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Translational paradigm of advanced nanoscale strategies for triple negative breast cancer (TNBC): mechanistic insights, metastatic pathways, and emerging theragnosis

Soumya Sonalisha,[a] Apoorv Kirti,[a] S. P. Asima,[a] Richeek Parashar,[a] Sreejita Pal,[a] Debidatta Barik,[a] Shaikh Sheeran Naser,[ab] Eliana B. Souto *[b] and Suresh K. Verma *[a]

Triple-negative breast cancer (TNBC) stands out as one of the most aggressive and therapeutically challenging subtypes of breast cancer, mainly due to the absence of estrogen, progesterone, and HER2 receptors. This review aims to consolidate current knowledge on the molecular and metabolic heterogeneity of TNBC, focusing on critical mutations in BRCA1/2 and TP53, which are pivotal in driving tumor progression and contributing to treatment resistance. This manuscript highlights the transformative potential of recent advancements in nanoscale strategies for diagnosis and therapy in the management of TNBC. Notably, multifunctional nanoparticles have shown promise in overcoming the limitations of conventional chemotherapy by facilitating targeted drug delivery, enabling image-guided therapy, allowing for controlled drug release, and minimizing systemic toxicity. The use of nanotechnology in precision oncology presents innovative strategies for the early detection of TNBC, effective treatment measures, and the personalization of therapeutic regimens. This review bridges the gap between molecular understanding and technological advancement, offering a comprehensive roadmap for the future clinical application of theragnostic approaches in the battle against TNBC. By fostering the understanding of pathophysiology of TNBC and advancing treatment methodologies, we aim to contribute to the state of the art knowledge towards improving therapeutic efficacy and better patient outcomes.

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[a] *School of Biotechnology, KIIT Deemed to be University, Bhubaneswar-751024, Odisha, India. E-mail: sureshverma22@gmail.com*
[b] *UCD School of Chemical and Bioprocess Engineering, University College Dublin, Belfield, Dublin 4, D04 V1W8, Ireland. E-mail: eliana.souto@ucd.ie*

Soumya Sonalisha

Soumya Sonalisha has completed her M. Tech in Biotechnology from KIIT University, Bhubaneswar, Odisha, India. She is currently involved as a Research Assistant in the Zebrafish Lab/Infection Biology Lab, School of Biotechnology, KIIT University, led by Prof. M. Suar and mentored by Dr Suresh K. Verma. Her working research field is the Zebrafish model and Nanotechnology for therapeutics.

Eliana B. Souto

Eliana B. Souto is a Full Professor of Pharmaceutical Engineering, UCD School of Chemical and Bioprocess Engineering, University College Dublin, Ireland. Professor Souto is graduated in Pharmaceutical Sciences from University of Coimbra and holds a Masters' degree in Pharmaceutical Technology from University of Porto, Portugal, and PhD in Pharmaceutical Nanotechnology and Biopharmaceutics from Free University of Berlin, Germany. Her research areas include drug delivery and she was ranked by Clarivate as a highly cited researcher in 2022, 2023, 2024 and 2025.

1. Introduction

Breast cancer is the second leading cause of cancer-related mortality among women worldwide.[1] Emerging evidence suggests that genetic and environmental factors, using hormone-mimicking chemicals in cosmetic products (notably parabens and phthalates), obesity, uncontrolled junk food intake, and carcinogen exposure can synergistically lead to breast cancer.[2–5] Breast cancer arises in milk ducts (ductal carcinoma), milk-producing lobules (lobular carcinoma), and other supporting stromal or epithelial cells. Its progression is a multifactorial and multistep process involving intricate interactions among cellular components and signaling cascades, where, most importantly, molecular markers, such as HER2, p53, BRCA1/2, Ki-67, Cyclin D1, and CXCR4, play crucial regulatory roles, thereby complicating its prevention and therapeutic management worldwide.[6]

