


Biocompatible Polymer Nano-Constructs: A Potent Platform for Cancer Theranostics

Technology in Cancer Research & Treatment
Volume 22: 1-7
© The Author(s) 2023
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15330338231160391
journals.sagepub.com/home/tct


Himani Kalita, PhD^{1,2}  and Manoj Patowary, PhD³

Abstract

Nano-constructs of biocompatible polymers have drawn wide attention owing to their potential as theranostics for simultaneous therapy and detection of cancer. The present mini review summarizes various nano-architectures of polymers that have been developed as theranostic agents for the simultaneous treatment and diagnosis of cancer in a single platform. Additionally, research prospects of polymeric cancer theranostics for the future have been highlighted.

Keywords

biocompatible, polymer, theranostic, cancer, nano-architectures

Abbreviations

ADA, alendronic acid; CT, computed tomography; EPR, enhanced permeability and retention; MRI, magnetic resonance imaging; NIR, near-infrared; PET, positron emission tomography; PDT, photodynamic therapy; PEG, polyethylene glycol; PSMA, Prostate-Specific Membrane Antigen; SPECT, single-photon emission computed tomography

Introduction

Theranostic platforms that assimilate both therapeutic and investigative competences in a single agent, bestows real-time identification of diseased region location, monitor of drug distribution/accumulation and visualization of therapeutic outcomes.¹ Among the deadly diseases, cancer (also termed as malignancy) represents an aggressive killer that kills millions of people every year and thus, has become a critical global healthcare problem.^{2,3} Intense research work, therefore, has been focused on the development of techniques to combat this life threatening disease, and theranostic management of cancer has gained wide attention in this context. Till date, numerous diagnostic modalities have been employed for the detection of cancer such as near-infrared (NIR) fluorescence, positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), computed tomography (CT), and photoacoustic imaging⁴ On the contrary, therapeutic modalities include chemotherapy, photothermal therapy (PTT), immunotherapy, gene therapy, photodynamic therapy (PDT), radiation, hyperthermia, etc. (Figure 1). Theranostics for cancer, therefore, integrates the combination of 2 or more of these modalities within a single platform.

Till date, theranostic platforms for cancer that have been developed include nano-formulations of polymers,⁵ dendrimers,⁶

liposomes,⁷ proteins,⁸ carbon nanotubes,⁹ metals,¹⁰ quantum dots,¹¹ etc Among these nano-formulations, polymers have gained wide significance owing to their excellent biocompatibility, good biodegradability, ease of synthesis, high drug loading capacity and long blood circulation time.² Additionally, polymeric theranostics exhibit improved specificity, triggered or sustained release, water solubility, bioavailability and targeting properties.¹² Nano-constructs of both natural and synthetic polymers have been widely developed and explored as theranostic platforms for cancer. These nano-constructs include various architectures such as vesicles, micelles, hyperbranched polymers, nanoparticles, and hydrogels. (Figure 2). These architectures improve the conjugation of diagnostic and therapeutic agents onto the polymeric nano-constructs and aids in accomplishing

¹ Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India

² Department of Chemistry, Savitribai Phule Pune University, Pune, Maharashtra, India

³ School of Engineering, MIT-ADT University, Pune, Maharashtra, India

Corresponding Author:

Himani Kalita, PhD, Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, 781039, India.
Email: hkalita74@gmail.com



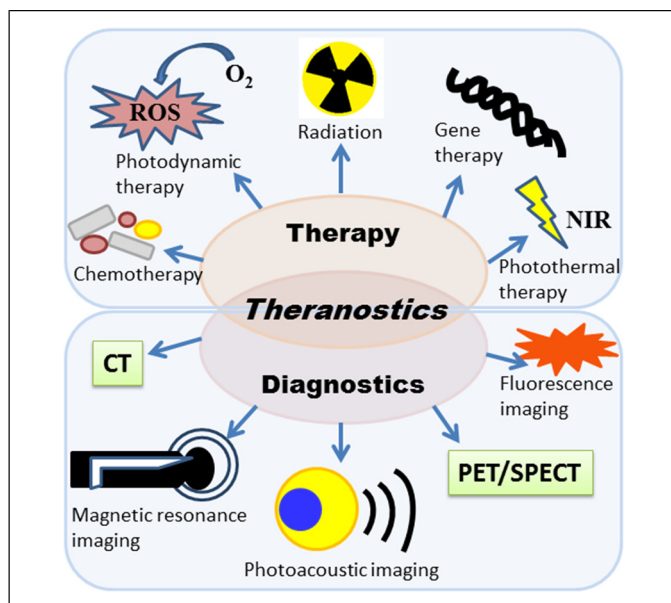


Figure 1. Few modalities of diagnosis and therapy in cancer theranostics.

