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Advanced disease therapeutics using engineered living drug delivery systems

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Biological barriers significantly impede the delivery of nanotherapeutics to diseased tissues, diminishing therapeutic efficacy across pathologies such as cancer and inflammatory disorders. Although conventional strategies integrate multifunctional designs and molecular components into nanomaterials (NMs), many approaches remain insufficient to overcome these barriers. Key challenges, including inadequate drug accumulation at target sites and nonspecific biodistribution, persist in nanotherapeutic development. NMs, which harness the ability to precisely modulate drug delivery spatiotemporally and control release kinetics, represent a transformative platform for targeted cancer therapy. In this review, we highlight the biological obstacles limiting effective cancer treatment and evaluate how stimuli-responsive NMs address these constraints. By leveraging exogenous and endogenous stimuli, such NMs improve therapeutic specificity, reduce off-target effects, and amplify drug activity within pathological microenvironments. We systematically analyze the rational design and synthesis of stimuli-responsive NMs, driven by advances in oncology, biomaterials science, and nanoscale engineering. Furthermore, we highlight advances across NM classes-including polymeric, lipid-based, inorganic, and hybrid systems and explore functionalization approaches using targeting ligands, antibodies, and biomimetic coatings. Diverse delivery strategies are evaluated, such as small-molecule prodrug activation, peptide- and protein-based targeting, nucleic acid payloads, and engineered cell-mediated transport. Despite the promise of stimuli-responsive NMs, challenges such as biocompatibility, scalable fabrication, and clinical translation barriers must be addressed. By elucidating structure–function relationships and refining stimulus-triggered mechanisms, these NMs pave the way for transformative precision oncology strategies, enabling patient-specific therapies with enhanced efficacy and safety. This synthesis of interdisciplinary insights aims to catalyze innovation in next-generation nanomedicine for cancer treatment.

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1. Introduction

Cancer remains a significant global health burden, evidenced by increasing malignancy incidence and mortality rates. Approximately 10 million individuals succumb to cancer annually.[1,2] In 2023, the United States anticipated 1.89 million new cancer cases and 619 321 cancer-related deaths, translating to nearly 1665 fatalities daily. The global oncology market, valued at US$ 203.42 billion in 2022, is projected to exceed US$ 470.61 billion by 2032, demonstrating a remarkable Compound Annual Growth Rate of 8.8% from 2023 to 2032.[3] Chemotherapy remains a cornerstone of cancer treatment due to its established efficacy.[4,5] However, limitations such as non-selective cytotoxicity, challenges in precise drug delivery to tumor sites, and the emergence of multi-drug resistance hinder its effectiveness. The complex tumor microenvironment and inter-individual variability further complicate the development of effective therapeutic strategies.[6,7]

To address these challenges, researchers have explored innovative drug delivery strategies. Stimuli-responsive nanomaterials (NMs) have emerged as a promising paradigm in cancer therapy, offering a distinct advantage over conventional NMs. Unlike conventional NMs, stimuli NMs can be activated by specific stimuli, enabling targeted drug delivery to precise locations.[8] These intelligent NMs efficiently aggregate at the desired site upon exposure to specific factors, releasing their therapeutic payloads and establishing an intelligent treatment modality.[9–11] Furthermore, their ability to co-deliver therapeutics and diagnostic agents has significantly advanced the fields of theranostics and NMs in cancer therapy.[12] A compre-

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hensive understanding of stimuli NMs necessitates a multidimensional exploration. Analogous to a versatile toolbox, stimuli nanoparticles (NPs) can be modified in terms of size, shape, surface properties, targeting capabilities, and composition in response to endogenous and exogenous cellular stimuli (Fig. 1A).[13,14] The selection of nanocarriers, the responsiveness of stimuli NMs to various stimuli, their tumor-targeting capabilities through surface functionalization, and their ability to deliver diverse drug types are crucial considerations in their design and application.

Furthermore, advocating for a rational design approach in crafting stimuli-responsive NMs, while leveraging state-of-the-art nanocarrier utilization, enhances the capability and complexity of these pioneering nanoscale technologies. Additionally, a deep understanding of the interplay between malignant tumors and the human immune system and the resulting systemic immunological effects has underpinned the development and implementation of various immunotherapy approaches in contemporary cancer treatment (Fig. 1B). This comprehensive review explores the multifaceted nature of stimuli NMs, likening them to a versatile toolbox with dynamic capabilities, positioned to revolutionize drug delivery and cancer treatment. This heralds a new era of precision medicine, offering immense potential for advancements in cancer therapeutics.

2. Type of stimuli nanomaterials/ nanocarriers

Stimuli-responsive nanomaterials (NMs) predominantly utilize drug nanocarriers to achieve controlled therapeutic release. To function as optimal stimulus-responsive agents, nanostructures must exhibit the following functional attributes: (1) rapid responsiveness to disease-specific physiological or external triggers, (2) high therapeutic payload capacity with retention stability, (3) retention of structural integrity under physiological conditions to govern spatiotemporal release kinetics, (4) tunable surface charge to enhance cellular internalization and tissue-specific targeting, (5) negligible off-target effects and biocompatible degradation into non-toxic byproducts, and (6) suppression of immunogenic or cytotoxic responses. Current research focuses on four primary classes of nanocarriers (Fig. 2): polymer-based NMs, including micelles and

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Dr Mamidi is a distinguished scientist at the University of Wisconsin–Madison, USA, where his research focuses on the development and validation of innovative nanobiomaterials and nanotherapeutics to enhance their therapeutic efficacy in cancer immunotherapy and gene delivery. Previously, as an Assistant Professor at Tecnológico de Monterrey (Tec), Dr Mamidi's team has engineered advanced biomaterials with customizable properties for diverse applications, including drug delivery, orthopedic implants, tissue engineering, and biomedical devices. His translational research emphasizes tissue–material interactions under clinically relevant conditions, accelerating the transition of innovative technologies from bench to bedside. With over 58 peer-reviewed publications in prestigious journals, his work has garnered more than 1750 citations, achieving an H-index of 26 and an i10-index of 43. His contributions have earned numerous accolades, including the 2015 Eli Lilly Award, the 2018 and 2021 National Research System (SNI) awards, and recognition as an outstanding professor at Tec in 2020. Beyond his research, Dr Mamidi actively serves in editorial roles for leading nanomedicine and biomaterials journals, reflecting his commitment to advancing scientific knowledge and fostering innovation. His interdisciplinary approach and dedication to translational science continue to shape the future of nanobiomaterials and their therapeutic applications.

Fátima Franco De Silva

Fátima is a dynamic Food Engineer dedicated to bridging nutrition, biotechnology, and sustainability. A graduate of Tecnológico de Monterrey (Tec), Mexico, she pioneers science-driven innovations addressing metabolic disorders and nutritional deficiencies. Her academic work in Dr Mamidi's lab at Tec focused on bioactive compounds, leading to high-impact research that merges food science with biomedical insights to create functional foods for public health. Her published research integrates food science and biomedical insights, advancing functional foods for public health. Professionally, she collaborates with industry leaders to develop groundbreaking solutions. She led the creation of Pre-Meal, a high-fiber dietary product designed to mitigate postprandial glucose spikes, supporting diabetes management. This project combined nutritional analysis, regulatory compliance, and consumer-driven market research. Fátima also spearheaded a plant-based, folic acid-fortified beverage to combat micronutrient deficiencies. Her work ensured nutritional integrity, employing advanced preservation methods and scalable distribution strategies. With expertise in regulatory landscapes, product innovation, and market dynamics, Fátima drives food system advancements that prioritize health and sustainability. By merging scientific rigor with entrepreneurial vision, she continues to shape a future where nutrition innovation fuels societal progress.

dendrimers, enable versatile design and tunable responsiveness to diverse stimuli (*e.g.*, pH, temperature). Biomimetic NMs, such as protein-based NPs, liposomes, and cell membrane-derived vesicles, capitalize on inherent biocompatibility and natural ligand–receptor targeting mechanisms. Inorganic NMs–gold NPs, mesoporous silica NPs, iron oxide NPs, carbon nanotubes, and quantum dots (QDs) exhibit distinct physicochemical properties (*e.g.*, plasmonic resonance, magnetic responsiveness, photoluminescence) that synergize drug delivery with diagnostic imaging. Emerging materials, including metal–organic frameworks (MOFs) and two-dimensional black phosphorus, present novel opportunities for engineering advanced stimuli-responsive systems with high surface-area-to-volume ratios and multifunctional cargo-loading capacities.

2.1. Polymer-based stimuli nanocarriers

Polymeric NMs drive transformative biomedical advancements, enabling drug delivery, tissue engineering, and medical device breakthroughs.[15,16] These NMs outperform conventional drugs by enhancing stability, extending half-life, and enabling controlled release of nucleic acids, proteins, and biologics.[17] Techniques like emulsion polymerization and solvent evaporation facilitate their synthesis, while ongoing research refines manufacturing for customizable, sustained-release systems.[18] This progress has propelled polymeric NMs from lab to clinical trials, with phase II trials demonstrating their potential to revolutionize therapeutic delivery, marking a pivotal shift in biotechnology and medicine.[18] Versatile drug delivery systems activate through precise manipulation of thermal, electrical, magnetic, or ultrasound stimuli. Integrating biological response elements into polymer design enhances controlled therapeutic outcomes. Poly(D,L-lactic-*co*-glycolic acid) encapsulates diverse drugs, with release kinetics tunable *via* molecular weight, lactide-to-ethyl ester ratio, and drug concentration.[19] Structural modifications, such as methyl group incorporation, increase hydrophobicity and reduce degradation.[19] Polymeric NMs combine inorganic components (carbon nanotubes, graphene, silica) with organic compounds (proteins, lipids) to form composite NMs, altering properties like solubility, stability, and biological distribution, prolonging blood circulation.[20–22] Synthetic tunability enables stimuli-responsive NMs to co-encapsulate diverse compounds, addressing multiple therapeutic or imaging goals with distinct release profiles.[23] These NMs, combine biological and synthetic merits, enhance half-life, and stability, and reduce immunogenicity, as demonstrated by PEG–protein conjugates.[24]

(a) Micelles. Polymer micelles, ranging from tens to hundreds of nanometers, feature a hydrophobic core and a hydrophilic corona, enhancing water solubility for hydrophobic compounds.[25] Reverse micelles invert this structure. These nanostructures encapsulate both hydrophilic and hydrophobic drugs, enabling controlled release, reduced side effects, and protection from degradation.[26] Advances in synthetic chemistry allow stimuli-responsive micelles with targeted drug delivery and reactive release capabilities.[27] Long-circulating micelles exploit enhanced permeability and retention (EPR) effects to accumulate in tumor vasculature, offering promise in systemic cancer therapy.[26,27] Their versatility supports applications in tissue engineering and drug nanocarriers.[26] This phenomenon can improve the stability and bioavailability of insoluble and nearly insoluble drugs.[28,29] pH-sensitive micelles exploit tumor microenvironment acidity to enable controlled drug release, overcoming multi-drug resistance and minimizing systemic side effects through targeted delivery.[30–32] These micelles, combined with thermosensitive polymers, facilitate chemo-photothermal therapy by responding to acidic conditions and photothermal hyperthermia.[33] Their low toxicity and biocompatibility extend their utility to ocular drug delivery, where biodegradable micellar systems like ginsenosides Rb1 micelles enhance drug bioavailability and reduce irritation.[34] Similarly, Myricetin (Myr) encapsulated in PVCL-PVA-PEG micelles improves solubility, stability, corneal permeability, and therapeutic efficacy, demonstrating promise for treating ocular diseases.[35] Stealth-functionalized NPs further expand applications, highlighting the versatility of micellar systems in nanomedicine.[36,37]

