labeled liposomes. Peptide-targeted ^{131}iodine-containing liposomes have also been used efficiently for the treatment of cervical cancer (Li et al. 2018; Brenner et al. 2023; Basu et al. 2024).

Howbeit, the majority of radio-liposomal formulations have not succeeded in clinical trials, and to date, no liposome-based radiopharmaceuticals have been approved for market release (Low et al. 2023).

Liposomes are highly versatile and can simultaneously incorporate both imaging and therapeutic agents without compromising their stability in the body. This makes them ideal for theranostic purposes (Al-Jamal and Kostarelos 2007; Janib et al. 2010). By incorporating both types of agents, liposomes can be used to evaluate the efficacy of cancer therapy. Liposomes have also been used as analytical tools for diagnostic purposes (Das et al. 2022).

Their simple synthesis, biocompatibility, ability to encapsulate hydrophilic and hydrophobic drugs, and long half-life after PEGylation make them particularly attractive for drug delivery applications (Xing et al. 2016; Lee and Im 2019).

The development of personalized chemotherapies, which involves delivering the right treatment to the right place at the right time, is crucial for effective cancer management. Nanomedicine, specifically image-guided drug delivery, has emerged as a promising strategy to achieve this goal.

(Lanza et al. 2014; Centelles et al. 2018; Tarighatnia et al. 2023). However, due to the heterogeneous and complex nature of tumors, accurate prediction and monitoring of treatment responses are essential (Chen et al. 2022). This can be achieved through non-invasive molecular imaging, which provides detailed data on tumor pathology (Tagami et al. 2011). By using contrast agents and appropriate modalities, specialized treatments tailored to each patient's molecular profile can be applied (MacRitchie et al. 2020).

The use of molecular imaging and personalized nanomedicine is becoming increasingly important in cancer treatment (Kircher et al. 2012). By providing accurate and detailed data on the mechanism of each section of a tumor, it is possible to tailor treatments to each individual patient (Mura and Couvreur 2012). This approach has the potential to improve prognosis and disease monitoring, as well as minimize inter-individual variations in therapeutic responses (Ryu et al. 2014).

Non-invasive imaging technologies and contrast agents are critical tools that allow for the detection of tumors and their diverse stages (Einstein et al. 1935; Lammers et al. 2012). By stratifying patients into groups with common features, clinicians can

design customized treatments that are specific to each person's individual molecular profile (Wang et al. 2018).

However, it is essential to translate personalized nanomedicine into clinical practice effectively (Einstein et al. 1935; Lammers et al. 2012). Targeted therapies should only be used in patients who show high levels of target site accumulation and respond well to primary cycles of treatment. In those cases where this is not the case, alternative therapeutic options should be considered (Lammers et al. 2011).

However, effective translation of these approaches into clinical practice is essential, and careful patient pre-selection based on non-invasive imaging data is a critical step toward achieving this goal (Einstein et al. 1935; Lammers et al. 2011, 2012; Mura and Couvreur 2012; Wang et al. 2018).

Nanotheranostics, particularly liposomal nanoparticles with theranostic features, offer a platform for patient pre-selection and personalized chemotherapeutic formulations (Somvanshi and Thorat 2022). Liposomes can be radiolabeled and used as agents for imaging and therapy, enabling real-time drug response monitoring and mechanistic process observation (Aranda-Lara et al. 2020). By designing liposomes with targeting features, they can diagnose gene aberrations and specific molecular features, distinguish various tumors with different molecular subtypes, and aid in the differentiation of tumor subtypes as well as monitoring drug response during the therapy (Marson et al. 2019; Zheng and Gao 2020). Liposomal nanotheranostic formulations also provide a platform for contrast agents to organize the basis of image-guided drug delivery, enabling payloads to be released at the site of the tumor and providing real-time and quantitative feedback obtained by in vivo imaging (Tang et al. 2018; Priester and Ten Hagen 2022). The multifunctionality and customizability of liposomes make them applicable in personalized medicine development to overcome the complexity and uniqueness of a patient's tumor (Shin et al. 2013). The composition of protein corona that covers liposomes once they disperse in biofluid may be a determinative factor for applying liposomes for therapeutic and diagnostic purposes, especially screening cancer tests (Colapicchioni et al. 2016; Hadjidemetriou 2017). Liposomal drug delivery offers an evolving field for improving image-guided drug delivery and therapy, where different liposomal formulations selectively accumulate in tumors and are detected by various imaging modalities (Priester and Ten Hagen 2022). These treatment models comprise multiple feedback loops to target drug delivery and personalized therapy, after selecting the optimal liposomal formulation in preclinical evaluations (Tang et al. 2018). The selected liposomal formulation will enter clinical phases after considering clinical translation-related implications, contributing to precise drug delivery, personalized adjustment of the drug dose, and synergistic cancer therapy (Fig. 1) (Lybaert et al. 2018; Tang et al. 2018).

The dynamic nature of tumors, their heterogeneity, and their evolution, underscores the necessity for adaptive and personalized treatment strategies (Kiran et al. 2024).

Liposomes in cancer imaging

Liposomes, as nanosystems for targeted drug delivery, have been extensively studied and successfully applied in clinical settings (Allen and Cullis 2013; Gu et al. 2020).

Liposomes are spherical bilayer vesicles composed of one or more layers of lipids that self-assemble in aqueous solutions (Has and Sunthar 2020; Liu et al. 2022b).

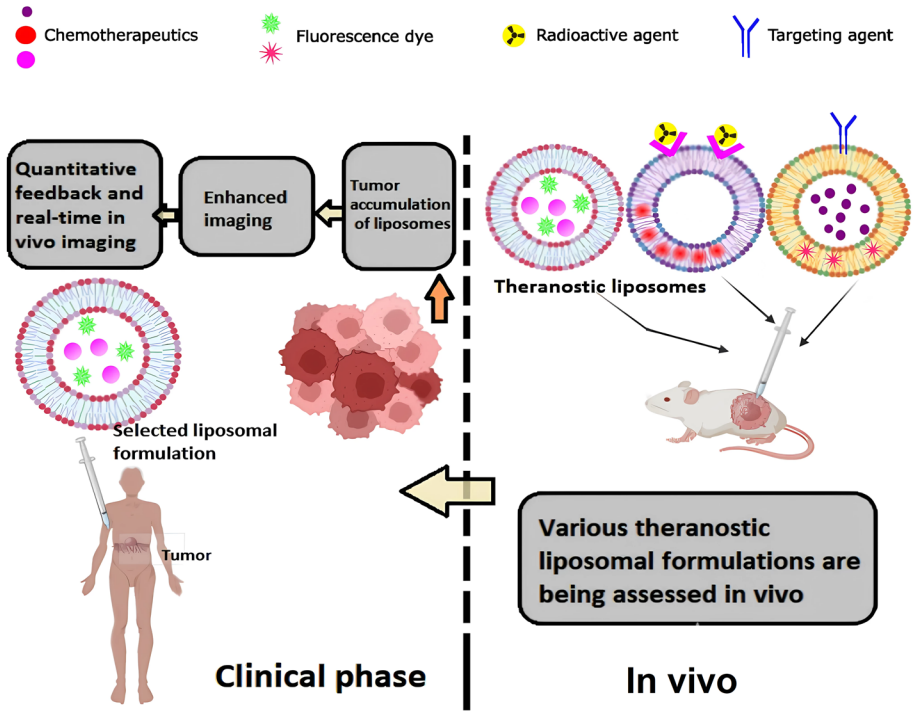


Fig. 1 Accumulation of three types of theranostic liposomes (indicated by yellow, purple, and blue) (with various formulations or components, imaging agents, fluorescence dye, radiopharmaceuticals and therapeutic agents) at the tumor site and their evaluation through pre-clinical and clinical stages. Real-time and quantitative feedback of liposomal drug delivery acquired noninvasively through a specific imaging modality can be further exploited to optimize and personalize therapy after the selection of an optimum liposomal therapeutic for an individual. The blue liposome successfully progressed to clinical usage, indicating its potential as an effective treatment option

They offer unique advantages in biomedical research due to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic drugs, and long half-life after PEGylation (Fulton and Najahi-Missaoui 2023; Wang et al. 2023a). Liposomes exhibit versatility in their application as theranostic agents. They can be actively or passively targeted to specific tissues, with ligands binding to receptors on target cells or through the EPR effect (Yue and Dai 2018; Yan et al. 2020; Kommineni et al. 2023).

In addition, liposomes can be labeled with various imaging agents and chelated with radionuclides or iodine-based agents, enabling the evaluation of therapeutic efficacy in individual patients (Srivatsan and Chen 2014; Yue and Dai 2018). A key advantage of liposomes is their ability to incorporate both imaging and therapeutic agents without compromising stability (Petersen et al. 2012). This dual functionality allows for the evaluation of cancer therapy efficacy and diagnostic purposes. Furthermore, liposomes have been employed as analytical tools for diagnostic purposes, showcasing their potential in theranostic applications (Musielak et al. 2021; Siafaka et al. 2021).

To maximize the clinical potential of liposomes, it is essential to develop strategies that enhance their performance and biocompatibility (Khan et al. 2020). One such approach is the utilization of patient-derived lipids, such as platelet and erythrocyte

cells, to improve delivery particle biocompatibility, particularly for precision medicine applications (Xing et al. 2016).

In addition, employing techniques with high efficiency for screening and surface-functionalizing nanoparticles with somatic lipid mixtures can accelerate the optimization process and facilitate translation into clinical practice (Pisani et al. 2009).

Imaging is a critical component of the theranostic field, providing a platform for diagnostic purposes in medicine and patient management (Theek et al. 2014; Weber et al. 2020). The diagnostic aspect of theranostics primarily revolves around imaging techniques utilizing various contrast agents to address challenges, such as early cancer diagnosis, tracking tumor metastasis, imaging tumor angiogenesis, detecting intracellular delivery of chemotherapeutics, and monitoring tumor therapy (Lanza et al. 2014; Schleich et al. 2015; Zare et al. 2022). Encapsulation of contrast agents by nano-carriers not only improves imaging but also reduces their toxicity and enhances their pharmacokinetics and bio-distributional features (Usman et al. 2017). This allows for non-invasive and quantitative pathological assessments to be performed (Dasgupta et al. 2020). This strategy supports cellular–molecular, functional and anatomical comprehension, and non-invasive evaluation which permits the diagnosis of physiological and pathophysiological abnormalities (Theek et al. 2014). Diverse imaging methods and tools are CT (computed tomography), PET, SPECT, MRI (magnetic resonance imaging), US (ultrasound), NIR (near-infrared), optical routes, such as fluorescence imaging through fluorescent markers (e.g., organic dyes and mineral quantum dots) and bioluminescence, PAI (photoacoustic imaging), SERS (surface-enhanced Raman spectroscopy) imaging, X-ray imaging, and Raman spectroscopy, which are appropriate for diagnosis as parts of theranostic agents (Guo et al. 2017; Hapuarachchige and Artemov 2020). These imaging platforms can also be directly used for verification of the surface receptors' expression at the target site (Hapuarachchige and Artemov 2020).