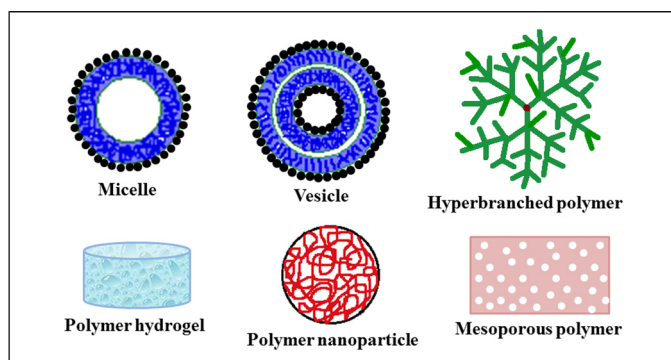


Figure 2. Various polymer nano-constructs in cancer theranostics.

their theranostic aspects. The current mini-review, therefore, focuses on the numerous nano-constructs of polymers (both synthetic and natural polymer) that have been developed and studied as theranostic platforms for the simultaneous detection and treatment of cancer. This mini-review will provide state-of-the-art literature to the researchers working in the area of polymeric theranostics for cancer.

Polymer Vesicles as Cancer Theranostics

Nanoscale architectures, viz. vesicles and micelles exhibit at least 1 dimension in 1 to 100 nm range. Polymer vesicles (or polymersomes) are nano-sized hollow spherical structures with a hydrophilic cavity and a hydrophobic membrane. Unlike polymer micelles that exhibit simple core-shell nano-structures, polymersomes possess more complicated structure.¹³ Prepared by self-assembly technique, polymer vesicles are well-developed nanoplatforms that exhibits

several excellent features such as versatile functionalities, smart and rapid response to different stimuli and high drug loading capacity.¹⁴ Polymer vesicles have been considered to be promising theranostic platforms for cancer and research work on them have been highlighted in several journals. For instance, bone-targeting polymer vesicle was prepared by the self-assembly of poly(ϵ -caprolactone)₆₇-b-poly[(L-glutamic acid)₆-stat-(L-glutamic acid-alendronic acid)₁₆] in water (size ~ 219 nm; zeta potential -49.9 ± 0.6 mV to -45.2 ± 1.3 mV) and subsequently studied as theranostic platform for treatment and diagnosis of malignant bone tumors.¹⁵ The alendronic acid (ADA) unit in the vesicle exhibits high affinity toward bone tissues by chelating Ca^{2+} ions in hydroxyapatite that are highly presented in bone tumors. Additionally, ADA- $^{99\text{m}}\text{Tc}$ chelation renders it a superior bone scintigraphic agent for bone-tumor-targeted SPECT imaging. The poly(ϵ -caprolactone) membrane circumvents premature removal of encapsulated chemotherapeutic drug (doxorubicin hydrochloride) in the lumens and, thus, effectively elongates blood circulation time of the drug resulting in increased drug concentration at the tumor site. In another approach, self-assembled lipid-polymer theranostic vesicle of 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidylcholine and triblock copolymer Pluronic F127 have been developed with covalently attached 5(6)-carboxyfluorescein (for fluorescence imaging) and studied for photodynamic applications against glioblastoma multiforme cell lines (T98G).¹⁶ The presence of F127 results in the formation of 100 nm sized small unilamellar vesicles with excellent solution stability, low polydispersity and zeta potential of 2.88 ± 1.01 mV. The photoactivatable PDT property of the vesicles was achieved using verteporfin as photosensitizer. The theranostic properties of the vesicle are completely photoactivatable and could be triggered at the wavelength of 470 nm. The presence of only $1.0 \mu\text{mol L}^{-1}$ of verteporfin in the vesicle showed 98% reduction in the viability of T98G cells, thereby inferring the theranostic potency of the developed lipid-polymer vesicle for cancer treatment. In a different work, self-assembled polymeric theranostic vesicle of amphiphilic block copolymers were developed containing quinone trimethyl lock-capped self-immolative side linkages and covalently bonded photosensitizers, viz. Nile Blue and coumarin and their theranostic potency was studied against A549 and HeLa cell lines.¹⁷ The developed theranostic vesicles (size 89-150 nm; zeta potential -8 mV to -3 mV) were NQO1 [NAD(P)H:quinone oxidoreductase isozyme 1] responsive that triggers both PDT and NIR fluorescence emission potency upon cellular internalization of the vesicles in tumor cells that contain overexpressed NQO1. The intracellular NQO1 enzymes trigger self-immolative quinone linkage cleavage and release of photosensitizers that eventually results in the simultaneous turn-on of NIR fluorescence emission and activated PDT. This process eventually transforms vesicles into cross-linked micelles which possess small size and hydrophilic cores that could be monitored directly through enhanced MRI signals. Polymer vesicles have been

similarly prepared and studied as theranostic platforms for the diagnosis and treatment of breast cancer,¹⁸ liver tumor,¹⁹ cervical cancer,²⁰ etc.