Amin Orash Mahmoudsalehi

Amin is a PhD candidate in Nanotechnology at Tecnológico de Monterrey (Tec), Mexico, specializing in corneal tissue simulation and advanced biomaterials for corneal stromal regeneration. Initially trained in Dr Mamidi's lab at Tec, Amin has developed a multidisciplinary expertise in biomaterials, tissue engineering, electrospinning, scaffold fabrication, and drug delivery systems. His research extends beyond ophthalmology, exploring engineered living drug delivery systems for advanced disease therapeutics. Amin has secured competitive research grants from institutions such as Shahid Beheshti University of Medical Sciences and Isfahan University of Medical Sciences, enabling innovative work on biomaterial-based regenerative strategies. His contributions are documented in high-impact peer-reviewed publications, advancing knowledge in tissue engineering, regenerative medicine, and drug delivery. Actively engaged in international collaborations, Amin also serves as a reviewer for scientific journals, further solidifying his standing in the research community. Recognized for his academic excellence, Amin holds a fully funded scholarship from Tecnológico de Monterrey, underscoring his potential as a leader in nanotechnology and regenerative medicine. His work exemplifies the transformative impact of interdisciplinary research, bridging biomaterials science with clinical applications to address complex biomedical challenges. Amin's dedication to innovation and collaboration positions him as a promising contributor to the future of regenerative therapies and advanced drug delivery systems.

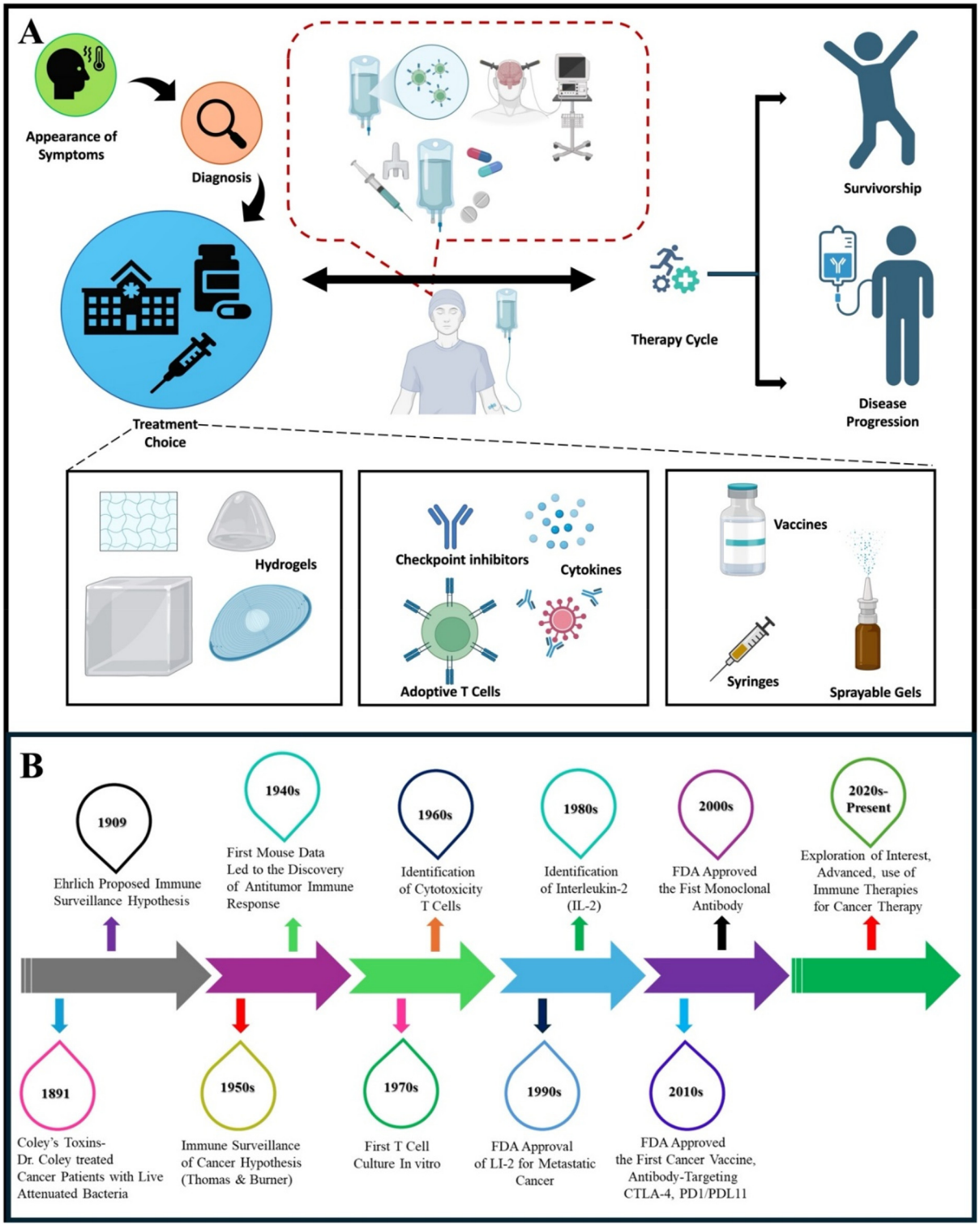

Fig. 1 (A) Therapeutic applications of various stimuli-responsive NMs for cancer treatment, and (B) key milestones that have influenced the historical evolution and advancements in immuno-oncology and immunotherapy.

(b) Dendrimers. Dendrimers feature radially symmetrical, nanoscale structures with tree-like branches, comprising inner and outer layers. The outer layer's functional groups enable drug conjugation and targeting, enhancing encapsulation efficiency, reducing toxicity, and enabling controlled release.[38,39] Synthesized *via* divergent or convergent methods, dendrimers exhibit tunable properties, including nanoscale size, high branching, water solubility, and biocompatibility,

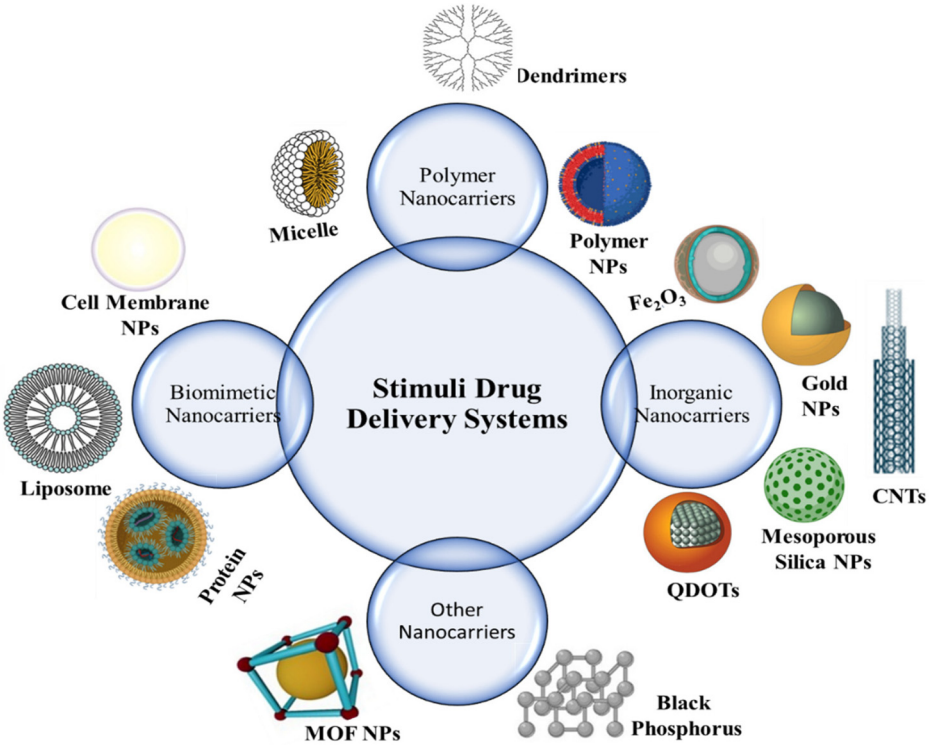

Fig. 2 Illustration of most commonly used stimuli-responsive nanocarriers for cancer treatment and other diseases.

making them ideal for pharmaceutical applications.[40–42] Their internal cavities and polyvalency improve drug solubility, reduce toxicity, and enhance potency, addressing challenges like water insolubility in anti-cancer APIs.[43–45] For instance, carbo-silane dendrimers enhance lipophilic cargo compatibility, while poly-amidoamine dendrimers facilitate blood–brain barrier penetration.[44,45] Polylysine dendrimers deliver cytotoxic drugs to tumors, demonstrating biodegradability and efficacy.[46] Dendrimers overcome drug resistance, toxicity, and controlled release challenges, positioning them as stimuli-responsive NMs with significant potential in cancer therapy and genetic material delivery.[47–50] the design and preparation techniques of the dendrimers were presented in Fig. 3.[49,50] Their versatility and unique properties underscore their promise in advanced drug delivery systems.

2.2. Biomimetic stimuli nanocarriers

Biomimetic smart nanocarriers represent a cutting-edge class of delivery systems engineered to emulate biological structures and functionalities, thereby enabling targeted drug delivery and therapeutic interventions. These nanocarriers are designed with biomimetic features, such as cell membrane coatings, site-specific targeting ligands, and stimuli-responsive behaviors, facilitating their effective interaction with biological systems. By leveraging these attributes, they can evade immune detection, selectively target specific cells or tissues, and achieve controlled release of therapeutic payloads. Furthermore, their design prioritizes biocompatibility and biodegradability, ensuring minimal systemic toxicity and adverse effects. Such advancements hold considerable promise for revolutionizing nanomedicine by enhancing the precision and efficacy of drug delivery (Fig. 4).[51,52]

(a) Protein nanomaterials. Protein-based NMs, derived from sources such as egg white, bovine serum, and human serum, offer facile synthesis, high drug-binding capacity, biocompatibility, biodegradability, and extended plasma half-life.[53] Their surface functional groups enable ligand conjugation and stimuli-responsive modifications.[54–57] For instance, Wang *et al.* developed macrophage-targeting, chondroitin sulfate-coated zein NPs (Mag@CS-Zein NPs) embedded in hydrogel microspheres, demonstrating enhanced cellular uptake, sustained drug release, and efficacy in alleviating colitis in mice, highlighting their potential for ulcerative colitis therapy.[58] Protein NMs also facilitate hydrophobic drug transport *via* noncovalent binding and interact with glycoprotein receptors to aid transcytosis.[56] A notable example is Abraxane, an FDA-approved albumin-bound paclitaxel (130 nm) for metastatic breast cancer, showcasing clinical efficacy.[57–60]

(b) Liposomes. Liposomes are amphipathic NMs composed of phospholipid bilayers, featuring hydrophilic phosphate heads and hydrophobic fatty acid tails. Their cell-mimicking structure enables fusion with cell membranes, enhancing cellular drug uptake. Liposomes can encapsulate lipid-soluble drugs within their membranes and water-soluble drugs in their aqueous core.[61–64] They are classified into multi-