Triple-negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer, primarily due to its distinct biological characteristics, extensive genetic heterogeneity, and capacity to modulate the surrounding tumor microenvironment. Unlike other breast cancer types, TNBC is devoid of estrogen, progesterone, and HER2 receptors, rendering it unresponsive to conventional hormone or HER2-targeted therapies.[7] Although TNBC has long been recognized for its aggressiveness, recent research has elucidated the specific molecular and cellular mechanisms underlying its malignancy. These insights are now paving the way for the development of novel and more precisely targeted therapeutic strategies.[8]

Suresh K. Verma

Suresh K. Verma is a senior scientist, currently working at the School of Biotechnology, KIIT University, Bhubaneswar, India. He has received his PhD degree in biotechnology specialization from KIIT University, Bhubaneswar, India. He has been a part of research groups in Karolinska Institute, Sweden; Uppsala University, Sweden; and Poznan University of Medical Sciences, Poznan, Poland. During his postdoctoral tenure, he has published 90 papers in many reputed journals and 12 book chapters published by ACS, RSC, Elsevier, CRC, and Springer publishers. He has also been an editor of two books based on nanotechnological advances for biological sciences in CRC Press. He is serving as an editor in many journals like Scientific Reports (Springer nature) and Discover Applied Sciences (Springer). He has also served as a guest editor in many special issues organized by reputed journals of Frontiers publishers, MDPI publishers, and other publishers. He has served as a reviewer for 200 journals published by ACS, RSC, Springer, Frontiers, Nature, and Elsevier. His work has also been awarded as a highly cited article RSC published in the Journal Green Chemistry.

A major factor contributing to the high mortality of breast cancer, particularly in aggressive subtypes like TNBC, is its ability to metastasize. Metastasis is the process by which cancer cells spread from the primary tumor site to distant organs, forming secondary tumors.[9] This phenomenon not only complicates treatment but also significantly worsens prognosis. The transition from a localized disease to a systemic one marks a critical turning point in cancer progression and is responsible for the majority of breast cancer-related deaths. Understanding the underlying mechanisms of metastasis is therefore vital for developing more effective therapeutic interventions aimed at limiting cancer spread and improving patient survival. The process of metastasis begins with the formation of a primary tumor, where abnormal cells proliferate within the breast tissue (Fig. 1).

The tumor cells eventually invade the surrounding extracellular matrix, breaching the basement membrane and entering nearby vasculature in a step known as vascular invasion. These cancerous cells are known as tumor cells in circulation once they are in the bloodstream. In the bloodstream, they are able to withstand physical stress and immunological surveillance and eventually undergo extravasation, exiting the blood vessels at distant sites. Following extravasation, tumor cells establish themselves in a favorable microenvironment known as the pre-metastatic niche.[10] This niche is shaped by interactions between malignant cells, immune cells, stromal components, and extracellular matrix molecules, facilitating the survival and colonization of the disseminated cells.[10] The next stage involves the formation of micro-metastases, small clusters of tumor cells that begin to grow in the distant tissue. Over time, these micro-metastases develop into overt metastatic tumors, completing the cascade of metastatic progression. This colonization at distant sites marks a paramount advance with an often-fatal stage of breast carcinoma. Understanding this cascade is essential for identifying therapeutic targets and developing strategies to intercept the metastatic process, ultimately improving survival outcomes in breast cancer patients.[11]

The absence of estrogen, progesterone, and HER2 receptors contributes to the proliferation and survival of breast cancer cells in TNBC. The major cause underlying most TNBCs is the dysfunction or mutation of the BRCA1 gene, which is strongly associated with the basal-like molecular subtype. A significant proportion of both hereditary and sporadic TNBC cases exhibit BRCA1 abnormalities that disrupt deoxyribonucleic acid (DNA) repair mechanisms, leading to genomic instability and aggressive tumor behavior. These cancers typically express basal cytokeratin (CK5, CK14, and CK17), P-cadherin, and Epidermal Growth Factor Receptor (EGFR), reflecting their origin from basal/myoepithelial cells of the mammary gland, which modulate the tumor microenvironment. Consequently, BRCA1 dysfunction not only contributes to tumor initiation and rapid progression but also explains the poor response of TNBCs to hormone or HER2-targeted therapies, emphasizing the need for BRCA1-based diagnostic and therapeutic strategies.[12]