Polymer Micelles as Cancer Theranostics

Akin to polymersomes, nano-sized polymer micelles are also prepared by self-assembly technique (Figure 3). The most important parameter that determines their thermodynamic stability is critical micelle concentration, which usually occurs in the μM range.²¹ However, factors such as pH, ionic strength, temperature and high shear forces during circulation in physiological systems, sometimes, might affect the stability of polymeric micelles that might lead to their subsequent dissociation after intravenous administration. Various research groups have studied the applicability of polymer micelles as cancer theranostics. Pan and co-workers have developed polymeric micellar nanoparticles using an amphiphilic triblock copolymer, viz. Pluronic F127 [poly(ethylene oxide)₁₀₆-block-poly(propylene oxide)₇₀-block-poly(ethylene oxide)₁₀₆] that encapsulates hydrophobic NIR heptamethine cyanine dye me-IR825 inside the core of the micelles.²² The developed theranostic micellar nanoparticles [size 19.5 ± 10.2 nm; zeta potential $+37.4 \pm 2.2$ mV (in pure water) and $+0.8 \pm 0.1$ mV (in 10 mM phosphate-buffered saline)] exhibit dual fluorescence emissions at ~ 610 nm (for in vitro mitochondrial fluorescence imaging, cancer/normal cell differentiation, and early stage cancer detection) and 845 nm (for in vivo NIR fluorescence imaging), in addition to showing in vitro and in vivo mitochondria-targeted PTT and in vivo photoacoustic imaging upon excitation at NIR region (808 nm). In vivo experiments in tumor-bearing nude mice revealed that the micelles could target tumor tissues after intravenous injection through enhanced permeability and retention (EPR) effect and be maintained at the tumor site for prolonged period. Furthermore, the degraded products of the micellar nanoparticles after PTT were observed to be biocompatible, inferring the posttreatment biosafety of the prepared micelles. In another work, polygalacturonic acid-polyacrylic

acid conjugated hybrid nano-micelles were fabricated as nano-elastic carrier for oral and injected dosage in the treatment of liver cancer with resistance to acidic milieu of upper gastrointestinal tract and alkaline pH of colon, along with cancer cell targeting (using folic acid as targeting agent), anti-immune recognition, high diffusion and drug loading capacity (loading efficiency 23%).²³ The nano-micelle (size 100-200 nm) successfully encapsulates LY2157299 (an anti-tumor molecule) and inhibits TGF- β to treat hepatocellular carcinoma cancer cells. Polymeric theranostic micelle of N-(2-Hydroxypropyl)methacrylamide polymer conjugated pyropheophorbide-a have also been synthesized (size of ~ 200 nm) and studied for PDT (at ~ 420 nm) and photodynamic diagnostics (at ~ 680 nm) for cancer treatment.²⁴

Hyperbranched Polymers as Cancer Theranostics

Hyperbranched polymers are 3D dendritic architectures with irregular asymmetrical branching, low polydispersity and a branching degree of 0.5 to 0.66. They were originally reported by Kim and Webster in the late 1980s.²⁵ They have been widely recognized as theranostic platform for their excellent multifunctionalization ability, biocompatibility, aqueous solubility, compact structure, low viscosity, and high stability. Hyperbranched polymers could be easily synthesized through one-step polymerization reactions with good yields and desired physicochemical features, while their large number of terminal functional groups facilitate in achieving the desired chemical modification. The large specific surface area of hyperbranched polymers significantly enhances their therapeutic loading capacities,²⁶ whereas improved chain flexibility and deformability enhances blood circulation duration drastically.²⁷ Furthermore, the enormous number of branches allows the successful attachment of a range of diagnostic and therapeutic agents for efficient cancer treatment. One of the most commonly used polymer to develop hyperbranched polymer theranostics is polyethylene glycol (PEG) which readily forms hyperbranched architectures with excellent biocompatibility. Pearce and co-workers developed PEG hyperbranched polymers (size 6.2 nm) through RAFT polymerization, which featured glutamate urea targeting ligand for overexpressed Prostate-Specific Membrane Antigen (PSMA) to target prostate cancer cells.²⁸ The hyperbranched polymers were incorporated with fluorescent cyanine-5 for fluorescent optical imaging and further loaded with chemotherapeutic drug, doxorubicin (loading efficiency $\sim 90\%$), via hydrazone formation that maintains drug release from the polymer in in vitro endosomal conditions with an eventual controlled drug release of 90% over 36 h. The drug-loaded polymer was localized into the cancer cells through receptor mediated internalization, which is followed by its release into the nucleus after hydrazone degradation. The same group in another work developed hyperbranched polymer of PEG (size 6.7 ± 1.6 nm) and covalently attached 8-mer peptide aptamer to it for targeting heat shock protein 70 (Hsp70) biomarker that is overexpressed