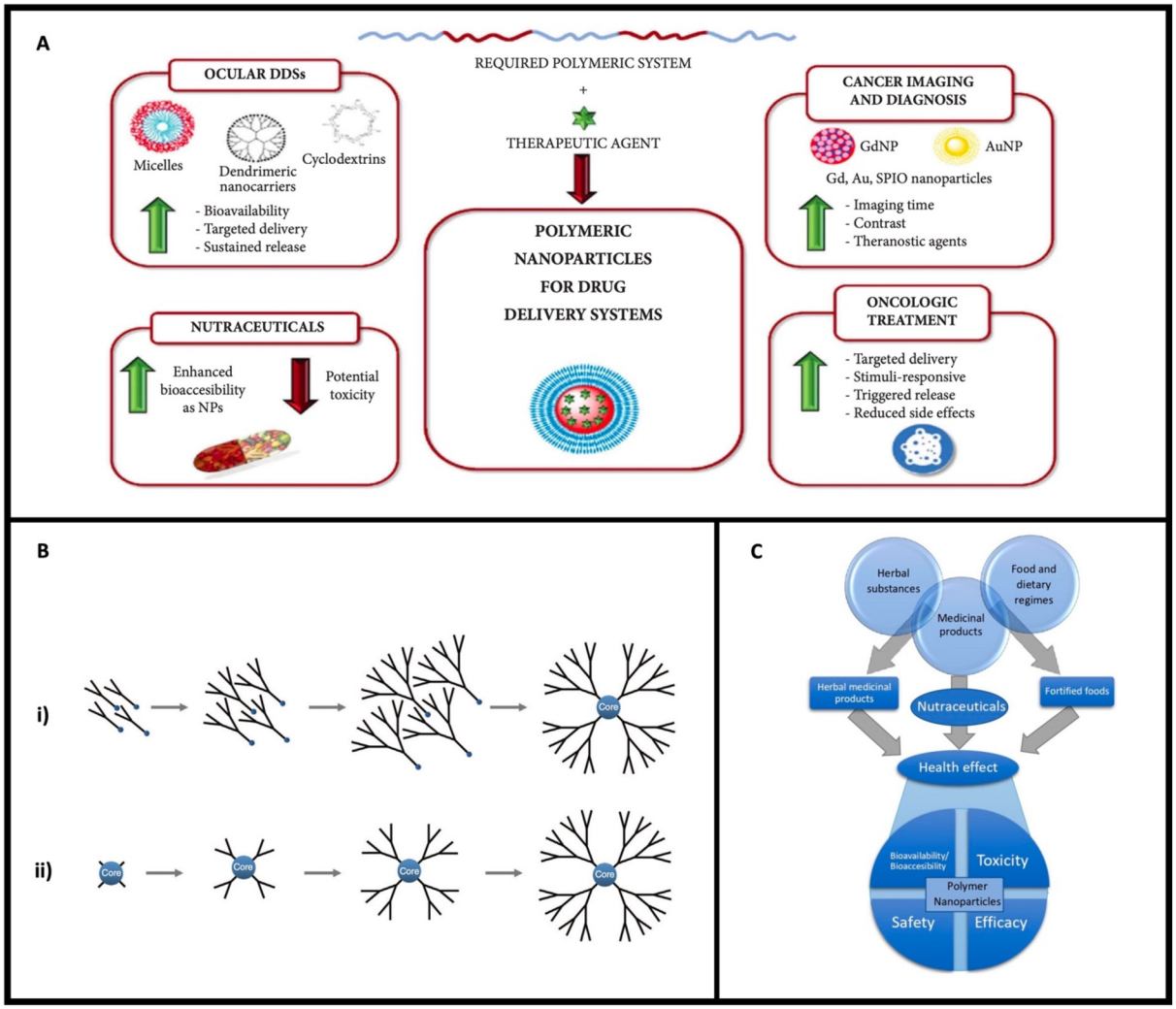

Fig. 3 (A) Use of polymeric nanoparticles for ocular drug delivery, for cancer diagnosis and treatment, as well as nutraceutical delivery. Reproduced with permission.[49] under the terms of the CC BY. © 2024 by the authors. (B) Representative synthetic routes for dendrimers: (i) convergent and (ii) divergent approaches. Reprinted with permission.[50] Copyright 2024, John Wiley and Sons. (C) Polymeric nanoparticles for nutraceuticals and different bioactive compounds for greater health and medical benefits. Reproduced with permission.[49] under the terms of the CC BY. © 2024 by the authors.

lamellar vesicles (MLVs) and uni-lamellar vesicles (ULVs), with ULVs further divided into large and small subgroups.[65] Traditional preparation methods, such as thin-film hydration and reverse-phase evaporation,[66] are limited by instability, low drug loading, rapid release, and short circulation times (Fig. 5).[67,68] Advanced techniques, including supercritical fluid technologies, address these limitations.[69] Functionalization strategies, such as PEGylation, improve stability and prolong circulation by evading the reticuloendothelial system.[70] Stimuli-responsive liposomes, sensitive to pH, enzymes, redox, light, or ultrasound, enable targeted drug release.[71] Radiolabeled liposomes facilitate tumor imaging and therapy while monitoring biodistribution.[72,73] Liposomes also co-deliver chemotherapeutics, imaging agents, and gene-editing tools,[74] with lipid nanoparticles (LNPs) enhancing tumor delivery and gene editing efficiency *via* Cas9 mRNA, FAK siRNA, and sgRNA co-delivery.[75] Prasad *et al.* developed light-triggered liposomes (NFGL) loaded with gold NPs and graphene quantum dots, demonstrating near-infrared (NIR)-mediated tumor reduction and ROS scavenging for cancer theranostics.[76] Table 1 highlights FDA-approved liposomal cancer drugs, underscoring their clinical relevance.[67,68,74–77]

2.3. Cell membrane-based drug delivery systems

Conventional NMs often encounter limitations such as rapid clearance from circulation, immune system recognition, and insufficient accumulation at target sites.[78] To overcome these challenges, cell membrane coating has emerged as an innovative strategy.[79–85] Cell membrane-coated NPs (CMCNPs) employ a biomimetic design, combining a nanoparticle core with a membrane derived from various cell types, including stem cells, cancer cells, white blood cells, or platelets

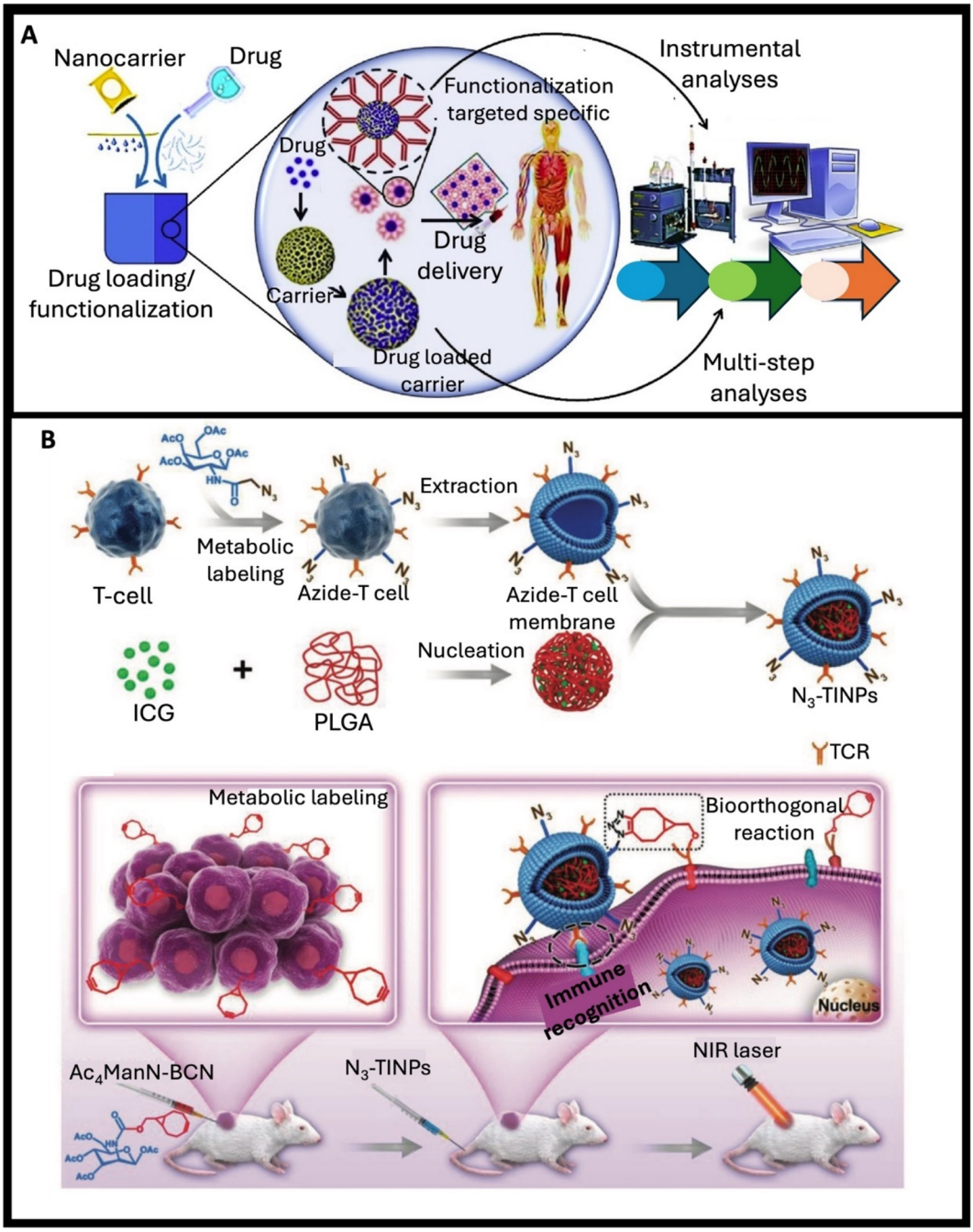

Fig. 4 (A) A schematic representation of drug-loaded nanocarriers for the targeted delivery to deal with a diseased cell. Reproduced with permission.[51] Copyright 2024, Elsevier. (B) Schematic illustration of N_3-labeled T cell membrane-biomimetic nanoparticles with a dual-targeting mechanism for highly efficient photothermal therapy. Reprinted with permission.[52] Copyright 2024, John Wiley and Sons.