Molecular imaging methods such as US, ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles for molecular MR imaging, PET, and SPECT are highly suitable for achieving molecular imaging goals, allowing for the measurement of tissue genetic aberrations and biological processes at the molecular and cellular levels for early diagnosis of cancer, tumor stage identification, pathological comprehension, and tumor prognosis (Thakor and Gambhir 2013; Theek et al. 2014; Yordanova et al. 2017). On the other hand, MRI and CT are not suitable for this purpose due to their low contrast agent sensitivity (Lammers et al. 2010; Kelkar and Reineke 2011; Theek et al. 2014).

Functional and anatomical imaging can be achieved using US, MRI, and CT, each with distinct benefits and drawbacks with regard to contrast, sensitivity, resolution, safety, cost, acquisition time, and clinical applications (Lammers et al. 2010; Kelkar and Reineke 2011; Theek et al. 2014). Amongst all diagnostic imaging modalities, ultrasound imaging has some unique advantages, being more cost-effective, real-time, portable, and safe enough, and its resolution and sensitivity can be upgraded using ultrasound contrast agents (Cai et al. 2012; Nicolson and Kircher 2021; Tarighatnia et al. 2022). Multimodal theranostic delivery systems, comprised of more than one diagnostic agent and usually a therapeutic agent encapsulated inside a nanocarrier with contrast ability for two or more imaging modalities, are particularly useful when multiple diagnostic modalities are required for imaging (Janib et al. 2010).

Table 1 Comparative efficacy of various clinical imaging modalities with potential of multimodal applications and their pros and cons

Imaging modality	Pros	Cons
CT[1] X-ray	Fast imaging High depth penetration High spatial resolution	Low sensitivity Poor soft tissue contrast Risk of radiation
MRI[2]	Without risk of radiation High spatial resolution High soft tissue contrast Without penetration limit to tumors	Expensive Long imaging time Poor sensibility
PET[3] SPECT[4]	Unlimited depth of penetration High sensitivity Fast imaging	Low spatial resolution Risk of radiation Expensive
US[5]	High sensitivity High spatial resolution Real-time Low cost Without risk of radiation Rapid Safe	Operator dependent Limited penetration Low resolution
Optical imaging	High sensitivity Real-time Cost-effective	Low penetration depth Low spatial resolution

[1] *Computed tomography*

[2] *Magnetic resonance imaging*

[3] *Positron emission tomography*

[4] *Single-photon emission tomography*

[5] *Ultrasound*

A comparison for various imaging modalities, their advantages and disadvantages is provided in Table 1.

Targeted nanoparticles must be designed to improve targeted contrast agents due to their broad surface-area-to-volume, which makes them potential carriers for functionalization with targeting molecules and high potency of loading (Janib et al. 2010; Patel and Janjic 2015; Ma et al. 2016). These particles also have a high plasma circulation time due to their physicochemical properties, and drugs and contrast agents can be included at predetermined levels on the surfaces of cells or inside them (Janib et al. 2010; Patel and Janjic 2015; Ma et al. 2016).

Intra-cellular agents or events, especially cellular–molecular ones, can be made visible using advanced opto-acoustic and optical techniques, facilitating detecting clinical resolution during interventions and allowing for accurate and valid assessment of tumor margins by a surgeon (Terreno et al. 2012). Theranostic liposomes with the capacity of multimodal imaging such as the combination of MRI, US, and fluorescence could be beneficial for theranostic purposes, serving as integrated diagnostic and treatment agents (Muthu and Feng 2013). Recent investigations have proven that liposomes could be applied as efficient diagnostic and treatment agents for theranostic approaches in cancer treatment (Kelkar and Reineke 2011).

Imaging for theranostic application is amenable through liposomes loaded with various contrast agents and also other nanoparticles such as quantum dots, gold nanoparticles, or magnetic nanoparticles incorporated into liposomes (Dasgupta et al. 2020). In this regard, Redolfi Riva et al. developed magnetic liposomes containing doxorubicin for

the treatment of liver cancer. The formulation showed good magnetic behavior and cytotoxicity of drug-containing magnetic liposomes with a high uptake by the related cancerous cells after applying an external magnetic field, rendering a theranostic platform for both diagnosis and treatment of hepatocellular carcinoma (Redolfi Riva et al. 2020). As a novel and innovative route of imaging, persistent luminescence liposomes could be considered optical nanoprobes for improvement of the capability of imaging techniques for characteristic long-lasting NIR luminescence in optical imaging without applying autofluorescence and excitation (Kasi et al. 2023). Recent investigations have proved that liposomes could be applied as integrated diagnostic and treatment agents for theranostic approaches (Mukherjee et al. 2022).

A summary of liposomal formulation application in multimodal imaging for tumor detection during chemotherapy or drug delivery monitoring has been shown in Fig. 2.

Cancer is a complex disease that poses a significant challenge due to its multifarious etiology and nature (Sahoo et al. 2020). Chemotherapeutic agents exhibit low specificity and high adverse off-target effects on healthy organs and tissues (Gonzalez-Valdivieso et al. 2021; Puccetti et al. 2024). Therefore, there is a need for theranostic nanoparticles that can specifically target tumors, report the relative characteristics of the tissues of interest, and selectively accumulate in the tumor while not affecting healthy tissues (Schleich et al. 2015; Sneider et al. 2017).

Nanotheranostics offers several advantages in cancer therapy, including noninvasive evaluation of biodistribution and accumulation in the target site, monitoring drug

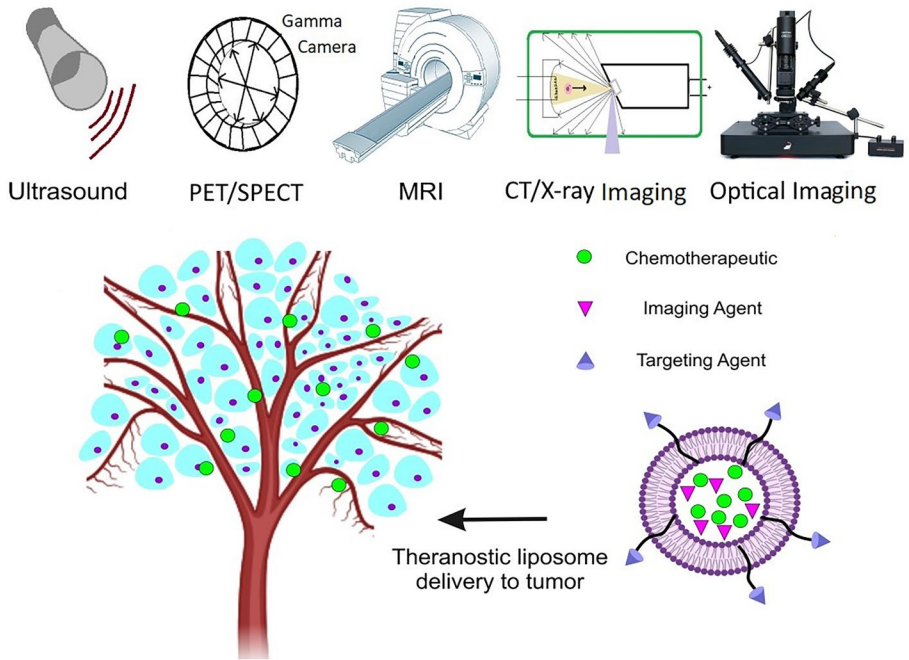


Fig. 2 Schematic representation of a liposomal therapeutic system designed for image-guided drug delivery. The liposomes are shown encapsulating a chemotherapy drug (represented by green dots) and conjugated with imaging agents (represented by purple triangles). Functionalization with targeting moieties enhances the potential of theranostic liposomes for either type of diagnostic features (MRI, ultrasonic, etc.). The imaging agents allow for real-time monitoring of the drug delivery process, facilitating precise targeting of cancer cells while minimizing off-target effects

release (Murar et al. 2022), improving the efficacy of therapy via targeted drug release, and predicting therapeutic response. By individualizing nanomedicine interventions, nanotheranostics can help pre-select patients before treatment and improve treatment outcomes (Schleich et al. 2015; Sneider et al. 2017; Somvanshi and Thorat 2022). This approach also enhances treatment response rates as well as decreases the likelihood of resistance or recurrence (Suhag et al. 2024).

Current cancer therapies consist of chemotherapy, radiotherapy, surgery, and immunotherapy (Arranja et al. 2017; Hashemzadeh et al. 2021).

However, due to the intra- and inter-heterogeneity, variability of cancerous tissues, and their resistance to drugs, responding to therapies remains a challenge. Molecular imaging combined with theranostic formulations offers a solution for designing targeted therapies based on diverse tumor phenotypes (Dammes and Peer 2020; Liu et al. 2022a).

Nanotechnology can simultaneously target multiple tumor markers, making it an ideal solution for this challenge (Sumer and Gao 2008). Molecular imaging is also useful in monitoring tumor response to treatments by imaging molecular markers of apoptosis or cell death (Savic et al. 2020).

Theranostic liposomes are useful agents in drug delivery monitoring, dose optimization of chemotherapeutics, and facilitating platforms for preclinical evaluations in terms of efficacy (Tang et al. 2018).

Overall, liposomes offer a promising platform for targeted drug delivery in cancer treatment due to their unique properties, such as targeting capabilities, simultaneous encapsulation of imaging and therapeutic agents, and efficient evaluation of therapeutic efficacy (Fernandes 2023). Further research and optimization of liposomal formulations will undoubtedly unlock their full potential as versatile and effective theranostic agents. As well, theranostic nanomedicine holds great promise in providing precision therapy for cancer treatment, particularly when combined with liposomal vehicles for targeted drug delivery.

Application of liposomes as theranostic agents in cancer therapy

Several liposomal formulations have been developed to efficiently load and deliver drugs to tumor tissues by incorporating targeting agents and multiple imaging and therapeutic agents, enabling better theranostic applications of liposomes (Saad and Hasan 2022).

To optimize liposomes for clinical use, it is important to develop strategies that improve their performance and clinical operation (Guimarães et al. 2021). One such strategy is to employ techniques with high efficiency for screening, followed by the use of patient-derived lipids, such as platelet and erythrocyte cells, which can enhance the biocompatibility of delivery particles, especially for precision medicine applications (Caballero et al. 2022).