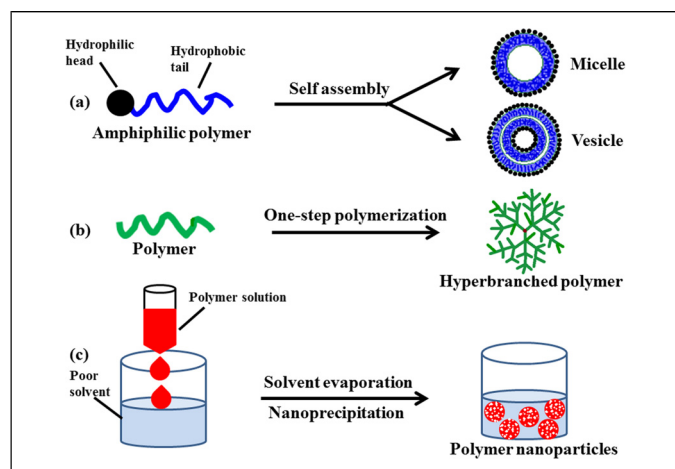


Figure 3. Schematic diagram for the preparation of (a) micelle and vesicle, (b) hyperbranched polymer, and (c) polymer nanoparticles.

in breast cancer cells.²⁹ The presence of 8-mer peptide aptamer provides both targeting and potential chemosensitization functionality to the theranostic agent. Additionally, the hyperbranched polymers were loaded with doxorubicin as a chemotherapeutic drug (via hydrazone bond that enables pH sensitive drug release at the mild acidic conditions in lysosomes/endosomes of tumor cells) and cyanine-5 as an optical imaging agent. The targeted hyperbranched polymer was observed to get accumulated in vesicles of live MDA-MB-468 cells, while in vivo studies in mice showed longer retention at the tumor site, possibly due to ligand-receptor interaction. Recently, carbon dot-drug conjugate (viz. carbon dot-hydrazine-doxorubicin) were synthesized and subsequently co-self-assembled with PEG-based hyperbranched polymer (acts as both gatekeeper and surfactant) to obtain pH/reduction dual-triggered theranostic agent (size 220 nm) for cancer treatment.³⁰ Another important class of hyperbranched polymer cancer theranostics is hyperbranched polyglycerols which exhibits good chemical stability, water solubility and inertness under biological conditions.^{31,32} Other hyperbranched polymer theranostics for cancer includes hyperbranched polyesters³³ and hyperbranched polyamidoamine.³⁴ Hyperbranched semiconducting polymer³⁵ has also been developed as cancer theranostics (Table 1).

Polymer Nanoparticles as Cancer Theranostics

Nanoparticles of polymers have been widely studied as cancer theranostics, till date, particularly due to their tunable size and multifunctionalization ability that aids in achieving aqueous solubility and attachment of both therapeutic as well as diagnostic modalities onto them. Among these polymeric nanoparticles, fluorescent nanoparticles especially conjugated polymer nanoparticles has gained enormous attention as they usually eliminates the requirement of external diagnostic (fluorescent) agents, vital in safe and inexpensive fluorescence imaging techniques. Additionally, conjugated polymer nanoparticles exhibit some excellent features such as desirable optical characteristics, small size, low toxicity, good photostability, ease of modification, high quantum yield, and excellent biocompatibility.³⁶ Conjugated polymer based NIR-II nanoparticles, viz. co-benzobisthiadiazole-dithienosilole (size 40-60 nm; zeta potential ~ -39 mV) with narrow bandgap was synthesized as cancer theranostics with superior photostability and photothermal conversion efficiency of 65%.³⁷ The nanoparticles exhibit significant photoacoustic imaging contrast augmenting capacity (1064 nm laser irradiation), excellent active targeting ability

and showed good PTT efficiency with a no recurrence tumor removal efficiency of 100% (in both in vitro and in vivo).