Approximately 15% to 20% of all breast cancers are TNBC.[13] Following their initial diagnosis, over half of the patients undergo a recurrence within 3 to 5 years. Therapy for women

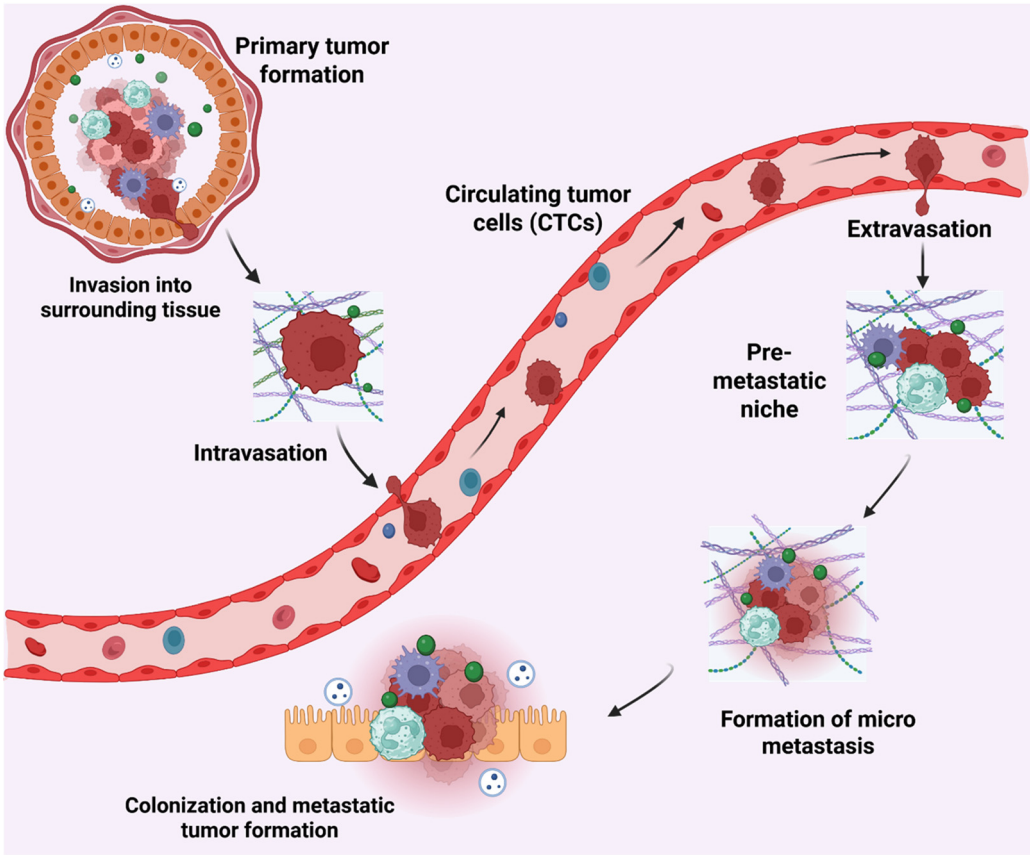

Fig. 1 Metastatic spread of tumors. It begins with the formation of a primary tumor from malignant cell growth. Tumor cells invade local tissues, enter the bloodstream as circulating tumor cells, and migrate to distant organs. After extravasation, they create a supportive pre-metastatic niche, which leads to micrometastases that can develop into full-blown metastatic tumors. Various molecular and environmental factors regulate the process (Authors' own artwork).