Somatic lipid mixtures can be leveraged to surface-functionalize nanoparticles, ensuring full biocompatibility with cells from the patient from whom they were derived (Shae 2019). This approach can also accelerate the process of liposome optimization and facilitate their translation into the clinic. While most usage of this technique has been limited to particles with solid cores, methods for processing cellular membranes could be expanded to produce liposomes that are fully biocompatible with other types of loadings (Xing et al. 2016).

Overall, liposomes hold great promise as a versatile and effective platform for targeted drug delivery in cancer treatment. They have unique properties that allow for targeting, simultaneous encapsulation of imaging and therapeutic agents, and efficient evaluation of therapeutic efficacy. Further research is needed to optimize liposomal formulations for clinical use, but the potential benefits of these theranostic agents cannot be overstated.

Functionalized or multi-nanoparticle hybrids with theranostic liposomes

Liposomes can be functionalized with a variety of nanoparticles to create theranostic hybrids that allow for simultaneous imaging and therapy (Lagopati et al. 2022).

Encapsulation of imaging agents, such as quantum dots (QDs) or gold nanoparticles within liposomes, enhances their biocompatibility, pharmacokinetic profile, and stability in plasma (Ahmadi et al. 2023). QDs can be used for in vivo imaging due to their photoluminescence emission, while gold nanoparticles have high diagnostic properties for brain tumor assessment (Sachin et al. 2017).

To this end, a liposomal formulation was designed for the theranostic targeting of brain tumors with gold nanoparticles incorporated in liposomes accompanied by docetaxel with vitamin E conjugated transferrin as the ligand for targeting brain tumor. This nanoparticle showed high cytotoxicity and enhanced brain distribution of docetaxel and efficient diagnostic properties of gold nanoparticles for brain tumor assessment (Sonkar et al. 2021).

One example of a functionalized liposome is transferrin-conjugated tocopheryl polyethylene glycol succinate (TPGS)-coated liposomes containing docetaxel and QDs for imaging and treatment of brain cancer. This formulation demonstrated efficient targeting properties and showed high levels of transportation of both QDs and docetaxel, effectively crossing the blood–brain barrier (BBB) (Sonali et al. 2016). Coating liposomes with TPGS has advantages over PEG-coated liposomes in terms of enhancement of cellular uptake in vitro as well as cytotoxicity against cancerous cells. These hybrid liposomes have immense potential in nanotheranostics for the imaging and therapy of cancer (Muthu and Feng 2013).

Folate-targeted theranostic liposomes containing paclitaxel, vinorelbine, and Tc-99 m radiolabeled have been developed for lung cancer therapy and imaging. These liposomes showed high cellular uptake and toxicity on cancerous lung cells, effective inhibition of tumor growth, and restriction of lung metastasis of non-small cell lung cancer (NSCLC). As well, the imaging potential was in the light of radiolabeling which realized the biodistribution measurement and monitoring of these liposomes (Karpuz et al. 2021). In a type of novel immunoliposome loaded with doxorubicin, synthesized via a pH-gradient method, the conjugates of ^{64}Cu-labeled and anti-EGFR (epidermal growth factor receptor) antibody-conjugated micelles were then inserted into them via a post-insertion method. ^{64}Cu, with a half-life of 12.7 h and decay properties, was selected as the radioisotope for molecular PET imaging for NSCLC therapy in A549 xenograft mouse model with efficient inhibition of tumor growth and superiority of the 64Cu-immunoliposomes in terms of PET images of the tumors comparing to the untargeted liposomes (Jeong et al. 2024). Another radiolabeled PEGylated liposomes (^{64}Cu-liposomes) in

neuroendocrine H727 tumor xenografts (as the rare and important tumor type) was also synthesized and evaluated for theranostic and radiotherapeutic potential through micro PET/CT. This liposomal formulation showed high potential as PET theranostic tracer for imaging with human use prediction (Petersen et al. 2016).

Furtherly, a PEGylated liposome-encapsulated rhenium-188 radiopharmaceutical suppressed the proliferation and epithelial–mesenchymal transition of human head and neck cancer cells in vivo with extended survival rate and improved internal circulation but without acute toxicity through repeated administrations (Chang et al. 2018).

GE11 peptide, as the potential EGFR-specific peptide, conjugated to liposomes showed an enhanced combined therapeutic efficacies of docetaxel and siRNA against the ABCG2 gene that regulates multidrug resistance in laryngeal cancer (Xu et al. 2017).

Liposomes functionalized with arginylglycylaspartic acid (RGD) peptide and TPGS have been shown to be beneficial for targeting brain tumors by helping to overcome the BBB and acting as reactive oxygen species (ROS)-reducing agents. This type of liposome, loaded with docetaxel as the chemotherapeutic agent and QDs as an imaging moiety, has shown positive results in mitigating tumor growth (Singh et al. 2016).

A kind of liposomal formulation containing quantum dots, superparamagnetic iron oxide nanoparticles, and cilengitide for MRI or NIR imaging and therapy of glioma was designed with high uptake by the C6 cell line under magnetic targeting, leading to enhanced cytotoxicity of cilengitide comparing to its free form. This dual-imaging nanocarrier also crossed the BBB efficiently with assistance from an external magnetic field and ultrasound which could be considered as another example of BBB delivery of theranostic agents (Xu et al. 2018). Immunoliposomes containing doxorubicin and luminescent QDs with targeting ligand anti-HER2 scFv have been used to enhance receptor-mediated endocytosis in cancerous cells. These liposomes showed efficient anticancer activity with prolonged circulation of QDs in athymic mice. In breast cancer mouse models, the localization of these immunoliposomes at tumor sites was confirmed by in vivo fluorescence imaging (Weng et al. 2008).

Liposomal formulations containing PEGylated QDs have been designed to enhance internalization into tumor cells, allowing for efficient labeling of cancer cells and a dramatic reduction in the QD dose required (Al-Jamal et al. 2008).

Generally now, co-delivery of various nanoparticles, especially when one component is a liposome, can be beneficial. For example, theranostic liposomes containing both hydrophobic QDs and hydrophilic topotecan were constructed for the co-delivery of therapeutic and imaging agents, improving bioavailability, enhancing therapeutic efficacy, and increasing drug stability. The incorporation of QDs into cells allowed for synchronous imaging (Seleci et al. 2017).

A nanosystem composed of NIR carbon dots loaded into liposomes and cinobufagin as the chemotherapeutic agent was developed with high uptake rates and delivery to tumor cells as well as enhanced anticancer activity of cinobufagin and liposome as photoluminescence emission enhancers of carbon dots (Ren et al. 2019).

Liposomes incorporating ultrasmall iridium nanocrystals have been developed for use in radiotherapy. These liposomes exhibit effective NIR-responsive catalytic activity toward H2O2 decomposition due to the radio-sensitization feature of iridium, demonstrating promising performance in enhancing radiotherapy efficacy (Feng et al. 2018).

Monoclonal antibodies can be efficient moieties in targeting cancer cells. For example, monoclonal antibody-targeted indocyanine green (ICG) liposomes containing doxorubicin were used for imaging through multispectral optoacoustic tomography, a multi-wavelength and multispectral method with high spatial resolution and deep penetration for non-invasive imaging of their distribution in MUC-1 positive tumor cells (Lozano et al. 2015).

Finally, dual-targeting by paramagnetic–fluorescent liposomes is also presumable for more accumulation of the nanoplatform in the tumor site, especially the endothelial tissue of the tumor, which is rich in vasculature. This study was performed with two angiogenesis-specific ligands, the αvβ3 integrin-specific RGD, and the galectin-1-specific anginex. They improved the internalization and specificity of the liposomal contrast agent to the tumor endothelium, suggesting a more reliable MRI record of angiogenic (Kluza et al. 2012).

This study is beneficial due to the high rate of tumor angiogenesis and the complexity of its vasculature, in which a personalized approach may be required for angiogenesis imaging. Due to the over-expression of neural cell adhesion molecule (NCAM) in Kaposi's cells and tumor endothelial cells, NCAM-coated PEGylated liposomes loaded with both doxorubicin and a gadolinium–DOTA–monamide (DOTAMA), were designed to enhance drug delivery with simultaneous in vivo MRI visualization in an immunodeficient mouse model of Kaposi's sarcoma expressing NCAM. This liposomal formulation enhanced doxorubicin internalization and apoptosis and efficacy to Kaposi's cells as detected by MRI (Grange et al. 2010).

Stimuli-responsive theranostic liposomes

The use of stimuli-responsive liposomes in theranostics has gained significant attention in recent years. These nanoparticles, including thermosensitive, pH-sensitive, and enzyme-responsive liposomes, have shown great promise in controlled drug release and real-time monitoring of therapeutic efficacy (Kaushik et al. 2022; Wang et al. 2023b).

Temperature-sensitive liposomes (TSLs) are a type of thermosensitive liposomes, which can be induced to release drugs by heat induction. In a study by de Smet et al., TSLs co-encapsulating doxorubicin and [Gd(HPDO3A) (H2O)] were used for local delivery of doxorubicin under MRI guidance in a tumor model. Ultrasound-induced hyperthermia was applied to trigger drug release from TSLs, resulting in higher concentrations of doxorubicin and [Gd(HPDO3A) (H2O)] in the tumor (de Smet et al. 2011).

Similarly, radiofrequency pulse was also found to induce high temperature and doxorubicin release from its core (Wang et al. 2015; Sneider et al. 2017).

In the study by N. Centellesa et al., a dual theranostic liposomal nanoparticle (MRI- and near infra-red fluorescence-triggered) was formulated which were imageable thermosensitive liposomes and encapsulated topotecan as the chemotherapeutic agent, which can be triggered by high-intensity focused ultrasound (HIFU). The uptake of liposomes by tumoral cells was enhanced by hyperthermia induced by HIFU, providing real-time monitoring of the tumor and delivery of chemotherapeutics to cancerous cells (Centelles et al. 2018; Zheng et al. 2023).

Similar to this method, doxorubicin encapsulated in TSLs was accompanied by the magnetic resonance-guided high-intensity focused ultrasound platform, and then

image-guided non-invasive hyperthermia was applied. Tumor concentration of the drug was found to be enhanced and in contrast to free doxorubicin or TSLs alone, this platform suggested an improved distribution of doxorubicin in both the tumor periphery and core while protecting the adjacent normal tissues (Ranjan et al. 2012). These strategies are amenable to providing prognostic tumoral information that could be clinically translated for obtaining personalized treatment strategies.