Conjugated polymers have also been combined with other nanoparticulate species to further improve their theranostic properties. For instance, poly(p-phenylene-co-cyclodextrin)-g-poly(ethylene glycol) conjugated polymer theranostics (size 114.4 ± 48.48 nm; zeta potential -31.8 ± 11.1 mV) was developed for use as fluorescent imaging and radiotherapy agent in cancer treatment (using U87 human primary glioblastoma cell lines).³⁸ The graft copolymer was further conjugated with Au nanoparticles which were observed to induce considerable enhancement in the radiotherapy efficiency, where otherwise unconjugated sample showed very less therapeutic efficiency. In another instance, conjugated polymer nanoparticles based theranostic nanomedicine (size ~ 105 nm; zeta potential $+0.8$ mV) with photoacoustic, NIR fluorescence and MRI-guided cancer PTT was developed by chelating gadolinium to the conjugated polymer of poly (fluorene-thiadiazoloquinoline)-poly(ethylene glycol), where chelated Gd^{3+} ions introduced MRI characteristics to the conjugated polymer nano-theranostic.³⁹

Other Polymer Nano-Constructs as Cancer Theranostics

Apart from these important nano-architectures, other polymeric nano-constructs such as hydrogels,⁴⁰ nanogels,⁴¹ and mesoporous,⁴² have also been studied as cancer theranostics. For instance, thermoresponsive injectable hydrogels of supramolecular poly(N-acryloyl glycinamide-co-acrylamide) (size 40 ± 5.3 nm; zeta potential ~ -11 mV) was fabricated for reconstructive mammoplasty and local therapy of breast cancer.⁴⁰ The hydrogel, additionally, bears polydopamine-coated gold nanoparticles and doxorubicin that delivers excellent photothermal and chemotherapeutic effects, respectively. The presence of Au nanoparticles assists in CT imaging. Gelation of the injected supramolecular polymer nanocomposite sol could be achieved in the resected cancerous breast cavity, thus acting as breast filler, avoiding the recurrence of breast cancer, and facilitating breast reconstruction. In a different approach, a special “*in situ* framework growth” technique was adopted to develop hollow mesoporous phototheranostic nanoparticles (size ~ 40 nm) for cancer treatment that involves co-hydrolysis of PEG₂₀₀₀-perylene diimide-silane and silica/organosilica precursors during the preparation of hollow mesoporous organosilica.⁴² *In situ* polymerization in the hollow structure produces thermosensitive polymer in the cavities that significantly enhances the drug loading capacity (hydrophobic drug SN38)

Table 1. Characteristics of various Polymer Nano-Constructs Used as Cancer Theranostics.

Polymer structure	Commonly used polymer type	Synthesis technique	Shape
Vesicles	Amphiphilic polymer	Self-assembly technique	Hollow sphere
Micelles	Amphiphilic polymer	Self-assembly technique	Hollow sphere
Hyperbranched polymers	Hydrophilic polymer	One-step polymerization	Asymmetrical dendritic architectures
Nanoparticles	Conjugated polymer	Solvent evaporation and nanoprecipitation	Spherical

Table 2. Few Clinical Trial Studies of Cancer Treatment Using Polymeric Nano-Constructs.

Study title	Conditions	Status	Assigned number
A trial of paclitaxel (Genexol®) and cisplatin versus paclitaxel-loaded polymeric micelle (Genexol-PM®) and cisplatin in advanced non-small-cell lung cancer	Non-small-cell lung cancer	Completed	NCT01023347
Clinical study examining the safety and efficacy of doxorubicin drug eluting microspheres transarterial embolization in the setting of hepatocellular carcinoma (HCC)	Hepatocellular carcinoma	Completed	NCT01116635
Study of CRLX101 (NLG207) in the treatment of advanced solid tumors	Solid tumor	Completed	NCT00333502
MucoLox formulation to mitigate mucositis symptoms in head/neck cancer	Head and neck cancer	Recruiting	NCT03461354
Effects of triptorelin when given every 6 months under the skin to adult males with cancer in the prostate (TriptoSwitch)	Prostate cancer	Recruiting	NCT05458856
Pilot trial of CRLX101 in treatment of patients with advanced or metastatic stomach, gastroesophageal, or esophageal cancer that cannot be removed by surgery	Adenocarcinoma of the esophagus	Completed	NCT01612546

and their release under NIR laser irradiation. The hollow mesoporous phototheranostics showed synergistic photothermal/chemotherapy effects and exhibit excellent fluorescence and photoacoustic imaging capabilities. Additionally, chemical chelation of organosilica shell with ^{64}Cu isotope bestows PET imaging abilities. In similar approach, Hanafy and co-workers developed multi branched/flower like shaped⁴³ and elongated spherical shaped⁴⁴ theranostic systems comprising of curcumin with mucoadhesive polymer (carboxymethyl cellulose) and chitosan-polyelectrolyte pairs (protamine and dextran) for treatment of liver and breast cancer, respectively.