bearing TNBC is still an enormous therapeutic challenge, marked by aggressive, accelerated tumor growth, elevated metastatic potential, and low survival rates. Conventional chemotherapy regimens, such as taxanes or anthracyclines, have the best response. These drugs freeze the mitotic spindle, causing cell cycle arrest at the G2/M phase, intercalating into DNA, inhibiting topoisomerase II, and producing reactive oxygen species (ROS), leading to extensive DNA damage and ultimately resulting in apoptosis.[14,15] Additionally, this kind of drug acts as a double agent; short-term taxanes commonly induce peripheral neuropathy, myelosuppression, and hypersensitivity reactions, while anthracyclines lead to dose-dependent cardiotoxicity, myelosuppression, and mucositis due to ROS-mediated cellular injury. These toxic effects significantly limit therapeutic dosing and long-term use.[16–18]

In recent decades, nanotechnology has gained popularity in medicine, namely in developing safer and more effective diagnostic tools, and in site-specific tumor targeting by means of surface-modified nanoparticles (NPs). NPs offer benefits in cancer therapeutics, such as improved pharmacokinetics, targeted cytotoxicity, decreased adverse reactions, and resistance to drugs.[19,20] NPs are tiny particles, whose sizes range from 1 to 1000 nm. They have unique characteristics, such as increased systemic exposure, enhanced tumor cell uptake, tissue-selective targeting, metastasis-suppressing effects, and the capacity to evade multi-drug resistance. Nanotechnology offers a viable technique for overcoming many disadvantages of conventional medicines, including non-specific biodistribution and systemic adverse effects.[21] Targeted delivery with NPs can extend drug circulation, boost targeted payload deposition, enable ligand-directed transport and stimuli-responsive release kinetics, greatly improve anticancer immunological activity, and change the immune-evasive niche.[22] Nanoparticles (NPs) are effective targeted drug and gene delivery systems because their nanoscale size, engineerable surface properties, and stimuli-responsive behavior enable precise control over biodistribution and cellular uptake.[23] Size-dependent accumulation through the enhanced permeability and retention (EPR) effect allows passive tumor targeting, while surface functionalization with ligands such as antibodies, peptides, or folic acid promotes receptor-mediated endocytosis. NPs protect drugs and nucleic acids from premature degradation, enhance intracellular trafficking and endosomal escape, and enable site-specific release in response to tumor-specific cues (*e.g.*, acidic pH, redox imbalance). Additionally, nanoparticle-mediated delivery can bypass efflux pumps, helping to overcome multidrug resistance and improve therapeutic efficacy.[22] A variety of NPs made of different materials, such as phospholipids, metals, or amphiphilic block copolymers combining hydrophobic poly(lactic-*co*-glycolic acid)(PLGA)

with hydrophilic polyethylene glycol (PEG), have shown promise in TNBC therapy by enhancing drug delivery and radiosensitization. Studies in MDA-MB-231 cells and murine xenografts demonstrate selective cytotoxicity, controlled release, and tumor targeting. These NPs exhibit high biocompatibility, prolonged circulation, and minimal systemic toxicity, making them promising candidates for safe and effective TNBC treatment.[24]

This review elucidates TNBC's genetic complexity, molecular subtypes, and treatment challenges while emphasizing emerging NPs for site specific targeting of chemotherapeutics, as well as theragnostic approaches for precise diagnosis and therapy with the ultimate aim to improve patient outcomes.

2. TNBC mutations affecting metabolic pathways

The onset and advancement of malignancies, including TNBC, are influenced by mutations. The unchecked expansion of cancer cells can result from mutations in genes related to cell division, growth, and repair. The aggressiveness of the disease can be influenced by the alteration of multiple genes. Fig. 2 shows a detailed overview of metabolic adaptations in primary tumor cells.