Another kind of thermosensitive liposomal formulation co-encapsulating Gd-DTPA (an MRI probe) and doxorubicin, with the purpose of simultaneous release and drug delivery reporting in a locally heated tumor, was developed. By applying MRI coupled with drug targeting, drug delivery was quantified and enhanced in a locally heated tumor and provided predictive modeling (for the therapeutic effect) and also real-time clinical responses. In this regard and for personalized therapy, MR imaging was carried out before and after the liposomal formulation was administered. MR-guided focused ultrasound was used to induce heating in the tumor site, and then the tumor was imaged through MR to attain the drug delivery quantity. In the case of low drug delivery, sonication time or drug dosage may be increased until the desired delivered quantity has been obtained for the individualized tumor therapy (Tagami et al. 2011; Rahiman et al. 2025).

NIR-active thermosensitive liposomes are another form of thermosensitive liposomes for chemotherapy purposes. ICG as the NIR dye provided imaging possibilities for monitoring the pharmacokinetics and biodistribution of these liposomes in a real-time manner (Turner et al. 2012).

In addition to hyperthermia, sonoporation can also enhance the permeability and transport of nanomedicine through the extracellular matrix of solid tumors. Liposomal nanobubble complexes containing paclitaxel were used for permeability enhancement, imaging, and triggered release of paclitaxel at the tumor site (Prabhakar and Banerjee 2019). In fact, using sonoporation and nanobubbles can alter the tumoral perfusion of nanomedicine and its extravasation, penetration, and transport through the extra-cellular matrix especially solid tumors in which therapeutics' penetration is a challenging hurdle (Snipstad et al. 2021).

The high-intensity focused ultrasound and temperature-sensitive liposomes that were discussed, allow for precise spatial targeting of tumor regions while sparing adjacent normal tissues. In fact, due to the high tissue penetration of ultrasound and its non-invasiveness, ultrasound-related nanotheranostics is considered promising in precision medicine (Qin et al. 2023). Pre-procedural imaging for instance by MRI may be used to quantify tumor biological and physiological properties to be applied in the treatment plan to customize the therapeutic procedure for an individual patient. These theranostic liposomes (by their imaging component) may reveal less well-vascularized tissues that may be better treated with ablation techniques or may reveal highly vascularized tumor tissues that may be better treated through vascular delivery of thermosensitive liposomes. These thermosensitive liposomes may report real-time drug delivery to refine the treatment during the procedure to propel the therapy into a personalized manner (Deckers and Moonen 2010; Negussie et al. 2011).

Under the ultrasound action, the liposomes generate microbubble vibrates in blood vessels suitable for precise targeting of breast cancerous cells when passed close to the tumor site in the body. Liposomes rupture at the target site and release the NO

therapeutic gas, allowing the gas to fully interact with the tumor cells and promote apoptosis. Liposomes are inherently echogenic which makes them suitable to be carriers for therapeutic gases and in the presence of ultrasound show a higher efficiency and lowered systematic toxicity of gases compared to direct inhalation of gasses (Chen et al. 2024). In this regard, the use of echogenic liposomes for intravenous delivery of NO demonstrated its ability to induce breast cancer cell death in MDA-MB-231 and MDA-MB-468 cell lines. Precision delivery of NO was achieved with a controlled release manner (Lee et al. 2014; Chen et al. 2024). A schematic of gas-loaded liposomes acting under ultrasound and apoptosis induction on cancerous cells is illustrated in Fig. 3.

NIR-active thermosensitive liposomes containing ICG provided imaging for real-time monitoring of pharmacokinetics and biodistribution.

Moreover, pH-sensitive PEGylated and folate-targeted liposomes loaded with ^{159}Gd and poly-L-lysine have shown enhanced animal survival through death induction in cancer cells by Gd radiation and simultaneous provision of scintigraphic images with high tumor uptake with long-circulating feature (Soares et al. 2015; Šimečková et al. 2020).

Finally, ROS-responsive liposomes have been designed with a lipid peroxidation sensor incorporated into the liposomal bilayer for the detection of ROS (through a ratiometric fluorescent nanoprobe), along with mitoxantrone as a chemotherapeutic agent, resulting in enhanced antitumor activity and imaging capability. This ROS-responsive liposomal formulation was designed with the features of light scattering and possessing fluorescence intensity (Chen et al. 2019).

Overall, these stimuli-responsive liposomes offer a promising avenue for precision therapy in tumor targeting, providing controlled drug release, real-time monitoring of therapeutic efficacy, and customization of treatment plans for individual patients.

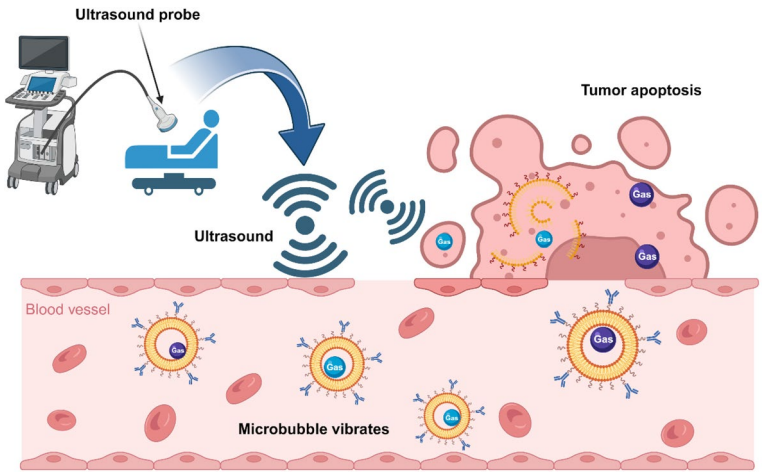


Fig. 3 Combination of liposome with gas as a therapy for cancer. Under ultrasound, the liposomes precisely target tumor cells through the induction of microbubble vibrates in blood vessels. At the tumor target site, the gas released from liposomes interacts with the tumor cells and promotes apoptosis. (Reused with permission from (Chen et al. 2024). Creative Commons CC–BY license)

Theranostic liposomes for gene delivery with siRNAs

Small interfering RNA (siRNA) plays a crucial role in gene delivery by leveraging the RNA interference (RNAi) pathway to achieve specific gene silencing. siRNAs can be incorporated into nanomedicine-based platforms especially lipid-based ones (in our case liposomes) to overcome delivery challenges to be applied for various diseases, especially various types of solid tumors (Li et al. 2021; Zhang et al. 2023; Qiao et al. 2024). Some siRNA-loaded liposomes for cancer therapy are also in the clinical trial process (e.g., EphA2 and PKN3 siRNAs) in both primary tumors as well as metastatic lesions, which substantiate their efficiency (Ozpolat et al. 2014). For liposome-mediated siRNA delivery, successful endosomal and lysosomal escape in targeted cells is the most challenging issue. Almost 1–2% siRNA endosomal escape occurs after cellular entry which could limit the use of liposomes for siRNA delivery. However, various modifications are used to tackle this issue (Gilleron et al. 2013; Liu et al. 2020). Efficient siRNA delivery could be realized by especially cationic liposomes which exhibit a relatively low rate of physiological toxicity compared with their synthesized primary amines (Lin et al. 2019; Chen et al. 2020).

A novel theranostic PEGylated siRNA liposome with magnetic resonance sensitivity (equipped with magnetic agents and fluorophores for MRI and fluorescence microscopy) was designed. By this nanoplatform, both liposome accumulation and siRNA delivery into tumors could be detected simultaneously in a real-time manner. The resulting functional siRNA delivery into mice OVCAR-3 xenograft tumors caused a significant reduction in anti-cancer survivin expression as well as tumor growth. 24 h post-administration, these liposomal formulations accumulated tumors by magnetic resonance contrast image enhancements (Gd) with fluorescence microscopy (Rhodamine as the fluorescent agent) which confirms the obtained results when simultaneously demonstrating the co-localization of liposomal formulation and siRNA within the ovarian xenograft tumors (Kenny et al. 2011).

In another study, liposome–gold nanorod hybrids for delivery of PLK-1 (important role in mitotic progression and DNA checkpoint) siRNA were prepared and developed for multispectral optoacoustic tomography for longitudinal visualization of the prepared nanohybrid localization within tumors. Furtherly, the NIR-797 fluorescent tag was used for labeling liposomes to allow validation by fluorescence cryo-slicing imaging. Using this liposome–nanohybrid in 4T1 (breast) and HT29 (colorectal) tumor models demonstrated that the administered dose remained stable after 24 h at the site of injection, which protected the PLK-1 siRNA from clearance by tumor and thus leading to apoptosis (Taruttis et al. 2014).

Lcn2 could be considered a promising anti-angiogenesis target and potential diagnostic biomarker for breast cancer. Lcn2 high levels are linked to breast cancer cell proliferation, angiogenesis, invasion, migration, immune regulation, prognosis, and chemotherapy resistance. In this regard, a novel Lcn2 siRNA liposome targeting intercellular adhesion molecule-1 (ICAM-1) was developed for silencing the Lcn2 gene in human triple-negative breast cancer MDA-MB-231 cells (Guo et al. 2016). In another study, the ligand Cyclo (Arg–Gly–Asp-D–Phe–Lys) (cRGD), which binds to the αVβ3 integrin highly expressed in tumor endothelial cells, was conjugated to a specialized pH-sensitive cationic liposome. Treatment with RGD-targeted liposomes

led to a notable decrease in CD31 levels in tumor endothelial cells, without affecting endothelial cells in other organs. In addition, tumor growth was reduced following three consecutive injections of the mentioned liposomal formulation (Sakurai et al. 2014).

A siRNA liposome delivery system was developed, integrating the asparagine–glycine–arginine peptide as a CD31 targeting motif and a photolabile-caged cell-penetrating peptide (pcCPP) to enhance siRNA delivery. The 4,5-dimethoxy-2-nitrobenzyl group was employed as a NIR two-photon excitation responsive caged compound, attached to the lysine side chains in the CPP sequence (CGRRMKWKK), to improve molecular uptake into cells. Upon exposure to NIR light, the inactive pcCPP transformed into an active CPP, promoting cell transduction and efficient siRNA delivery. This process was monitored using in vivo Cy5 fluorescence imaging and was shown to inhibit tumor growth (Yang et al. 2015).

A PEGylated cationic liposome containing the aptamer AS1411, specifically targeting nucleolin overexpressed on cancer cell surfaces, was employed to deliver anti-BRAF siRNA in an A375 melanoma model. Cy5.5-labeled siRNA imaging demonstrated effective tumor-specific delivery and resulted in tumor growth inhibition, although some accumulation in the kidneys was observed. Real-time PCR and western blot analysis confirmed the downregulation of BRAF. While acting as the anticancer agent, this platform aids in imaging and monitoring the therapy (Li et al. 2014).