The tremendous scientific research in the area of polymer nano-construct theranostics has inspired for their clinical investigation to progress in the direction of cancer treatment. Clinical trials involve several steps (viz. Phases I, II, III, and IV) as discussed in the review article by Essa et al.⁴⁵ Table 2 lists few polymer nano-constructs that have completed or are undergoing clinical trial studies for cancer treatment.

Conclusions

In conclusion, biocompatible polymers with nanoscale architectures have been a rising star of cancer theranostics. The future is also bright as tremendous research efforts have been focused on their design, synthesis and assessment of their applicability as theranostic platforms that could eventually be translated into the clinic. We envisage that this mini review presents an impetus to the scientific community and provides novel perspectives into polymeric theranostics for cancer treatment.

Author's Contribution

HK wrote the manuscript. MP reviewed and edited the manuscript. All authors revised the manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Our study did not require an ethical board approval because it did not contain human or animal trials.

ORCID iD

Himani Kalita  <https://orcid.org/0000-0001-6494-5669>

References

- Guo B, Sheng Z, Hu D, et al. Molecular engineering of conjugated polymers for biocompatible organic nanoparticles with highly efficient photoacoustic and photothermal performance in cancer theranostics. *ACS Nano*. 2017;11(10):10124-10134. doi: 10.1021/acsnano.7b04685
- Ali I, Alsehli M, Scotti L, et al. Progress in polymeric nanomedicines for theranostic cancer treatment. *Polymers (Basel)*. 2020;12(3):598. doi: 10.3390/polym12030598
- Jaymand M. Chemically modified natural polymers-based theranostic nanomedicines: Are the golden gate toward *de novo* clinical approach against cancer? *ACS Biomater Sci Eng*. 2020;6(1):134-166. doi: 10.1021/acsbmaterials.9b00802
- Upponi JR, Jerajani K, Nagesha DK, et al. Polymeric micelles: Theranostic co-delivery system for poorly water-soluble drugs and contrast agents. *Biomaterials*. 2018;170:26-36. doi: 10.1016/j.biomaterials.2018.03.054
- Indoria S, Singh V, Hsieh MF. Recent advances in theranostic polymeric nanoparticles for cancer treatment: A review. *Int J Pharm*. 2020;582:119314. doi: 10.1016/j.ijpharm.2020.119314
- Jędrzak A, Grześkowiak BF, Coy E, et al. Dendrimer based theranostic nanostructures for combined chemo- and photothermal therapy of liver cancer cells in-vitro. *Colloids Surf B Biointerfaces*. 2019;173:698-708. doi: 10.1016/j.colsurfb.2018.10.045
- Prabhakar A, Banerjee R. Nanobubble liposome complexes for diagnostic imaging and ultrasound-triggered drug delivery in