(Fig. 6).[86–89] The typical preparation process involves isolating plasma membranes from selected cell sources and encapsulating core NMs within membrane vesicles. These biomimetic CMCNPs, with their tunable nanomaterial properties, represent a promising class of stimuli-responsive NMs for targeted cancer therapy, attracting considerable attention.[84] For instance, platelet membrane-coated NMs co-loaded with Doxorubicin internally and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) externally have demonstrated significant anticancer efficacy in animal models with both subcutaneous tumors and metastatic lesions, highlighting their therapeutic potential.[85,90]

2.4. Inorganic stimuli nanocarriers

(a) Gold nanomaterials. Gold NMs have emerged as prominent tools in nanotechnology and medicine due to their inimi-

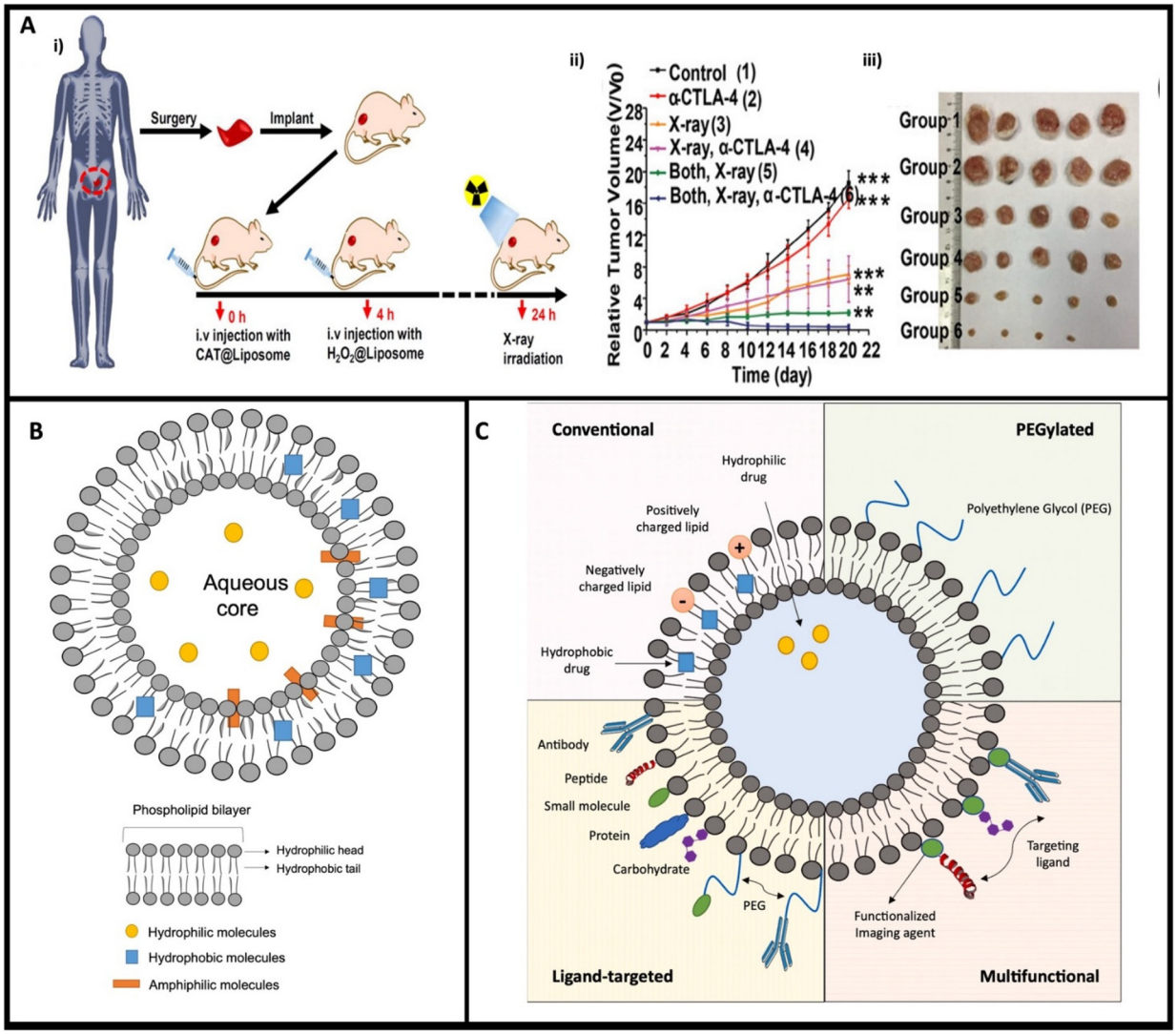

Fig. 5 (A) (i) Proposed mechanism for how to set up the *in vivo* PDX tumor model for radio-immunotherapy, (ii) tumor growth curves, and (iii) photos of tumors following various treatments in different mouse groups. Reprinted with permission.[67] Copyright 2024, American Chemical Society. (B) Representation of the general structure of liposomes and (C) Different types of liposomes used in therapeutic applications. Reproduced with permission.[68] Copyright 2024, Elsevier.

table properties, including high surface area, surface plasmon resonance, and multifunctionalization capabilities.[91] They have synthesized *via* physical, chemical, or biological methods, gold NMs exhibit non-toxicity, biocompatibility, and tumor-targeting efficiency, making them ideal for cancer therapy and diagnostics.[92,93] Biosynthesis using plants or microbes offers an eco-friendly alternative to chemical synthesis. Gold NMs, such as nanorods, nanocages, and nanostars, demonstrate exceptional optical and physical properties, enabling applications in photothermal therapy (PTT), photodynamic therapy (PDT), biosensing, and imaging.[94–97] For instance, Zhang *et al.* developed a Ti_3C_2-MXene Au nanocomposite for combined enzyme kinetics therapy, PTT, and dual-mode imaging, showcasing their versatility.[98] Their tunable surface chemistry allows functionalization with drugs, ligands, and genes, enhancing targeted delivery and therapeutic efficacy.[99–103] For example, glutamine- and lysine-modified gold NMs enable tumor-specific PTT *via* intratumor enzyme-catalyzed reactions.[100,101] Additionally, tumor-homing peptide-labeled gold NMs improve targeted drug delivery.[102–108] These tailored properties make gold NMs invaluable for molecular recognition, chemical sensing, imaging, and drug delivery (Fig. 7).[105–107]

(b) Mesoporous silica nanomaterials. Mesoporous silica nanoparticles (MSNs), characterized by pore diameters of 2–50 nm, are widely studied for their uniform porosity, high surface area, tunable particle size, and biocompatibility.[109,110] These properties enable efficient drug loading and functionalization, making MSNs ideal stimuli-responsive nanocarriers.[111] MSNs are categorized into mesoporous silica NMs and hollow/

Table 1 Liposomes promoted FDA-approved cancer drugs

Approval date	Drug	Commercial name	Treatment
Nov 17, 1995	DOX Hydrochloride	DOXIL	Ovarian cancer, AIDS-related Kaposi's Sarcoma, Multiple Myeloma
Apr 08, 1996	Daunorubicin Citrate	DaunoXome	HIV-associated Kaposi's sarcoma
Aug 11, 1997	Amphotericin B	AmBisome	Infections caused by *Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, *Candida krusei*, *Candida lusitaniae*, *Candida parapsilosis*, *Candida tropicalis*, *Cryptococcus neoformans*, and *Blastomyces dermatitidis*
Apr 01, 1999	Cytarabine	DepoCyt	Lymphomatous meningitis
May 29, 2002	Verteporfin	Visudyne	Classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis
May 18, 2004	Morphine sulfate	DepoDur	Analgesia after major surgery
Oct 28, 2011	Bupivacaine	EXPAREL	Postsurgical local analgesia, postsurgical regional analgesia by blocking brachial nerve plexus
Aug 09, 2012	Viincristine Sulfate	MARQIBO	Philadelphia chromosome-negative acute lymphoblastic leukemia
Oct 22, 2015	Irinotecan	ONIVYDE	metastatic pancreatic adenocarcinoma
Aug 3, 2017	Daunorubicin and Cytarabine	VYXEOS	Therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes
Sep 28, 2018	Amikacin	ARIKAYCE	Mycobacterium avium complex lung disease
Nov 16, 2023	Capivasertib	Truqap	Breast cancer
Nov 15, 2023	Repotrectinib	Augtyro	To treat ROS1-positive non-small cell lung cancer
Nov 8, 2023	Fruquintinib	Fruzaqla	To treat refractory, metastatic colorectal cancer
May 25, 2023	Flotufolastat F 18	Posluma	To use with positron emission tomography imaging in certain patients with prostate cancer
Jan 27, 2023	Elacestrant	Orserdu	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy

Table was generated using the FDA. Drugs. Fda.gov. **https://www.fda.gov/drugs**.[77]

rattle-type MSNs, synthesized *via* soft or hard template methods.[112] However, conventional MSNs face challenges such as nonspecific protein binding, hemolysis, and macrophage uptake, limiting their circulation half-life. PEGylation mitigates these issues by providing stealth properties.[113] Stimuli-responsive MSNs, functionalized with co-polymers or targeting ligands (*e.g.*, peptides, folate), enable controlled drug release in response to pH, redox, temperature, light, or enzymes.[114–117] For instance, temperature-responsive MSNs with gold nanodots facilitate precise molecular capture and on-demand release, highlighting their potential in biomedical applications.[114] These advancements underscore MSNs' versatility in targeted drug delivery and diagnostics.

(c) Iron oxide nanomaterials. Iron oxide NMs, including maghemite and magnetite, exhibit superparamagnetism at sizes of 10–20 nm, enabling magnetization under external magnetic fields without residual magnetism upon removal.[118,119] This property makes them valuable for magnetic resonance imaging (MRI) contrast enhancement. Synthesized *via* thermal decomposition, co-precipitation, hydrothermal, and other methods, iron oxide NMs are increasingly explored for targeted drug delivery using stimuli-responsive polymer coatings.[120] These coatings undergo physical and chemical transitions in response to temperature, pH, or magnetic fields, enabling controlled drug release.[121,122] For instance, polymer-coated iron oxide NMs demonstrate pH- and temperature-dependent behavior, allowing precise regulation.[123] Additionally, their cationic modifications facilitate nucleic acid transport, leveraging the negative charge of phosphate groups.[124] These properties position iron oxide NMs as versatile theranostic agents, combining diagnostic and therapeutic functionalities for advanced biomedical applications.

(d) Carbon nanotubes. Carbon nanotubes (CNTs), a class of carbon allotropes, are cylindrical structures formed from rolled graphene sheets, existing as single-walled (SWCNTs) or multi-walled (MWCNTs) variants.[125,126] Their unique NIR absorption properties make them ideal for photothermal ablation, while their ability to traverse cellular barriers enables targeted delivery.[127] CNTs are synthesized *via* methods such as chemical vapor deposition and laser ablation, though controlling size, purity, and mechanical strength remain challenging.[128] SWCNTs, with fewer structural defects, exhibit superior drug delivery capabilities compared to MWCNTs.[127] Functionalization enhances solubility, reduces toxicity, and prolongs circulation by evading the reticuloendothelial system.[129,130] For instance, PEGylated SWCNTs conjugated with cyclosporin A *via* cleavable ester bonds demonstrate effective drug delivery potential.[131] Functionalized CNTs can cross the blood–brain barrier, deliver nucleic acids (*e.g.*, siRNA, plasmid DNA), and enable thermal ablation of tumors.[132–136] Additionally, they serve as diagnostic tools for early cancer detection, highlighting their versatility in cancer theranostics.[129]

(e) Quantum dots. Quantum dots (QDs), discovered in 1981 by Ekimov and Onushchenko, are NMs renowned for their unique photochemical, optical, and electronic properties, stemming from the quantum confinement effect.[137] Initially employed for bioimaging, QDs have expanded into biosensing, drug delivery, theranostics, cancer immunotherapy, and gene therapy.[137] Despite their potential, few QDs are approved for