A multifunctional liposomal system, labeled with two receptor-specific peptides that target the low-density lipoprotein receptor-related protein receptor (Angiopep-2) and the neuropilin-1 receptor, was utilized to deliver siRNA and docetaxel in a glioblastoma model. In vivo fluorescence imaging detected a specific accumulation of Cy5.5-labeled siRNA in intracranial glioblastoma. This liposome system, combining VEGF siRNA and docetaxel therapy, achieved VEGF silencing, inhibited tumor growth, and extended survival time (Yang et al. 2017).

A hypoxia-responsive cationic liposome was synthesized by malate dehydrogenase lipids with nitroimidazole groups for encapsulation of PLK-1 siRNA through electrostatic interactions. Glioma cells were targeted by these liposomes and the cellular uptake of these liposomes was enhanced effectively because of increased positive charges induced by low pH and hypoxia of tumor niche as well as effectively inhibiting the growth of glioma cells. Nitroimidazoles converted to aminoimidazole under hypoxia, gaining additional positive charges. PLK-1 siRNA delivery was confirmed by in vivo Cy5.5 imaging, leading to tumor growth inhibition over 27 days (Liu et al. 2017).

As well as siRNAs, DNA plasmids could also be delivered for theranostic purposes by liposomal platforms. Magnetic cationic liposomes showed a high capacity to form complexes for transfection of antibiotic-free pFAR4-luc plasmid into CT-26 cells. Microbubble and liposome complex as a detection modality enables real-time, deep tissue imaging (microbubbles) and significantly enhances signal contrast. This liposomal complex can be remotely activated by a US scanner, simplifying instrumentation and offering high spatiotemporal precision for treatment. US pulses increase cell membrane permeability, enhancing the delivery of therapeutic liposomes (Do et al. 2020).

siRNA lipoplexes (siRNA complexed with cationic liposomes) mixed with anionic polymers (polyglutamate), showed enhanced gene silencing efficiency and reduced cellular

toxicity via increased recovery of siRNA in liver and lung in comparison with lipoplexes without anionic polymer. The tested gene for silencing with these nanoliposomes was the luciferase gene through luciferase-targeted siRNA lipoplexes using a cell line that constitutively expresses the luciferase gene (melanoma (B16-Luc)) in vivo (Schlegel et al. 2011, 2013). This prepared siRNA did not consider any theranostic performance; however, it showed enhanced efficacy of siRNA-mediated gene silencing using liposomes.

Liposomes for PDT and PTT

Photodynamic therapy (PDT) involves administering photosensitizers or prodrugs to cancerous cells, which are then activated by laser light (Diode laser) of a specific wavelength (630–730 nm) (Pignatelli et al. 2023). This leads to a series of photochemical and photo-biological reactions that culminate in the irreversible destruction of tumor cells due to hypoxia (an oxygen-independent process) (Feng et al. 2017; Yang et al. 2024). Similarly, photo-thermal therapy (PTT) involves irradiating cancerous cells with NIR radiation (800–980 nm), resulting in thermal tissue damage (Siafaka et al. 2020; Kong et al. 2021; Overchuk et al. 2023). PTT results in tumor cell ablation by thermal sensitization of the tumor cells, while PDT leads to necrosis, apoptosis, and autophagy-related cell death in terms of tumor eradication (Yang et al. 2024).

For instance, chlorophyll derivatives such as pyropheophorbide acid have been loaded into liposomal formulations as contrast agents for imaging or photosensitizers for PDT (Pucci et al. 2021).

These nanoliposomes exhibit intrinsic fluorescence properties, high NIR absorbance, and extra radiolabeling capacity, making them suitable for multimodal imaging including fluorescence imaging, photoacoustic (PA), and SPECT/CT imaging, in addition to PDT and inhibition of tumor growth (Zhou et al. 2019a).

Another promising strategy for anticancer nanotheranostics is the use of NIR dyes such as ICG and perfluorooctyl bromide (PFOB) entrapped within nanoliposomes, resulting in enhanced PDT and PTT through synergistic effects (Sheng et al. 2018; Xu et al. 2021).

Such lipid-based formulations also exhibit significant oxygen loading capacity due to high PFOB oxygen affinity, which eliminates the tumor's hypoxic condition, leading to enhanced PDT. In preclinical studies, these liposomal formulations have demonstrated complete inhibition of breast tumor growth, as well as reduced hypoxia-inducible factor expression and elevated levels of oxygenated hemoglobin in the tumor, further highlighting their potential for precision therapy (Fig. 4) (Sheng et al. 2018).

Another example of theranostic liposomes is PEGylated liposomes functionalized with gadolinium (III) diethylenetriamine penta acetic acid salt, which acts as an MRI contrast agent, and zinc phthalocyanine (ZnPc), which serves as a photosensitizer for PDT. This bimodal nanocarrier has demonstrated promising effects in cervical cancer cell lines, serving as both a contrast imaging agent and a therapeutic tool. The structure and theranostic features of this system are illustrated in Fig. 5 (Skupin-Mrugalska et al. 2018).

Multispectral optoacoustic tomography (MSOT) is an emerging imaging technique in which cancer cells can be ablated (Ntziachristos and Razansky 2010).

One approach involves using a nanoliposomal formulation loaded with doxorubicin and the NIR dye ICG, which serves as both a fluorescence probe and a

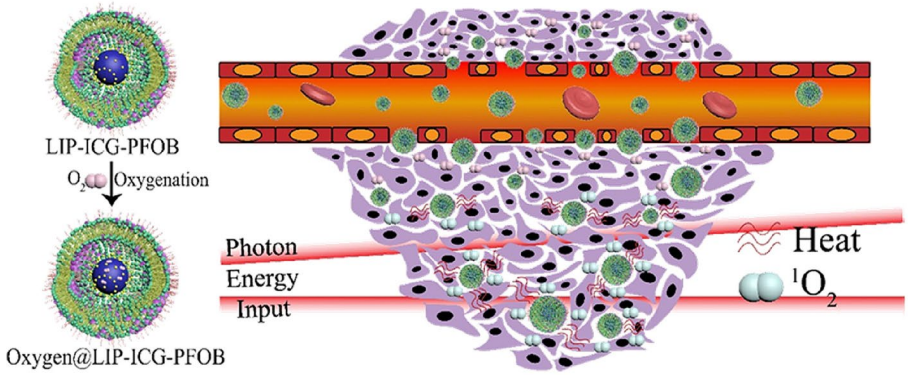


Fig. 4 Enhanced multimodal image-guided phototherapy using liposomal formulations of NIR dyes and photosensitizers. In this approach, liposomes containing the photosensitizer chlorophyll derivative pyropheophorbide acid (PPa) and the NIR dye ICG are used to perform PDT and PTT in breast cancer cells. The nanoliposomes also entrapped PFOB, which exhibits high oxygen affinity and loading capacity, leading to the elimination of tumor hypoxia and enhanced PDT. The resulting formulation exhibits promising contrast imaging features when imaged via CT and fluorescence imaging. (Sheng et al. 2018). License code: 5544110712266)

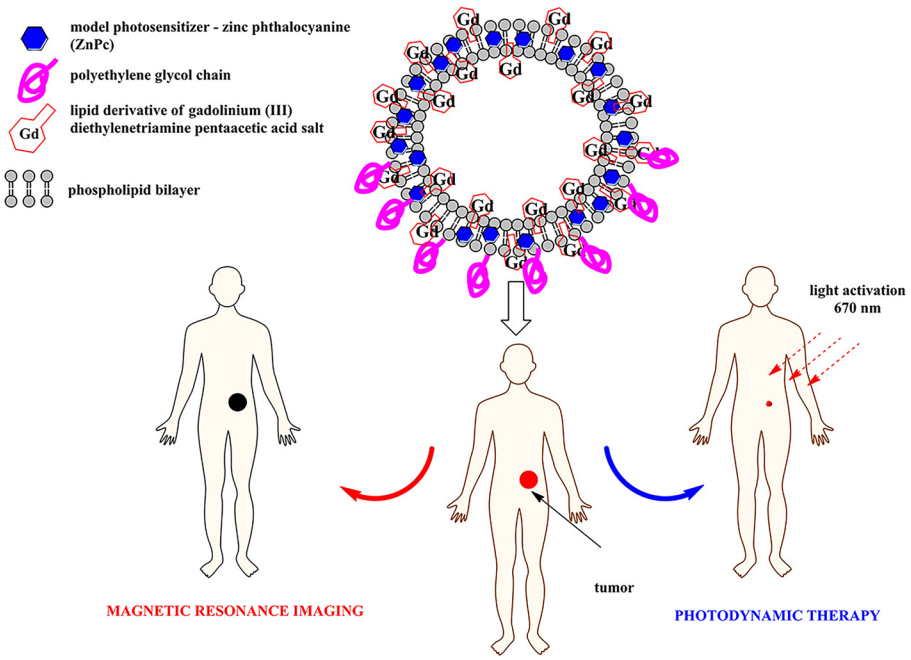


Fig. 5 Designed liposomes for the delivery of both a photosensitizer (ZnPc) and a contrast agent (a lipid derivative of gadolinium (III) chelate) for use in both PDT and MRI. This bimodal nanocarrier exhibits promising potential as a theranostic platform for cervical cancer treatment. (Skupin-Mrugalska et al. 2018). License code: 5544130077017)

photosensitizer for PDT. This formulation was exposed to NIR pulses for real-time imaging and as a stimulus for the disintegration of the liposomal formulation, triggering the release and action of the therapeutic agents. The potential of this approach was demonstrated in an orthotopic graft model of breast cancer in mice, where the

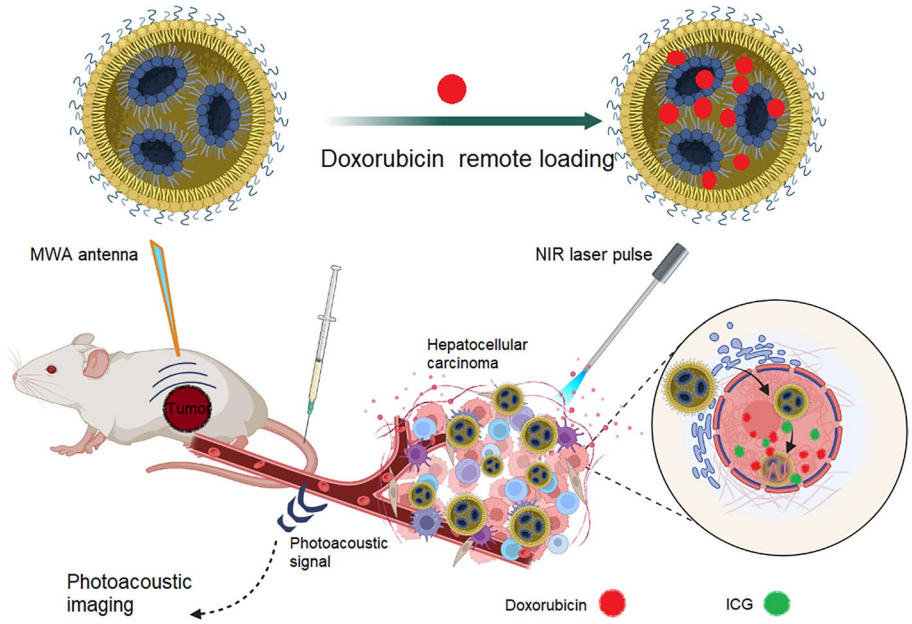


Fig. 6 Schematic illustration of theranostic liposomes loaded with doxorubicin and ICG for effective PAI and excellent coadjutants combined with microwave ablation for hepatocellular carcinoma. This bimodal nanocarrier exhibits promising potential as a theranostic platform for cancer treatment. (Reproduced from (Zhou et al. 2019b) with modifications)

doxorubicin–ICG-loaded liposomes exhibited selective accumulation at the morbid site, providing prognostic data that could be used to design personalized therapeutic nanoplatforms with novel strategies. The structure and theranostic features of this system are illustrated in Fig. 6 (Ichihara et al. 2018; Zhou et al. 2019b).