- cancers: A theranostic approach. *ACS Omega*. 2019;4(13):15567-15580. doi: 10.1021/acsomega.9b01924
8. Moroz A, Wang YH, Sharib JM, et al. Theranostic targeting of CUB domain containing protein 1 (CDCP1) in pancreatic cancer. *Clin Cancer Res*. 2020;26(14):3608-3615. doi: 10.1158/1078-0432
 9. Mostafavi E, Irvani S, Varma RS, Khatami M, Rahbarizadeh F. Eco-friendly synthesis of carbon nanotubes and their cancer theranostic applications. *Mater Adv*. 2022;3(12):4765-4782. doi: 10.1039/D2MA00341D
 10. Li J, Chen T. Transition metal complexes as photosensitizers for integrated cancer theranostic applications. *Coord Chem Rev*. 2020;418:213355. doi: 10.1016/j.ccr.2020.213355
 11. Tade RS, Patil PO. Theranostic prospects of graphene quantum dots in breast cancer. *ACS Biomater Sci Eng*. 2020;6(11):5987-6008. doi: 10.1021/acsbmaterials.0c01045
 12. Sarcan ET, Silindir-Gunay M, Ozer AY. Theranostic polymeric nanoparticles for NIR imaging and photodynamic therapy. *Int J Pharm*. 2018;551(1-2):329-338. doi: 10.1016/j.ijpharm.2018.09.019
 13. Zhu Y, Yang B, Chen S, Du J. Polymer vesicles: Mechanism, preparation, application, and responsive behavior. *Prog Polym Sci*. 2017;64:1-22. doi: 10.1016/j.progpolymsci.2015.05.001
 14. Wang F, Xiao J, Chen S, et al. Polymer vesicles: Modular platforms for cancer theranostics. *Adv Mater*. 2018;30(17):1705674. doi: 10.1002/adma.201705674
 15. Zhou X, Yan N, Cornel EJ, et al. Bone-targeting polymer vesicles for simultaneous imaging and effective malignant bone tumor treatment. *Biomaterials*. 2021;269:120345. doi: 10.1016/j.biomaterials.2020.120345
 16. de Oliveira DCS, de Freitas CF, Calori IR, et al. Theranostic verteporfin-loaded lipid-polymer liposome for photodynamic applications. *J Photochem Photobiol B Biol*. 2020;212:112039. doi: 10.1016/j.jphotobiol.2020.112039
 17. Yao C, Li Y, Wang Z, Song C, Hu X, Liu S. Cytosolic NQO1 enzyme-activated near-infrared fluorescence imaging and photodynamic therapy with polymeric vesicles. *ACS Nano*. 2020;14(2):1919-1935. doi: 10.1021/acsnano.9b08285
 18. Ge X, Fu Q, Su L, et al. Light-activated gold nanorod vesicles with NIR-II fluorescence and photoacoustic imaging performances for cancer theranostics. *Theranostics*. 2020;10(11):4809-4821. doi:10.7150/thno.44376
 19. Liu Q, Chen S, Chen J, Du J. An asymmetrical polymer vesicle strategy for significantly improving T1 MRI sensitivity and cancer-targeted drug delivery. *Macromolecules*. 2015;48(3):739-749. doi: 10.1021/ma502255s
 20. Hsu CY, Nieh MP, Lai PS. Facile self-assembly of porphyrin-embedded polymeric vesicles for theranostic applications. *Chem Commun*. 2012;48(75):9343-9345. doi: 10.1039/C2CC33851C
 21. Yang C, Huang S, Wang X, Wang M. Theranostic unimolecular micelles of highly fluorescent conjugated polymer bottlebrushes for far red/near infrared bioimaging and efficient anticancer drug delivery. *Polym Chem*. 2016;7(48):7455-7468. doi: 10.1039/C6PY01838F
 22. Pan GY, Jia HR, Zhu YX, Sun W, Cheng XT, Wu FG. Cyanine-containing polymeric nanoparticles with imaging/therapy-switchable capability for mitochondria-targeted cancer theranostics. *ACS Appl Nano Mater*. 2018;1(6):2885-2897. doi: 10.1021/acsanm.8b00527
 23. Hanafy NAN, Quarta A, Ferraro MM, et al. Polymeric nanomicelles as novel cargo-carriers for LY2157299 liver cancer cells delivery. *Int J Mol Sci*. 2018;19(3):748. doi:10.3390/ijms19030748
 24. Fang J, Šubr V, Islam WM, et al. N-(2-hydroxypropyl)methacrylamide polymer conjugated pyropheophorbide, a promising tumor-targeted theranostic probe for photodynamic therapy and imaging. *Eur J Pharm Biopharm*. 2018;130:165-176. doi:10.1016/j.ejpb.2018.06.005
 25. Kim YH, Webster OW. Hyperbranched polyphenylenes. *Macromolecules*. 1992;25(21):5561-5572. doi: 10.1021/ma00047a001
 26. Yi X, Xu M, Zhou H, et al. Ultra-small hyperbranched semiconducting polymer nanoparticles with different radioisotopes labeling for cancer theranostics. *ACS Nano*. 2018;12(9):9142-9151. doi: 10.1021/acsnano.8b03514
 27. Hu X, Liu G, Li Y, Wang X, Liu S. Cell-penetrating hyperbranched polyprodrug amphiphiles for synergistic reductive milieu-triggered drug release and enhanced magnetic resonance signals. *J Am Chem Soc*. 2015;137(1):362-368. doi: 10.1021/ja5105848
 28. Pearce AK, Simpson JD, Fletcher NL, et al. Localised delivery of doxorubicin to prostate cancer cells through a PSMA-targeted hyperbranched polymer theranostic. *Biomaterials*. 2017;141:330-339. doi: 10.1016/j.biomaterials.2017.07.004
 29. Zhao Y, Houston ZH, Simpson JD, et al. Using peptide aptamer targeted polymers as a model nanomedicine for investigating drug distribution in cancer nanotheranostics. *Mol Pharmaceutics*. 2017;14(10):3539-3549. doi: 10.1021/acs.molpharmaceut.7b00560
 30. Li G, Pei M, Li X, Liu P. Fluorescent traceable nanoparticles by co-self-assembly of carbon dot-drug conjugate and biodegradable hyperbranched polymer for diagnosis and therapy. *Particuology*. 2022;62:79-87. doi: 10.1016/j.partic.2021.04.016
 31. Jafari M, Abolmaali SS, Najafi H, Tamaddon AM. Hyperbranched polyglycerol nanostructures for anti-biofouling, multifunctional drug delivery, bioimaging and theranostic applications. *Int J Pharm*. 2020;576:118959. doi: 10.1016/j.ijpharm.2019.118959
 32. Rahman M, Alrobaian M, Almalki WH, et al. Superbranched polyglycerol nanostructures as drug delivery and theranostics tools for cancer treatment. *Drug Discov Today*. 2021;26(4):1006-1017. doi: 10.1016/j.drudis.2020.11.007
 33. Heckert B, Banerjee T, Sulthana S, et al. Design and synthesis of new sulfur-containing hyperbranched polymer and theranostic nanomaterials for bimodal imaging and treatment of cancer. *ACS Macro Lett*. 2017;6(3):235-240. doi: 10.1021/acsmacrolett.7b00008
 34. Yang J, Lu W, Xiao J, et al. A positron emission tomography image-guidable unimolecular micelle nanoplatfor for cancer theranostic applications. *Acta Biomater*. 2018;79:306-316. doi: 10.1016/j.actbio.2018.08.036