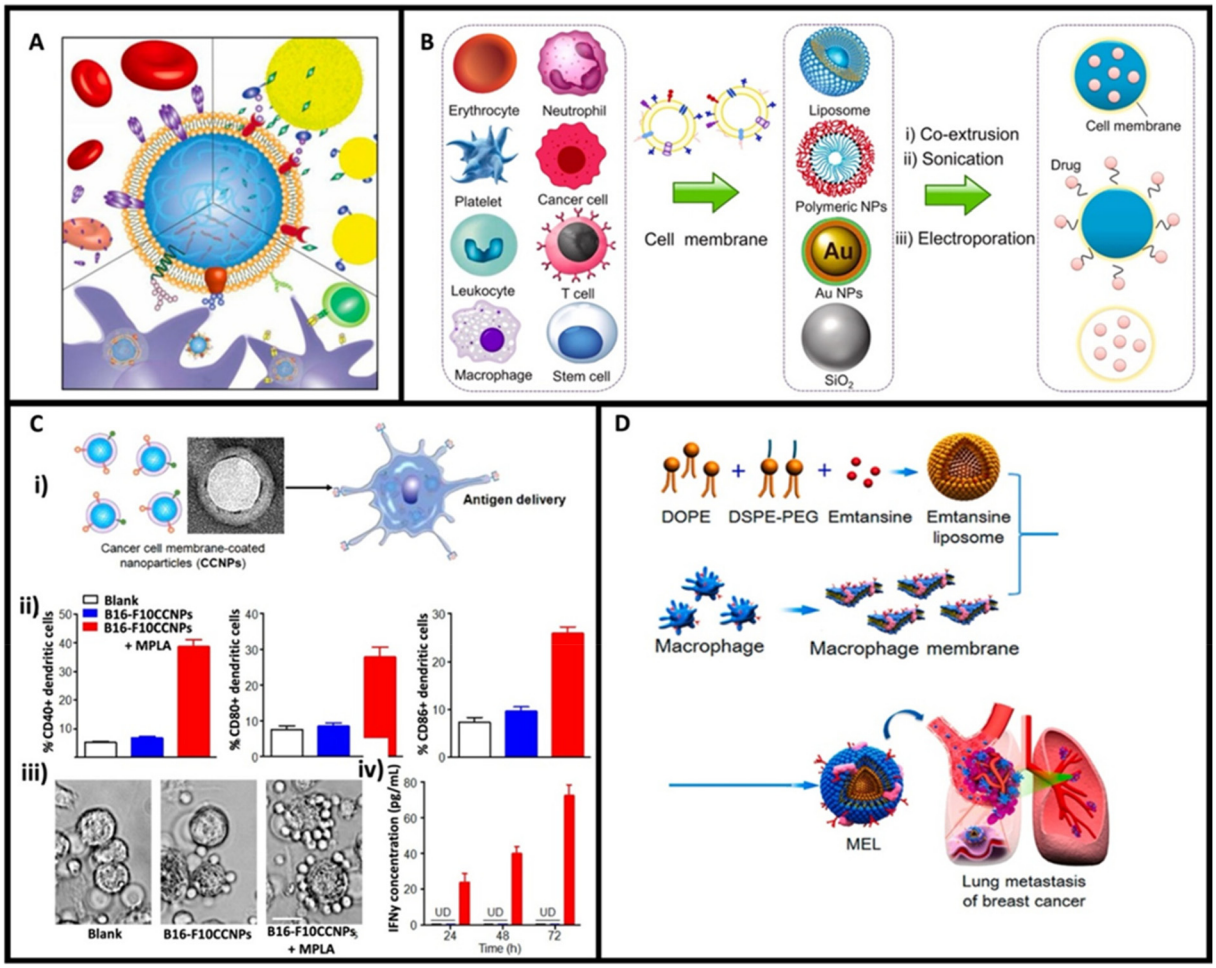

Fig. 6 (A) Three applications of cell membrane-coated nanoparticles. Reprinted with permission.[86] Copyright 2024, American Chemical Society. (B) Schematic representations of the various types and sources of cell-derived biomimetic NPs for cancer therapeutic drug delivery. Reproduced with permission.[87] Copyright 2024, Elsevier. (C) Cancer cell membrane-coated nanoparticles (CCNPs) for anticancer vaccination. (i) Depiction of CCNPs for antigen delivery to dendritic cells. (ii) Quantitative flow cytometry data of dendritic cell maturation when incubated for 48 hours with CCNPs coated with membrane from B16-F10 mouse melanoma cancer cells (B16-F10 CCNPs), with or without the adjuvant MPLA. (ii) Phase contrast microscopy images of splenocytes derived from pmel-1 transgenic mice when incubated with dendritic cells pulsed with B16-F10 CCNPs, with or without MPLA. Scale bar = 25 μm. (iv) IFNγ ELISA of supernatant collected from co-culture at 24, 48, and 72 hours. UD, undetectable by ELISA. Reprinted with permission.[88] Copyright 2024, American Chemical Society. (D) Macrophage membrane-coated nanoparticles for cancer chemical and photothermal therapy. MEL was designed by coating an isolated macrophage membrane onto the emtansine liposome to confer the biomimetic functions of the macrophage, thereby promoting the specific targeting ability of metastatic sites and improving the therapeutic effect on cancer metastasis. Reprinted with permission.[89] Copyright 2024, American Chemical Society.

medical use, though several are in clinical trials.[138,139] QDs enable real-time tumor monitoring during drug release,[140] with commercial QDs typically comprising a semiconductor core, a ZnS shell, and a capping layer.[141] Their small size (2–10 nm), flexible surface chemistry, and photophysical properties make them ideal for drug delivery tracking and surface modification.[142] QDs are synthesized *via* top-down methods (*e.g.*, molecular beam epitaxy) or bottom-up approaches (*e.g.*, colloidal self-assembly).[143] Functionalization is critical for QDs, as they are prone to nonspecific uptake by the reticuloendothelial system.[144] PEGylation enhances tumor accumulation *via* the enhanced permeability and retention (EPR) effect, while surface modification with ligands like peptides or folate enables active tumor targeting.[145] QDs' intrinsic fluorescence is leveraged for cancer imaging, exemplified by CISe/ZnS core–shell QDs doped with manganese and functionalized with folic acid, which exhibit high NIR-II fluorescence efficiency (31.2%) and MRI contrast.[146–149] Graphene quantum dots (GQDs), functionalized with TAT peptides and folic acid, demonstrate targeted anticancer activity by selectively damaging cancer cell DNA.[147–149,152–154] These advancements underscore QDs' versatility in cancer theranostics and imaging (Fig. 8).[150,151]

2.5. Other advanced stimuli nanomaterials

Beyond the previously discussed intelligent NMs that demonstrate advantages in cancer therapy, there is increasing scientific interest in recently developed advanced stimuli-responsive

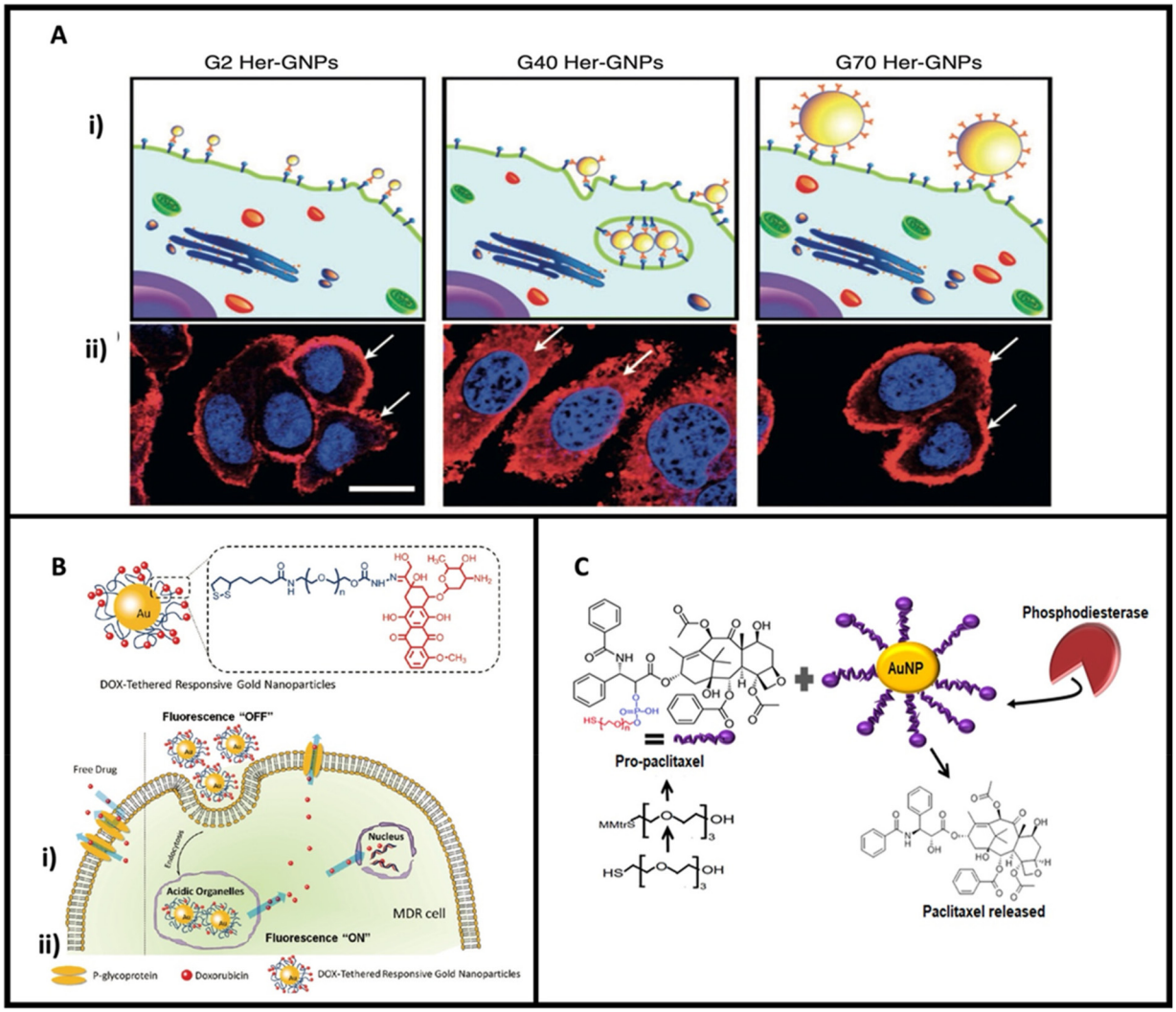

Fig. 7 (A) (i) Schematic and (ii) fluorescence images showing size-dependent uptake of gold nanoparticles (AuNPs) functionalized with herceptin antibodies. Reproduced with permission.[105] © 2024, Springer Nature. (B) (i) Schematic illustration of DOX-tethered responsive gold nanoparticles (Au NPs); (ii) schematic illustration of the cooperation between enhanced DOX cellular entry and a responsive intracellular release of DOX into the cells to overcome drug resistance. Reprinted with permission.[106] Copyright 2024, American Chemical Society. (C) Enzyme-mediated drug release from AuNPs. Reproduced with permission.[107] © 2024, Taylor & Francis Group.

NMs. Notable examples include metal–organic frameworks (MOFs), black phosphorus (BP), and topologically heterogeneous NMs, among others. These emerging NMs have attracted significant attention due to their peerless physicochemical properties and considerable potential for applications in cancer therapy.