The hypoxic tumor microenvironment is a challenge for PDT, especially in solid tumors (Lee et al. 2022).

To address this issue, a PEGylated theranostic liposome was developed to encapsulate Chlorin e6 (Ce6) as a photosensitizer, a prodrug named Tirapazamin as a hypoxia-activated chemotherapeutic agent, and a gene probe for detecting intracellular miRNA biomarkers. Laser irradiation induces hypoxia, leading to the disintegration of the liposome contents and activation of Tirapazamin for improved cancer cell killing. The gene probe also serves as a detection marker for revealing oncogenic intracellular miRNA biomarkers (Zhang et al. 2018). The liposomal construction and mechanism of action are summarized in Fig. 7. A similar study was conducted using a liposomal formulation with Ce6, ICG, gadolinium III (GdIII), and targeting the liposome surface with RGD. Exposure of ICG to NIR light activates the photodynamic and fluorescence effect of Ce6, generating cytotoxic singlet oxygen that destroys cancer cells. The PDT-induced hypoxia also activates the prodrug for a synergistic chemotherapeutic effect (Dai et al. 2019). This strategy improves the anticancer efficacy compared to PDT alone and allows for the diagnosis of cancer-induced biomarkers through a hypoxia-responsive chemotherapeutic release system (Zhang et al. 2018; Dai et al. 2019).

To achieve selective bioimaging and controlled chemotherapeutic delivery with enhanced PDT, anti-HER2 peptide was conjugated to liposomes containing doxorubicin and photo-exciting methylene blue attached NaYF4: Yb, Er (Panikar et al. 2019).

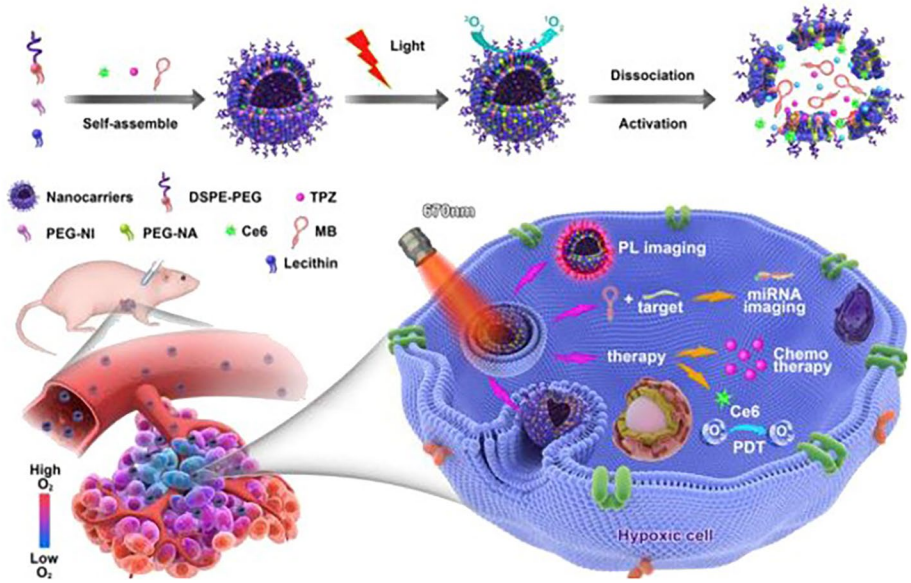


Fig. 7 Light-triggered hypoxia-activated PDT by a theranostic liposomal formulation. A PEGylated liposome encapsulates Ce6 as a photosensitizer, a prodrug named Tirapazamin as a hypoxia-activated chemotherapeutic agent, and a gene probe for detecting intracellular miRNA biomarkers. Upon laser irradiation, hypoxia is induced, leading to the disintegration of the liposome contents and activation of Tirapazamin for improved cancer cell killing. The gene probe also serves as a detection marker for revealing oncogenic intracellular miRNA biomarkers (Zhang et al. 2018). License code: 5462990833134)

In addition to PDT, SERS can be used for tumor diagnosis and combined with PTT for remote-controlled therapy. For this purpose, a targeted liposome decorated with gold nanocages as nanoprobes was constructed and showed significant enhancement of cellular uptake and effective cancer cell ablation by PTT (Farahavar et al. 2021).

Multifunctional theranostic nanoparticles have also been synthesized for cancer treatment. RGD-modified ICG was encapsulated inside liposomes for PTT and PDT by simultaneous production of hyperthermia and reactive oxygen species to target tumor vessels and cells overexpressing αvβ3 integrin in laryngeal cancer (Wu et al. 2020). A liposomal formulation of paclitaxel containing Gd and RGD ligand was used for imaging and targeting tumoral vessels and microenvironment with high sensitivity and promising anticancer efficiency (Ren et al. 2015).

A multifunctional theranostic platform with dual imaging modalities that combines PTT and chemotherapy was exploited for breast cancer therapy. A DiR liposomal theranostic platform containing an inactive cisplatin prodrug showed strong NIR absorbance and fluorescence for both in vivo NIR fluorescence and PA imaging. The photothermal effect of DiR synergistically enhanced the chemotherapeutic effect both in vitro and in vivo (Feng et al. 2016).

A biocompatible multifunctional nano-hybrid nanorods gold-therapeutic liposome-encapsulated doxorubicin was constructed with folic acid targeting. Gold nanorods were assembled on both the interior and exterior surfaces of the liposome (Fig. 8) to provide strength and prevent early drug release. This NIR-responsive liposome was exposed to the plasmonic heating of gold nanorods after NIR irradiation for PTT and high contrast

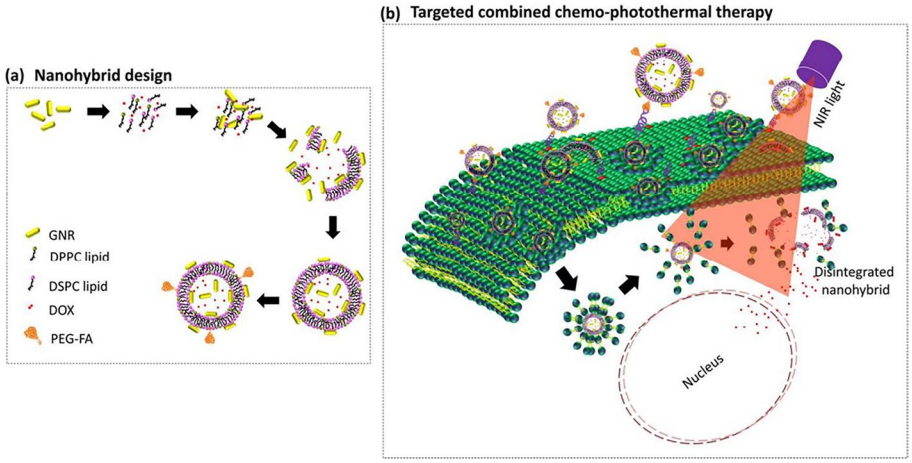


Fig. 8 Schematic illustration of a gold nanorod and liposome nanohybrid synthesis, disintegration, and targeted PTT with NIR-assisted disintegration of gold nanorods and liposomes. The biocompatible nano-hybrid is comprised of gold nanorods assembled on both the interior and exterior surfaces of a liposome, providing strength and preventing early drug release. This NIR-responsive liposome shows a synergistic therapeutic effect for photothermal and chemotherapy on breast cancer cells. (Reprinted with permission from (Chauhan et al. 2017). *Copyright © 2018, American Chemical Society*)

in CT imaging, effective cell uptake, and the synergistic therapeutic effect for photothermal and chemotherapy on breast cancer cells (Chauhan et al. 2017).

The results of such studies especially that relative to the comprehension of cancer biomarkers or mechanistical imaging will help direct the standard of medicine and therapy to a more personalized approach. Knowledge of tumor biology and construction by imaging and diagnostic modalities will provide remarkable insights into the therapies that are most effective on an individual basis, minimizing unessential and toxic chemotherapeutics and resulting in an improved patient outlook and health standard.

In 2019, a new chemiluminescent liposome composed of Bis (2,4,6-trichlorphenyl) oxalate and curcumin was synthesized to detect hydrogen peroxide selectively, leading to the successful treatment of ROS-related tumors (Mohammadi et al. 2019). A graphene oxide liposome encapsulating carbon quantum dots and doxorubicin was used for the mitigation of breast cancer with high uptake of the constructed liposomes by these cells and dual synchronous chemotherapy and photothermal therapy triggered by NIR irradiation (Hashemi et al. 2019).

A multifunctional hybrid liposomal formulation loaded with ICG for photothermal therapy after NIR laser illumination for generation of hyperthermia for tumor ablation and gadolinium (Gd) for MR imaging guidance during photothermal therapy was a successful nanotheranostic method for the destruction of solid tumors (Dai et al. 2019).

A NIR-responsive liposomal system composed of a photothermal agent (Cypate) and doxorubicin incorporated in a thermosensitive liposome was developed for the rapid release of its contents as a photothermal and chemotherapeutic agent. This liposomal formulation could enhance doxorubicin accumulation in the tumor and inhibit tumor growth with fewer adverse effects of doxorubicin (Chen et al. 2017). Another thermosensitive doxorubicin liposomal formulation with bubble-generating

capability was formulated with folate as the targeting agent and accompanied by photothermal therapy with the same drug release procedure as the previously mentioned study (Guo et al. 2015).