35. Yi X, Xu M, Zhou H, et al. Ultra-small hyperbranched semiconducting polymer nanoparticles with different radioisotopes labeling for cancer theranostics. *ACS Nano*. 2018;12(9):9142-9151. doi: 10.1021/acsnano.8b03514
36. Koralli P, Tsikalakis S, Goulielmaki M, et al. Rational design of aqueous conjugated polymer nanoparticles as potential theranostic agents of breast cancer. *Mater Chem Front*. 2021;5(13):4950-4962. doi: 10.1039/D1QM00479D
37. Wei Z, Xin F, Zhang J, et al. Donor-acceptor conjugated polymer-based nanoparticles for highly effective photoacoustic imaging and photothermal therapy in the NIR-II window. *Chem Commun*. 2020;56(7):1093-1096. doi: 10.1039/C9CC07821E
38. Barlas FB, Aydindogan E, Arslan M, Timur S, Yagci Y. Gold nanoparticle conjugated poly(p-phenylene- β -cyclodextrin)-graftpoly(ethylene glycol) for theranostic applications. *J Appl Polym Sci*. 2019;136(12):47250. doi: 10.1002/app.47250
39. Hu X, Tang Y, Hu Y, et al. Gadolinium-chelated conjugated polymer-based nanotheranostics for photoacoustic/magnetic resonance/NIR-II fluorescence imaging-guided cancer photothermal therapy. *Theranostics*. 2019;9(14):4168-4181. doi:10.7150/thno.34390
40. Wu Y, Wang H, Gao F, Xu Z, Dai F, Liu W. An injectable supra-molecular polymer nanocomposite hydrogel for prevention of breast cancer recurrence with theranostic and mammoplastic functions. *Adv Funct Mater*. 2018;28(21):1801000. doi: 10.1002/adfm.201801000
41. Vijayan VM, Beeran AE, Shenoy SJ, Muthu J, Thomas V. New magneto-fluorescent hybrid polymer nanogel for theranostic applications. *ACS Appl Bio Mater*. 2019;2(2):757-768. doi: 10.1021/acscabm.8b00616
42. Yang Z, Fan W, Zou J, et al. Precision cancer theranostic platform by in situ polymerization in perylene diimide-hybridized hollow mesoporous organosilica nanoparticles. *J Am Chem Soc*. 2019;141(37):14687-14698. doi: 10.1021/jacs.9b06086
43. Hanafy NAN, Leporatti S, Kemaary ME. Mucoadhesive curcumin crosslinked carboxy methyl cellulose might increase inhibitory efficiency for liver cancer treatment. *Mat Sci Eng C*. 2020;116:111119. doi: 10.1016/j.msec.2020.111119
44. Hanafy NAN. Optimally designed theranostic system based folic acids and chitosan as a promising mucoadhesive delivery system for encapsulating curcumin LbL nano-template against invasiveness of breast cancer. *Int J Bio Macro*. 2021;182:1981-1993. doi: 10.1016/j.ijbiomac.2021.05.149
45. Essa ML, El-Kemaary MA, Saied EME, Leporatti S, Hanafy NAN. Nano targeted therapies made of lipids and polymers have promising strategy for the treatment of lung cancer. *Materials (Basel)*. 2020;13(23):5397. doi:10.3390/ma13235397