(a) Metal–organic frameworks. Metal–organic frameworks (MOFs) are crystalline materials composed of metal ions or clusters linked by organic ligands, offering synthetic tunability and structural regularity.[154] These properties enable the integration of NMs and biomolecules into a unified framework, enhancing catalytic efficiency and preserving biomolecular activity in intracellular environments.[154] Multifunctional MOFs outperform individual components in cancer therapy, with their size and functions tailored through ligand design and *in situ* growth/postmodification of NMs or biomolecules.[155,156] MOFs are synthesized *via* solvothermal, mechanochemical, coprecipitation, microwave, and sonochemical methods, and their applications span photodynamic therapy (PDT), photothermal therapy (PTT), radiotherapy, chemotherapy, immunotherapy, and theranostics.[157] To address biocompatibility, MOFs are combined with functional materials to create multifunctional hybrids for cancer therapies, including PDT, PTT, immunotherapy, and combination therapy.[158] For instance, an endogenous copper-based MOF nanoenzyme synergized near-infrared PTT with chemodynamic therapy to treat colon cancer effectively.[159] This biomarker-triggered "turn-on" approach simplifies nanomedicine design and enhances targeted therapy. Another study developed a tumor-specific cascade nanoreactor combining ferrop-

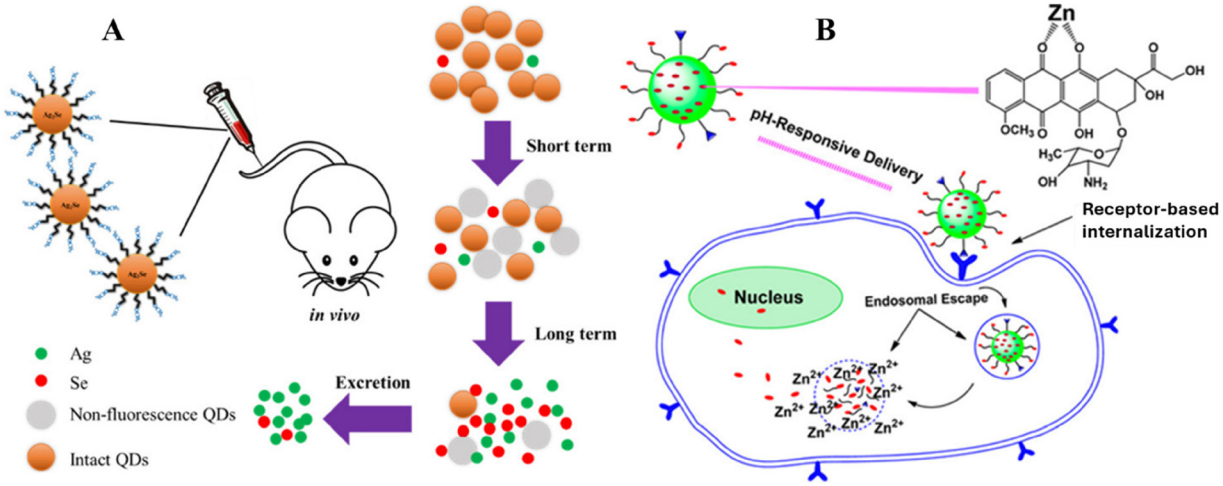

Fig. 8 (A) Graphical representation of the hyaluronic acid–ZnO quantum dots–dicarboxyl-terminated poly(ethylene glycol) (HA-ZnO-PEG) drug delivery system. Reprinted with permission.[150] Copyright 2024, American Chemical Society. (B) Scheme of aggregated QD formation. Reprinted with permission.[151] Copyright 2024, American Chemical Society.

tosis and starvation therapy. The membrane-coated nanoreactor demonstrated homologous targeting and immune evasion, accumulating specifically in tumors to improve therapeutic efficacy and safety through glucose depletion, nutrient cutoff, and Fenton reactions.[160] These advancements highlight the potential of MOFs in precision cancer therapy.[161–164]

(b) Black phosphorus. Black phosphorus (BP) has garnered considerable interest due to its unique physical, chemical, and biological properties.[165] As the most stable allotrope of phosphorus, BP features sp^3-hybridized phosphorus atoms arranged in vertically stacked, wrinkled layers stabilized by weak van der Waals interactions. Among these, high-energy mechanical milling (HEMM) is the most widely utilized method for producing BP-NMs.[165] These NMs exhibit exceptional biocompatibility and biodegradability, making them highly suitable for biomedical applications.[166,167] BP's distinctive photothermal properties, particularly under NIR radiation, enable its use in stimuli-responsive NMs for cancer photoacoustic (PA) imaging and photothermal therapy (PTT).[168,169] A notable advancement is the solventless HEMM approach, which yields water-soluble, biocompatible PEGylated BP NMs with high efficiency. These PEGylated BP NMs demonstrate uniform size distribution, high biocompatibility, photostability, and efficient heat generation under NIR light.[170,171] Consequently, they represent a promising class of nanotheranostic agents, offering significant potential for advancing PTT and PA imaging in cancer therapy. Researchers synthesize BP using various methods, such as mineralization routes, high-pressure techniques, and mechanical milling (Fig. 9).[172,173]

2.6. Topologically/precision heterogeneous nanomaterials

Nanoparticles (NPs) synthesized in laboratories often exhibit heterogeneity, either at the suspension level or within individual particles.[175,176] Organic and inorganic NPs in solution frequently vary in size, shape, morphology, and other properties, obscuring the identification of specific biological pathways influenced by these variations. At the single-particle level, NPs lack complete homogeneity in surface and structural features, including targeting motif distribution, surface charges, ligand densities, and topological characteristics.[175,176] Such heterogeneity significantly affects NP interactions with proteins or cell membranes, influencing biodistribution, pharmacokinetics, and biological fate, while potentially inducing cytotoxicity or immune activation. These challenges hinder the effective use of NPs in biomedical delivery, therapy, and the development of personalized medicines. Recent efforts have focused on addressing NP heterogeneity for medicinal applications.[177] Precision NPs (PNPs), or nano-assemblies, have emerged as promising platforms for modulating bioprocesses. PNPs exhibit finely tailored surface or structural heterogeneity with minimal interparticle variation, enabling precise control over biological interactions.[179–181] By leveraging controlled heterogeneity, PNPs enhance the therapeutic efficiency and reduce the adverse effects of NP-based carriers, offering significant potential for advancing biomedical delivery and therapy.[177]

3. Stimuli-responsive approaches

Intelligent NMs function as a versatile toolkit, adapting their properties to internal and external stimuli.[178–181] This adaptability enhances cellular uptake, endosomal escape, and controlled payload release. Stimuli responsiveness is achieved either through inherently sensitive NMs, such as gold NMs responsive to light and heat or by modifying NMs with responsive functional groups. We explore systems utilizing pH variations, enzyme concentrations, redox potential, and specific analytes. Fig. 10 illustrates these stimuli-responsive conditions, highlighting both endogenous and exogenous stimuli.

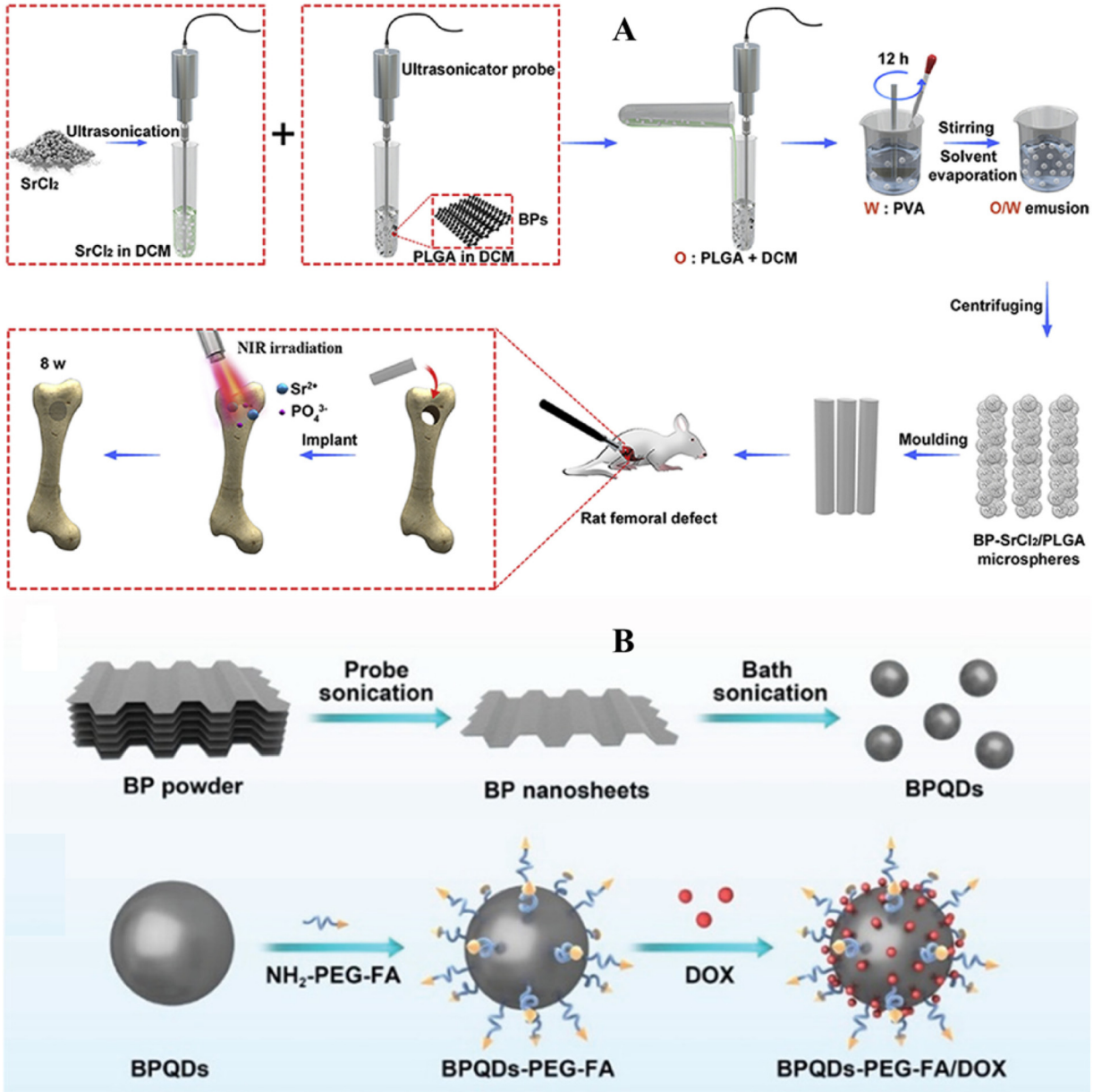

Fig. 9 (A) Preparation process of the BP-SrCl2/PLGA microspheres for bone regeneration. Reproduced with permission.[171] Copyright 2024, Elsevier. (B) Schematic depiction of preparing (BPQDs)-PEG-FA/DOX. (i) Schematic illustration of the preparation of BPQDs. (ii) Schematic illustration of BPQD-based drug delivery system. Reproduced with permission.[174] Copyright 2024, John Wiley and Sons, under the terms of the CC BY © 2024 by the authors.