For efficient delivery of quantum dot-encapsulated theranostic liposomal formulations to the tumor, photothermal therapy strategy was applied. For this purpose, the nitric oxide-mediated tumor microenvironment remodeling strategy enhanced the accumulation of liposomes inside the tumor with high therapeutic efficacy (Tang et al. 2022).

It is noteworthy that photoactivatable agents such as photosensitizers and photothermal agents act as diagnostic agents through fluorescence or hyperthermia, respectively. However, photoacoustic images are versatile imaging tools for deeper morbid tissue imaging than fluorescence imaging (Jeong et al. 2021). The limitations suggested for PDT and PTT are considered limited light depth penetration, which can restrict the treatment to superficial tumors or the tumors which are accessible via endoscopic or interstitial light delivery methods. Tumors located in deeper tissues may not receive sufficient light to activate the photosensitizers or photothermal agents effectively (Wilson and Weersink 2020; Bhole et al. 2021).

During PTT, generated heat can potentially damage normal tissues surrounding the tumor. This risk increases with the depth of the tumor and the intensity of the applied laser (Nasseri et al. 2022).

Moreover, achieving high drug loading and maintaining the stability of liposomal formulations can be challenging (Sawant and Torchilin 2012). The encapsulation efficiency and stability of photosensitizers or photothermal agents within liposomes can impact the overall effectiveness of the therapy (Jin and Zheng 2011).

In PDT, the efficacy of the treatment can be compromised in hypoxic tumor microenvironments, where the lack of oxygen hinders the production of ROS to kill tumor cells (Wan et al. 2021). To minimize side effects, it is important to optimize the dose, timing, and duration of light exposure to achieve the desired therapeutic effect while avoiding excessive damage to healthy tissues (Zecha et al. 2016).

Table 2 summarizes the studies on liposomal theranostic formulations for tumor therapy.

Limitations and challenges of theranostic liposomal nanoconjugates and their translation into the clinic

Theranostics in the nanotechnology field face several barriers to their translation into clinical applications. The leading barriers can be biological or commercialization challenges. One of the biological challenges is nano–bio-interactions, where nanoparticles can interact with proteins upon entering biological systems, leading to alterations in their size, pharmacokinetics, biodistribution profile, stability, and toxicity (Shi et al. 2017; Singh et al. 2020). As well, in the field of cancer, tumor penetration and accumulation could be another challenge despite the EPR effect which allows liposomes to accumulate in tumor tissues. Deep tumor penetration and efficient accumulation within the tumor microenvironment could limit liposomal formulations for penetrating solid tumors (Seleci et al. 2017; Kalyane et al. 2019; Zi et al. 2022).

Table 2 Different pre-clinical evaluations of theranostic liposomal formulations for cancer therapy

Lipid composition	Therapeutic agent	Targeting agent/Guiding modality	Targeted tumor	Imaging agent	Main effect	Reference
DPPC[1]: Chol[2]	Docetaxel	Transferrin	Brain tumor	QD[24]	↑ Targeting efficiency and cellular internalization	(Sonali et al. 2016)
DSPC[3]: DMPC[4]: EPC[5]: Chol	Topotecan	-	Cervical cancer cells	QD	↑ biocompatibility and cellular uptake of the imaging agent/↑ cytotoxicity and efficacy of the therapeutic agent	(Seleci et al. 2017)
DPPC: DSPE-PEG2000[5]: DSPE-PEG2000[6] Folate: Rh-PE[7]: Chol	Paclitaxel/Vinorelbine	Folate	Non-small Cell Lung Cancer	Tc-99m[25]	Metastasis cessation	(Karpuz et al. 2021)
DPPC: DSPE-MPEG2000: Chol	Cinobufagin	-	Breast cancer	NIR carbon dots	↑ carbon dots photoluminescence ↑ efficacy of the therapeutic agent	(Ren et al. 2019)
DPPC: Chol	Docetaxel	RGD[26]	Brain tumor	QD	Brain delivery of a theranostic NP[27]	(Singh et al. 2016)
DSPC: Chol: DSPE[8]	Doxorubicin	anti-HER2[28]	Breast cancer	QD	efficient internalization in HER2-overexpressing tumor cells via receptor-mediated endocytosis	(Weng et al. 2008)
DOPC[9]: DOPE[10]: Chol	–	–	melanoma	QD	efficient NP uptake by living cells in the absence of cell death/↑ penetration and retention into the tumor interstitium	(Al-Jamal et al. 2008)
EPC: Chol	Docetaxel	Transferrin	Brain tumor	Gold NP	Brain delivery of a theranostic NP	(Sonkar et al. 2021)
DPPC: DSPE-mPEG$_{5k}$:Chol	–	NIR[29] laser	Breast cancer	Iridium	↑ radiotherapy efficacy	(Feng et al. 2018)
HSPC[11]: DSPE-PEG2000: Chol	Doxorubicin	anti-MUC1 "humanized" monoclonal antibody hCTM01	breast cancer/colon adenocarcinoma	ICG[30] by multispectral optoacoustic tomography	non-invasive and longitudinal imaging of liposomal distribution within the MUC-1 positive tumors	(Lozano et al. 2015)
DPPC: PEG2000-DSPE: egg yolk lecithin: Chol	Cilengitide	Magnetic field	Glioma	SPION[31]/QD	dual-imaging and therapeutic effect leading to resection of tumor by surgery	(Xu et al. 2018)
POPC[12]: DSPE: DSPE Chol: Gd-DOTAMA[13]	Doxorubicin	NCAM[32]	Kaposi's Sarcoma	Gd	specific drug delivery and imaging by liposomes in NCAM-expressing tumors	(Grange et al. 2010)

Table 2 (continued)

Lipid composition	Therapeutic agent	Targeting agent/Guiding modality	Targeted tumor	Imaging agent	Main effect	Reference
DPPC: HSPC: Chol: DPPE[14]-PEG2000: DOTA[15]-DSPE	Doxorubicin	MRI by ultrasound induced hyperthermia	Gliosarcoma	Gd(HPDO3A)(H2O)	↑ concentration of the therapeutic agent	(de Smet et al. 2011)
DOPE: DSPE-PEG2000: CHEMS[16]	–	Folate	Ehrlich ascites carcinoma	Gadolinium-159	↑ survival	(Soares et al. 2015)
DOPC: DSPE-PEG2000: Chol	Mitoxantrone	–	Mouth carcinoma	C11-BODIPY Lipid Peroxidation Sensor)	Stimulus sensing and controlled drug release	(Chen et al. 2019)
DPPC: DSPC: MSPC[17]: PEG2000 -DSPE	Topotecan	ultrasound	Ovarian cancer	[Gd(HPDO3A)(H2O)]/NIRF[33]	Image-guidance drug delivery	(Centelles et al. 2018)
MSPC: DPPC: DSPE-PEG-2000	Doxorubicin	ultrasound	rabbit VX2 tumor model (a virus-induced anaplastic squamous cell carcinoma)	Gd/ultrasound	Image-guidance drug delivery	(Ranjan et al. 2012)
DPPC: DOPE	Paclitaxel	ultrasound	Breast cancer/Head and neck cancer/pancreatic ductal adenocarcinoma	ultrasound	Ultrasound-Triggered imaging and drug delivery	(Prabhakar and Banerjee 2019)
DPPC: DSPE-mPEG$_{5k}$: Chol	Pyropheophorbide acid	–	Breast cancer	pyropheophorbide acid	PDT [34]/multi-modal imaging features	(Zhou et al. 2019a)
DPPC: DSPE-PEG2000: Chol	ICG perfluorooctyl bromide	Phototherapy	Breast cancer	ICG	Enhanced multi-modal imaging	(Sheng et al. 2018)
POPC: chicken egg PG: DOTAP[18]: GdDTPA1[19]: PEG2000-DPPE	ZnPc	PDT	Ovarian cancer	Gd/ZnPc[35]	MRI dual imaging and synchronous PDT	(Skupin-Mrugalska et al. 2018)
-	Au nanocages	PTT by NIR irradiation	melanoma	SERS[36] imaging	In situ diagnosis Remote-controlled thermal demolition of cancerous cells	(Farahavar et al. 2021)
DPPC: DSPE-PEG-NHS: DOTAP: Chol	ICG	RGD	laryngeal carcinoma	ICG	PTT[37]/PDT	(Wu et al. 2020)
DSPC: DSPG-N: MPEG-2000-DSPE: Rhod-DMPE[20]	Paclitaxel	RGD	non-small-cell lung cancer	Gd	↑sensitivity/deep tissue penetration/good anticancer efficiency	(Ren et al. 2015)
DPPC: DSPC	Doxorubicin/Gold Nanorods	FA[38]	Breast cancer	Gold Nanorods	PTT/targeted internalization of nanohybrid followed by drug release in the cytoplasm and the nucleus	(Chauhan et al. 2017)

Table 2 (continued)

Lipid composition	Therapeutic agent	Targeting agent/Guiding modality	Targeted tumor	Imaging agent	Main effect	Reference
Lecithin: Chol: DSPE-mPEG2000	Tirapazamine	Laser-induced hypoxia	Breast cancer	$Ce6^{39}$	A hypoxia-responsive drug-release nanosystem for simultaneous diagnosis and therapy	(Zhang et al. 2018)
DSPE-PEG2000-Mal	Tirapazamine	cRGD	lung cancer	$Ce6/Gd^{III}$	multimodal imaging (fluorescence/photoacoustic/magnetic resonance imaging)	(Dai et al. 2019)
$POPC^{21}$	Curcumin	-	Melanoma	Peroxyoxalate/Curcumin	Detection of hydrogen peroxide at nanomolar levels	(Mohammadi et al. 2019)
DPPC: Chol: Brij 78	Doxorubicin	NIR	Breast cancer	Carbon QD	A theranostic stimuli-sensitive system with PTT capability	(Hashemi et al. 2019)
DPPC: Brij78	Doxorubicin	–	Carcinoma	Gd	MRI real-time monitoring of drug delivery with thermosensitive liposomes	(Tagami et al. 2011)
Chol: soy lecithin	Doxorubicin	anti-HER2 peptide	Breast cancer	methylene blue attached NaYF4:Yb,Er	Chemo-PDT	(Panikar et al. 2019)
DMPE: DSPE-PEG-2000	ICG	–	Colon tumor	Gd	PTT and synchronous MRI guidance	(Dai et al. 2019)
DPPC: Chol: $DSPE\text{-}PEG_{2000}$	Doxorubicin	NIR	Breast cancer	Cypate	PTT and bubble generation with thermosensitive liposomes	(Chen et al. 2017)
DPPC: DSPE-PEG2000: Chol	Doxorubicin	Folate/NIR	epidermoid carcinoma/lung cancer	IR-780	PTT and bubble generation with thermosensitive liposomes	(Guo et al. 2015)
DPPC: Chol: $DHSG^{22}$: DSPE-PEG5000	Doxorubicin	External Magnetic Field	Hepatocellular Carcinoma	dextran-coated magnetic nanoparticles	↑ Targeting efficiency	(Redolfi Riva et al. 2020)