3.1. Endogenous stimuli

(a) pH-Responsive systems. pH-Responsive NMs exploit the acidic tumor microenvironment, driven by the Warburg effect, where glycolysis produces lactic acid, lowering extracellular pH (6.5–7) compared to healthy tissues (pH ~ 7.4). Intracellular compartments like lysosomes (pH ~ 4.4–5) and endosomes (pH ~ 5–6.4) are even more acidic, enabling precise pH-triggered drug release.[182–184] Systems such as chitosan (pK_a ~ 6.3) and PEG-poly(β-amino ester) micelles (pH 6.4–6.8) release therapeutic agents like TNFα and camptothecin in acidic conditions.[185] Charge reversal strategies, such as TAT-peptide-decorated liposomes and polyhistidine-based micelles, enhance cellular uptake by exposing cell-penetrating peptides at low pH.[186,187] pH-Sensitive coatings, like poly(methacrylic acid)-based copolymers, protect drugs in the gastric cavity and release them in the intestine.[188–192]

(b) Redox-responsive systems. Redox-responsive NMs leverage the elevated glutathione (GSH) levels in tumor cells (2–10 mM intracellular *vs.* 2–10 μM extracellular).[192] PEG-based polyplex micelles and siRNA-grafted polymers enhance gene silencing in reducing environments.[193] Oxidation-respon-

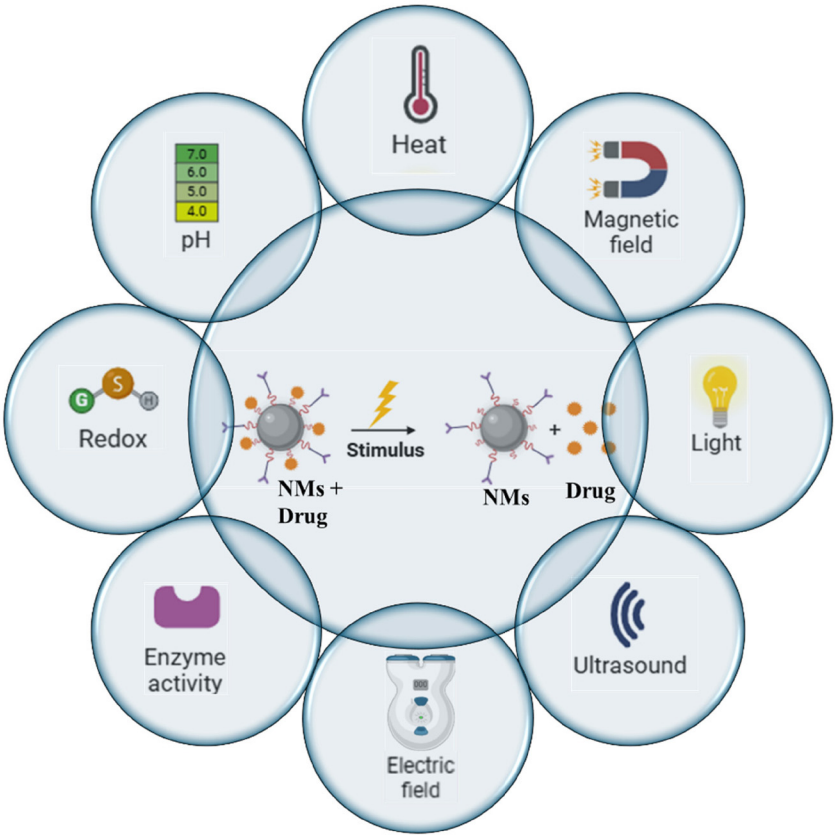

Fig. 10 Stimuli-responsive nanomaterials. The figure illustrates endogenous and exogenous stimuli, that can trigger responsive actions in drug delivery.

sive systems, such as thioketal-based NMs, target inflammatory tissues with reactive oxygen species (ROS) accumulation, delivering TNFα–siRNA for therapeutic gene silencing.[194–197] Despite challenges, redox-responsive strategies hold promise for precise drug delivery in complex biological environments. Disulfide-linked micelles, dendrimers, and liposomes disassemble under reductive conditions, enabling cytosolic drug release.[198–202]

(c) Enzyme-sensitive systems. Enzyme-responsive NMs exploit overexpressed enzymes in pathologies like cancer and inflammation.[203,204] Peptide bond cleavage by proteases (*e.g.*, matrix metalloproteinases (MMPs), thrombin, plasmin) triggers drug release or material degradation.[205–208] Cathepsin B-sensitive prodrugs and esterase-responsive systems enable temporal control in drug delivery.[209–212] Lipases, elastases, and caspases further expand theragnostic applications, offering targeted and responsive therapeutics for cancer and wound monitoring.[213]

3.2. Exogenous stimuli-sensitive systems

Exogenous stimuli-responsive drug delivery systems enable the controlled release of therapeutic agents in response to external physical, chemical, or biological cues. These systems offer precise spatiotemporal control over drug release, enhancing therapeutic efficacy while minimizing off-target effects. This section examines strategies that utilize externally applied stimuli, including temperature variations, magnetic fields, ultrasound, light, and electric fields, to achieve targeted and on-demand drug delivery.

(a) Temperature-responsive systems. Temperature-responsive drug delivery systems, widely explored in oncology, leverage nanocarriers that undergo sharp property changes with temperature fluctuations, enabling controlled drug release. These systems, often based on lower critical solution temperature (LCST) or upper critical solution temperature (UCST) properties, utilize thermally responsive polymers like poly(*N*-isopropyl acrylamide) (PNIPAM) and cellulose derivatives.[214–216] Below the LCST, polymers are hydrophilic; above, they become hydrophobic, facilitating payload release. Temperature-sensitive liposomes (TSLs), such as ThermoDox in phase II trials, release drugs rapidly at hyperthermic conditions (40–42 °C), targeting cancers like breast and hepatocellular carcinoma. Innovations like leucine zipper peptide–liposome hybrids and bubble-generating liposomes enhance functionality and imaging. Despite challenges in material design, TSLs remain the most advanced candidates for clinical applications.[215,216]

(b) Magnetic field. Magnetic field-responsive drug delivery systems employ magnetic NPs for targeted and on-demand therapeutic release, guided by external magnetic fields.[217,218] These systems enable precise drug accumulation at target sites, often enhanced by magnetic resonance imaging for theranostic applications. Magnetic guidance, using extracorporeal fields,

improves tumor targeting in cancer therapy.[219] Candidate nanosystems include core–shell NPs, magneto-liposomes, and porous metallic nanocapsules, though *in vivo* efficacy varies.[220–222] The integration of magnetic responsiveness with diagnostics and therapy highlights their potential, despite challenges in standardized evaluation and comparison across systems.[217,218]

(c) Light-sensitive approaches. Light-sensitive drug delivery systems enable precise, localized therapeutic release using light as an external trigger, minimizing off-target effects.[223] These systems leverage visible, UV, and NIR (NIR) light, with parameters like intensity and wavelength dictating outcomes. For instance, azobenzene photoisomerization facilitates controlled release, while photoactivatable platinum(IV) amphiphiles enable targeted nanomedicine with imaging and therapeutic capabilities.[224] NIR-absorbing materials, such as gold NPs, overcome tissue penetration limitations, enhancing anticancer efficacy.[226–229] Plasmonic nanobubbles and gold-coated systems further advance light-triggered delivery.[230,231] Light-responsive systems, particularly NIR-based, hold significant promise for precise, controlled drug release in cancer therapy and beyond.[222–229]

(d) Electrical field. Electric field-responsive systems enhance drug delivery, particularly in cancer therapy, with FDA-approved applications like glioblastoma treatment.[230] These systems enable precise, non-invasive control, exemplified by wireless dressings integrating sensors and electrically triggered antibiotic release for wound management.[231] Multiwalled carbon nanotubes and chitosan nanohydrogels further refine electrostimulated drug release.[232] Magneto-/electro-responsive polymers (MERPs) offer dynamic properties for biomedical and smart material applications, though biological compatibility requires further study.[233] Electroporation enhances drug permeability, with advancements in PEG-coated silica NPs and transferrin-decorated liposomes for gene and oligonucleotide delivery.[234,235] Iontophoresis boosts transdermal and ocular drug delivery, yet challenges like tissue penetration and damage limit broader therapeutic use.[230–236]

(e) Ultrasound. Ultrasound-induced drug delivery enables precise, localized release with minimal harm to healthy tissues, leveraging its non-invasive nature and adjustable penetration depth.[237] Ultrasound triggers drug release *via* thermal or mechanical effects, such as cavitation, destabilizing nanocarriers and enhancing vessel permeability for improved cellular uptake. Ultrasound-responsive NMs enhance imaging diagnostics and enable image-guided, pulsatile drug delivery, crossing barriers like the blood–brain barrier.[237] Low-frequency ultrasound, while effective, risks metastatic dissemination; microbubbles and perfluorocarbon nanoemulsions mitigate this by lowering cavitation thresholds and promoting tumor-targeted release. Bubble liposomes enhance transfection efficiency, particularly for gene delivery, by inducing endosomal escape and pore formation, bypassing degradative pathways.[238] Ultrasound's safety, non-invasiveness, and deep tissue penetration make it a prevalent trigger in cancer therapy.[237,238]

(f) Multi-stimuli-sensitive drug delivery systems. Multi-stimuli-sensitive systems enhance drug delivery by responding to simultaneous stimuli, leveraging conditions like pH gradients and oxidative environments in pathologies.[215] For instance, pH/redox dual-sensitive NPs with acid-cleavable and redox-reducible linkers improve drug release and therapeutic efficacy *in vivo*.[215] Combining pH and temperature responsiveness in liposomes or ionically self-assembled NMs further refines drug release.[154] Light and pH dual-sensitivity exploits surface resonance properties of metals like palladium, while temperature and magnetic field responsiveness enable targeted methotrexate delivery. Ultrasound and enzyme dual-sensitivity enhances drug release from bubble liposomes.[239] Carbon NM-integrated chitosan hydrogels demonstrate pH/temperature-responsive release, promising for gastrointestinal and colon-targeted delivery.[240] Despite their versatility, these systems often remain complex and conceptual, requiring rigorous *in vitro* and *in vivo* validation to confirm stimulus-specific regulation and clinical viability.[215,240]

4. Personalized nanomedicine: tailoring therapeutics for precision medicine

Personalized nanomedicine represents a paradigm shift in healthcare, enabling tailored therapeutic strategies that account for individual patient variability in disease mechanisms, genetic profiles, and physiological responses. NMs play a pivotal role in this advancement, leveraging their inherent advantages-tunable physicochemical properties, high surface-to-volume ratios, and multifunctionality- to optimize drug delivery, enhance diagnostic precision, and improve therapeutic outcomes. By integrating molecular data (*e.g.*, genomic, proteomic, or metabolomic signatures) with advanced nanocarrier designs, personalized nanomedicine can deliver bioactive agents with spatiotemporal control, enabling targeted modulation of disease pathways while minimizing off-target effects.[241] Clinically, NMs have demonstrated transformative potential in early disease detection, high-resolution imaging, and precision delivery of therapeutics. For instance, nanoscale platforms enable the identification of molecular biomarkers for cancers and metabolic disorders, facilitating early diagnosis and timely intervention. In oncology, nanocarriers have been deployed to improve treatments for metastatic breast and ovarian cancers by enhancing tumor accumulation and reducing systemic toxicity. Innovations like red blood cell membrane-coated NPs exemplify this progress, demonstrating prolonged circulation times and improved biocompatibility in preclinical models.[242] Despite these advances, critical challenges persist. The design of personalized nanomedicines requires a deep understanding of nano-bio interactions, particularly protein corona formation, which influences targeting efficiency and immunogenicity. Key barriers include optimizing nanocarrier stability, minimizing immunotoxicity, and achieving subcellular-level targeting (*e.g.*, organelles like mitochondria or nuclei). Additionally, scalable manufacturing of

patient-specific nanotherapies remains a bottleneck, necessitating advances in modular production platforms and quality-control protocols to meet regulatory standards.[243]

The future of personalized nanomedicine hinges on interdisciplinary collaboration to address these challenges. By coupling artificial intelligence-driven biomarker discovery with modular nanocarrier systems, researchers can accelerate the development of "smart" therapeutics tailored to individual patient needs. Current efforts focus on refining stimuli-responsive NMs (*e.g.*, pH- or enzyme-activated systems) and leveraging multi-omics data to predict patient-specific responses.[244,245] While challenges in clinical translation persist, particularly in cost-effective manufacturing and rigorous validation, the integration of nanotechnology with precision medicine holds unparalleled potential to redefine treatments for complex diseases, from cancer to neurodegenerative disorders.