Table 2 (continued)

Lipid composition	Therapeutic agent	Targeting agent/Guiding modality	Targeted tumor	Imaging agent	Main effect	Reference
DPPC: Chol: DSPE-PEG2000	Doxorubicin/ICG	NIR	Hepatocellular Carcinoma	ICG	↑ antitumor efficacy of doxorubicin	(Zhou et al. 2019b)
DMPC: POE[23]	ICG	–	Breast cancer	ICG	Cancer diagnosis ability and synchronous therapy	(Ichihara et al. 2018)
POPC: Chol: DSPE-mPEG2000	Doxorubicin	EGFR[40]	NSCLC	Copper-64	Targeted therapy and imaging	(Jeong et al. 2024)
DSPC: Chol: DSPE-mPEG2000	–	Radiotherapeutics	Neuroendocrine carcinoma (H727)	Copper-64 Lutetium-177	PET theranostic tracer for imaging	(Petersen et al. 2016)
DSPC: Chol: DSPE-mPEG2000	–	Radiotherapeutics	Head and neck cancer	Rhenium-188	Inhibition of proliferation and epithelial–mesenchymal transition	(Chang et al. 2018)
EPC: DSPE-PEG2000: DSPE-PEG2000-MAL[41], DOTAP: Chol	Docetaxel	GE11 peptide/siRNA against the ABCG2 gene	laryngeal cancer	-	regulates multidrug resistance	(Xu et al. 2017)
Gd. DOTA.DSA[42]: CDAN[43], DOPC: DSPE-PEG2000: DOPE-Rhodamine	Survivin siRNA	External Magnetic Field (MRI)	human ovarian cancer cells (OVCAR-3)	Gd/ Rhodamine	Simultaneous MRI/fluorescence monitoring ↓ surviving expression	(Kenny et al. 2011)
DOTAP: Chol: DSPE-PEG	PLK-1 siRNA	Gold nanorods by multispectral optoacoustic tomography	4T1 (breast) and HT29 (colorectal) cancer cells	Gold nanorods/NIR-797 fluorescent	optoacoustic tomography combined with fluorescence cryo-slice imaging	(Taruttis et al. 2014)
DMAPAP[44]:DOPE: DPPC: DSPC: PEG2000 PE[45]	pFAR4-luc plasmid	Iron oxide External Magnetic Field (MRI)	CT-26 (colorectal carcinoma)	Iron oxide	image-guided gene delivery	(Do et al. 2020)

*[1] Dipalmitoyl phosphatidylcholine [2] Cholesterol [3]Distearoyl phosphatidylcholine [4]Dimyristoylphosphatidylcholine [5]Egg L -α-phosphatidylcholine [6] 1, 2-Distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) [7]Rhodamin-phatidylethanolamine [8]Distearoyl-sn-glycero-3-phosphoethanolamine [9]1,2-Dioleoyl-sn-glycero-3-phosphocholine [10]1,2-Dioleoyl-sn-glycerol-3-phosphoethanolamine [11]Hydrogenated soy phosphatidylcholine [12]1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine [13]gadolinium- tetraazacyclododecanetetra acetic acid-monamide [14]1,2Dipalmitoylsnglycero-3-phosphoethanolamine [15]tetraazacyclododecanetetraacetic acid [16]Cholesteryl hemisuccinate [17]1-myristoyl-2-stearoyl-sn-glycero-3-*phosphatidylcholine *[18]Dioleoyl-3-trimethylammonium propane [19]gadolinium-diethylenetriamine penta-acetic acid [20] rhodamin1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine [21]1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine [22]1,5-O-dihexadecyl-*N*-succinyl-l-glutamate [23]polyoxyethylene [24] Quantom dot [25]Technetium-99 m [26] tripeptide Arg-Gly-Asp [27]nanoparticle [28]human epidermal growth factor receptor-2 [29]near infra-red [30]Indocyanine green [31] Superparamagnetic iron oxide nanoparticles [32] Neural cell adhesion molecule [33] near infrared fluorescence [34] Photodynamic therapy [35] Zinc phthalocyanine [36] Surface-enhanced Raman scattering [37] Photothermal therapy [38] Folic acid [39] Chlorin e6 [40] Epidermal growth factor receptor [41]Maleimide [42]Gadolinium (III) 2-[4,7-bis-carboxymethyl-10-[(N,N-distearylamidomethyl-Na-amido-methyl]-1,4,7,10-tetra azacyclododec-1-yl]-acetic acid [43]N1-cholesteryloxycarbonyl-3,7-diazanonane-1,9-diamine [44]2-(3-[bis(3-aminopropyl)amino]propylamino)-N-ditetradecyl -carbamoylmethylacetamide [45]1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]*

Another challenge is that therapeutic and diagnostic agents within one platform may not always adequately meet the needs for theranostic applications. A study demonstrated that the optimal nanoparticle size for drug delivery is not necessarily the optimal size for imaging (Dreifuss et al. 2015).

The difficulty in formulating a reproducible and controllable synthesis procedure is another challenge in the clinical translation of theranostic nanoparticles (Zheng et al. 2021). Liposomal nanoformulations can be unstable in the bloodstream which may cause premature drug release and thus reduce the efficacy of the drug. The premature degradation of liposomes can also result in the release of free drugs, which may cause systemic toxicity (Zafar et al. 2023). In the case of personalized medicine using liposomal delivery, liposomes instability remains a significant challenge. Liposomes may fuse together or aggregate in the liquid phase, making them unstable during storage and disrupting the elicited immune response (Ye et al. 2021). The immune system can recognize liposomal nanoformulations as foreign entities, which may also lead to their rapid clearance from the body. Thus, this event can reduce the circulation time and bioavailability of the loaded therapeutic and consequently diminish its therapeutic effect (Inglut et al. 2020).

The complex and laborious procedure of producing nanoplatforms results in poor batch-to-batch reproducibility, low yield, and diverse physical and chemical characteristics, making large-scale synthesis inefficient (Singh et al. 2020). Commercializing nanotherapeutics involves monitoring processes in terms of regulatory factors, such as safety profiles, quality control, manufacturing procedures, and patent conservation, which all can delay their availability for clinical use. Deficiencies in safety and regulatory guidelines, as well as a wide gap between the scientific community and regulatory authorities, may become apparent and need addressing (Gaspar 2007).

Manufacturing and the related costs of liposomal formulations may also limit their use in clinical settings. The need for specialized equipment and stringent quality control measures also adds to these costs (Shah et al. 2020; Khan et al. 2024).

Toxicological aspects, particularly metal ingredients in theranostic liposomal formulations, need cautious consideration as they become critical in clinical stages (Agnihotri et al. 2022).

Despite these challenges, theranostic liposomes, with their efficient accumulation in tumor sites, ease of functionalization, and versatility, can be exploited to create "smart liposomes" for tumor detection, treatment, and monitoring treatment response (Carrese et al. 2022).

In summary, while there are several challenges associated with the clinical translation of nanotherapeutics, including liposomal formulations, addressing these challenges can pave the way for their successful use in personalized medicine. Theranostic liposomes have the potential to revolutionize cancer diagnosis and treatment, and ongoing research is dedicated to developing more effective and safe formulations.

Conclusion and future perspectives

In this review, we discussed the potential of nanotheranostic liposomes as a means of enhancing the efficacy of therapeutic and diagnostic agents for cancer therapy. Liposomal formulations have the potential to revolutionize personalized medicine by enabling precise drug delivery to target sites while minimizing toxicity to healthy tissues.

Several nanotheranostic liposomes have been developed and extensively used for different purposes, including biodistribution evaluation, treatment-response prediction, target-site localization, and improvement of the efficacy of anticancer therapy by multimodal methods. Furthermore, through contrast agents, it is possible to monitor the fate of nanotheranostics, particularly stimuli-responsive nanocarriers, in real-time, providing valuable information to clinicians about their therapeutic effectiveness.

However, challenges in the clinical translation of nanotherapeutics, such as the reproducibility and controllability of synthesis procedures, regulatory factors, and toxicological aspects, need to be addressed to realize the full potential of these targeted nanotherapeutics. To overcome these challenges, efforts should be made to improve the complexity and safety of nanotheranostic agents.

Moreover, molecular imaging of nanotheranostics can facilitate the process of personalized medicine by visualizing the delivery of drugs in nanotheranostic targeting systems to the morbid site and the state of releasing their contents there. Going forward, the development of novel theranostic liposomes with promising applications will require ongoing preclinical studies that could serve as tools in clinical decision-making for personalized medicine.

Future clinical directions for targeted diagnosis and therapy using liposomal formulations may consider the use of antibodies and/or peptides which are expected to enhance the specificity and efficacy of drug delivery to the diseased tissues. Furthermore, more investigation on the integration of stimuli-responsive liposomes may be beneficial which improves the precision and effectiveness of treatment.

In conclusion, personalized nanomedicine using nanotheranostic agents is an innovative field in cancer therapy that has great potential for improving patient outcomes. We are optimistic that, with continued research and development, many promising theranostic liposomes will reach the clinical stage and contribute to the future of targeted and personalized medicine.

Abbreviations

BBB	Blood–brain barrier
Ce6	Chlorin e6
CT	Computed tomography
DOTAMA	Tetraazacyclododecanetetraacetic acid–monamide
EGFR	Epidermal growth factor receptor
Gd	Gadolinium
HIFU	High-intensity focused ultrasound
ICG	Indocyanine green
MRI	Magnetic resonance imaging
MSOT	Multispectral optoacoustic tomography
NCAM	Neural cell adhesion molecule
NIR	Near-infrared
NSCLC	Non-small cell lung cancer
PA	Photoacoustic
PAI	Photoacoustic imaging
PDT	Photodynamic therapy
PET	Positron emission tomography

PFOB	Perfluorooctyl bromide
PPa	Pyropheophorbide acid
PTT	Photothermal therapy
QDs	Quantum dots
RGD	Arginylglycylaspartic acid
ROS	Reactive oxygen species
SERS	Surface-enhanced Raman spectroscopy
SPECT	Single-photon emission computed tomography
TPGS	Tocopheryl polyethylene glycol succinate
TSLs	Temperature-sensitive liposomes
US	Ultrasound
USPIO	Ultra-small iron oxide
ZnPc	Zinc phthalocyanine

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