5. Nanomedicine: advances and challenges in clinical translation and FDA approvals

Nanomaterials (NMs) have demonstrated significant clinical success in oncology, diagnostic imaging, and vaccine development. As modular platforms, they integrate diagnostic or therapeutic payloads (*e.g.*, small molecules, biologics), synthetic polymers, and biological components such as peptides, antibodies, and lipids. Through precise engineering, NMs can traverse biological barriers, navigate complex microenvironments, and achieve spatiotemporal control in cargo delivery to target cells. The Emergency Use Authorization of COVID-19 mRNA vaccines encapsulated in lipid nanoparticles (LNPs) underscores their transformative potential in addressing global health crises. These systems leverage unique physicochemical properties to protect payloads (*e.g.*, nucleic acids, drugs), enable targeted delivery, and modulate release kinetics.[246] Key milestones include the 1995 FDA approval of Doxil®, a PEGylated liposomal doxorubicin (DOX),[247] and the recent authorization of LNP-based mRNA vaccines.[248,249] Such innovations have advanced treatments for cancers, genetic disorders,[250] and infectious diseases, with over 100 candidates in active clinical trials.[251] Despite progress, clinical translation remains challenging. While most approved nanomedicines are lipid-based, many experimental formulations lack clinically relevant considerations, hindering scalability and regulatory compliance.[252] Challenges span formulation stability, toxicity profiles, physiological interactions, immunogenicity, and manufacturing reproducibility, necessitating robust preclinical validation, chemistry-manufacturing-controls, and post-approval pharmacovigilance.[253,254]

Contemporary clinical trials increasingly employ nanomedicine strategies to enhance monotherapy efficacy, with recent progress driven by genetic cargo (*e.g.*, RNA and gene therapies) rather than small-molecule drugs. Notably, small-molecule therapies, including kinase inhibitors, remain underrepresented. Spark Therapeutics' Luxturna®, the 2017 FDA-approved gene therapy for inherited retinal dystrophy, marked a pivotal milestone. Subsequent phase I/II trials utilized DOTAP/cholesterol NPs to deliver the tumor-suppressing

Table 2 Clinical status of nanomaterials-based drug delivery systems

Formulation	Name	Payload/cargo	Application	Year of approval
PEGylated liposome	Doxil Caelyx (Janssen)	DOX	Ovarian cancer, HIV-associated Kaposi's sarcoma, multiple	FDA (1995) EMA (1996)
Albumin-particle	Abraxane (Celgene)	Paclitaxel	Advanced non-small cell lung cancer, metastatic pancreatic cancer, metastatic breast cancer	FDA (2005) EMA (2008)
Liposome (non-PEGylated)	Myocet (Teva UK)	DOX	Breast cancer	EMA (2000)
Liposome (non-PEGylated)	DaunoXome (Galen)	DOX	HIV-associated Kaposi's sarcoma	FDA (1996)
Liposome (non-PEGylated)	Marqibo (Spectrum)	Vincristine	Philadelphia chromosome-negative acute lymphoblastic leukemia	FDA (2012)
Hafnium oxide nanoparticles	NBTXR3 Hensify (Nanobiotix)	Stimulated with external radiation to enhance tumor cell death *via* electron production	Squamous cell carcinoma	CE Mark (2019)
Liposome	VYXEOS CPX-351 (Jazz Pharmaceuticals)	Cytarabine : daunorubicin (5 : 1 molar ratio)	Acute myeloid leukemia	FDA (2017) EMA (2018)
PEGylated liposome	Onivyde MM-398 (Merrimack)	Irinotecan	Metastatic pancreatic cancer	FDA (2015)
Lipid microspheres	Definity (Lantheus Medical Imaging)	Perflutren	Ultrasound contrast agent	FDA (2001)
Iron dextran colloid	Feridex I.V. (AMAG), Endorem	Iron	Iron imaging of liver lesions	FDA (1996) Discontinued (2008)
Phospholipid stabilized microbubble	SonoVue (Bracco Imaging)	Hexafluoride	Ultrasound contrast agent	EMA (2001)

The table was made from **https://clinicaltrials.gov/**.

FUS1 gene, identified through homozygous deletions in lung cancer.[255,256] Emerging small-molecule trials include nanoparticle albumin-bound rapamycin combined with chemotherapy for pediatric solid tumors and mTOR-mutant cancers,[257] while pH-sensitive micellar epirubicin and CPC634 docetaxel NPs exploit tumor microenvironment cues. IMX-110, a dual-loaded nanoparticle co-delivering curcumin and DOX, has entered phase I/II trials for advanced solid tumors. Nanoplatin®, a cisplatin formulation, is undergoing phase III evaluation in Asia and U.S. basket trials.[258] RNA therapeutics continue to show promise: a phase I/II trial of TKM-080301, an LNP-encapsulated siRNA targeting PLK1, demonstrated antitumor activity in adrenocortical carcinoma.[259] Ongoing Phase I trials evaluate LNPs targeting EphA2[260] and MTL-CEBPA siRNA for hepatocellular carcinoma.[261] Patisiran, an LNP-formulated siRNA for hereditary transthyretin amyloidosis, emerged as the first FDA-approved siRNA therapy in 2018. Several stimuli-responsive drug delivery systems are currently under clinical evaluation:

- **ThermoDox**: A thermosensitive liposomal formulation in phase II trials for breast cancer and phase III trials for hepatocellular carcinoma.
- **NanoTherm**: An iron oxide-based nanomaterial approved for the treatment of glioblastoma.
- **Magnetic Targeted Carrier-Doxorubicin (FeRX)**: A system that has entered phase II trials for liver cancer and phase III trials for unresectable hepatocellular carcinoma.

In addition, several clinical trials and FDA-approved NMs were tabulated in Table 2. Despite these advances, targeted delivery systems for small-molecule drugs remain underexplored, highlighting a critical area for clinical innovation. Successful translation demands interdisciplinary collaboration to optimize pharmacokinetics, therapeutic indices, cost-effectiveness, and disease-specific complexity. Addressing these challenges will unlock nanomedicine's full potential to revolutionize global healthcare. Overall, this section highlights the diversity of nanoparticle architectures, elucidates their mechanistic advantages over conventional drug administration, and assesses their transformative potential in clinical paradigms. Our analysis prioritized ongoing trials of nanoparticle formulations under regulatory review while examining the expanded applications of approved nanotherapies-both for authorized indications and novel uses. Furthermore, we emphasize underappreciated biological, technological, and methodological barriers to translation, offering actionable insights to optimize development and deployment.

6. Future perspectives and concluding remarks

While drug delivery systems often incorporate specific ligands for disease targeting, their efficacy remains suboptimal, typically less than 5% of the administered dose reaching the intended tumor or affected tissues. This limitation stems from the structural heterogeneity of biological targets, restricted access to target cells, and physiological barriers such as elevated interstitial pressure, desmoplastic reactions, and compromised endothelial blood vessels. Furthermore, the enhanced permeability and retention (EPR) effect, frequently observed in preclinical models, often fails to translate effectively in clinical settings. In this context, stimuli-responsive NMs represent a promising strategy for overcoming these challenges. By leveraging endogenous (*e.g.*, pH, redox potential, enzymatic activity) and exogenous (*e.g.*, temperature, light, magnetic fields) stimuli, NMs enable precise and localized drug release. The versatility of stimuli-responsive NMs offers significant design flexibility, allowing for tailored therapeutic approaches. However, despite promising *in vitro* results, only a handful of stimuli-responsive systems-such as thermosensitive iron oxide nanoparticles and liposomes-have advanced to clinical trials. This limited translation is primarily due to challenges in scalability, architectural complexity, and the need for rigorous biocompatibility and degradability assessments. Key barriers include achieving sensitivity to subtle environmental variations (*e.g.*, pH, temperature, redox potential) and addressing the limited penetration depth of externally applied stimuli. Additionally, the clinical viability of many stimuli-responsive nanocarriers is hindered by concerns over toxicity, which is influenced by factors such as composition, biophysical properties, and administration routes. As a result, nanocarriers with simpler designs and easier development pathways, such as temperature-triggered liposomes (*e.g.*, ThermoDox and Doxil), have shown greater clinical promise and are currently in advanced stages of development. Moving forward, it is imperative to focus on refining clinically viable systems that exhibit enhanced sensitivity to precise environmental cues. Significant advances in drug delivery and materials chemistry have laid the groundwork for sophisticated stimuli-responsive nanocarriers. However, prioritizing the development of systems with improved biocompatibility, scalability, and clinical applicability will be critical for bridging the gap between preclinical success and therapeutic impact. This review underscores the need to redirect efforts toward overcoming these challenges, particularly in the context of orphaned diseases and niche therapies, to propel the full potential of stimuli-responsive nanomedicines.

In summary, intelligent NMs have emerged as powerful tools in the realm of advanced cancer therapy, offering significant potential as carriers for targeted and responsive drug delivery. Their exceptional properties enable healthcare practitioners to explore novel therapeutic modalities or enhance existing treatments, paving the way for more effective and personalized cancer care. This review highlights the transformative potential of stimuli-responsive NMs in advancing safer and more efficient cancer therapies. By enabling targeted drug delivery, on-demand drug release in response to specific stimuli, and the co-delivery of combination therapies, these systems hold great promise for the development of durable therapeutic strategies and innovative treatment approaches. Despite the remarkable progress in this field, challenges remain in translating many stimuli-responsive nanocarriers

from preclinical success to clinical application. Issues such as scalability, biocompatibility, and sensitivity to subtle environmental cues continue to hinder their widespread adoption. Nevertheless, ongoing research has led to the development of innovative NMs with substantial clinical potential, propelling and offering hope for the emergence of new therapeutic options. While setbacks in clinical translation are not uncommon, the continued refinement of these systems, coupled with a focus on clinically viable designs, will be critical to leverage their full potential. As the field evolves, stimuli-responsive NMs are poised to play an increasingly pivotal role in shaping the future of cancer therapy.

Data availability

We confirm that no primary research results, software, code, or new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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