A significant gene linked to TNBC is BRCA1/2. The BRCA1 and BRCA2 gene products play a critical role in initiating and regulating the transcriptional processes involved in the DNA damage response, cell cycle regulation, and the control of cell growth and differentiation. The BRCA1 and BRCA2 proteins are crucial for repairing DNA double-strand breaks through the homologous recombination repair (HRR) pathway; hence, they maintain genomic integrity. Breast tumors associated with BRCA1 mutations often display basal-like molecular characteristics, corresponding to the BL1 (Basal-Like 1) subtype. Owing to their unique molecular characteristics, these tumors frequently exhibit increased susceptibility to neoadjuvant chemotherapy protocols, especially those incorporating anthracyclines and taxanes.[25]

Apart from BRCA1/2, other gene mutations have also been studied for TNBC. TNBC commonly has somatic mutations in

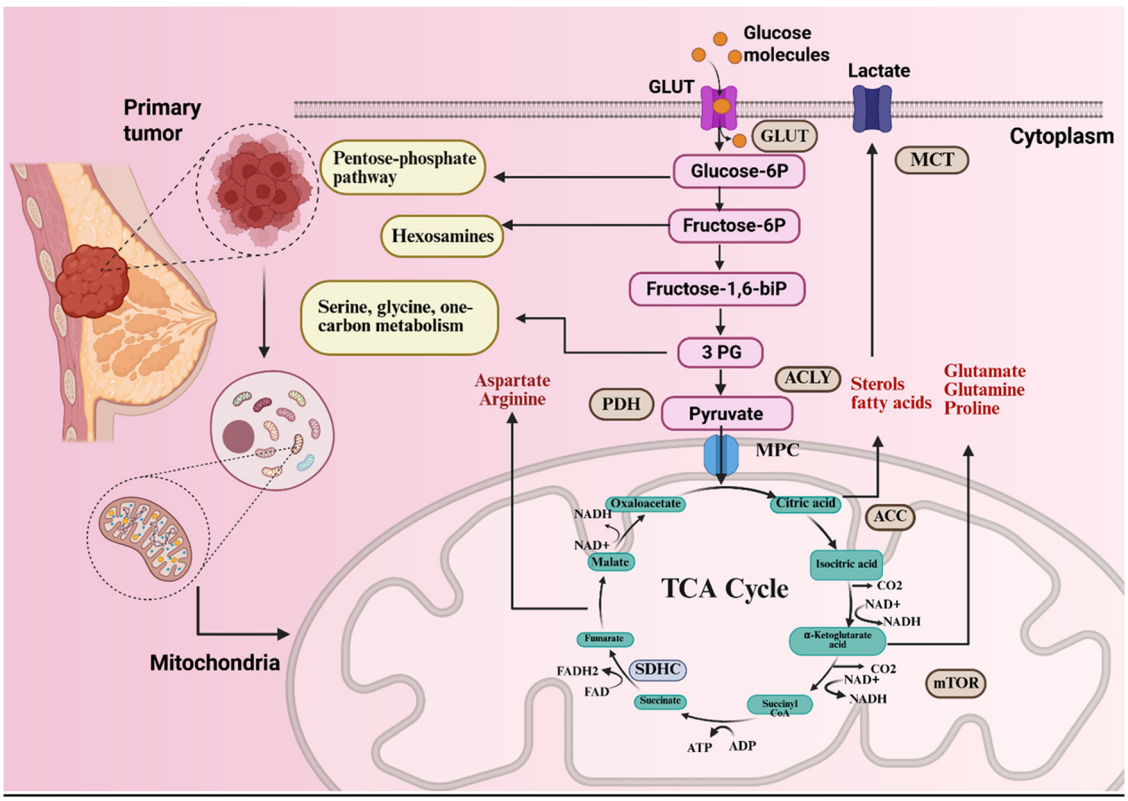

Fig. 2 Metabolic reprogramming linking glycolysis and mitochondrial metabolism in cancer cells. The schematic illustrates enhanced glucose uptake by glucose transporter (GLUT) and its conversion through glycolysis, generating intermediates that feed anabolic pathways, including the pentose phosphate pathway (PPP), hexosamine biosynthetic pathway, and serine–glycine–one-carbon metabolism. Glucose is phosphorylated to glucose-6-phosphate (Glucose-6P), converted to fructose-6-phosphate (Fructose-6P) and fructose-1,6-bisphosphate (Fructose-1,6-biP), yielding 3-phosphoglycerate (3-PG) and ultimately pyruvate. Pyruvate enters mitochondria *via* the mitochondrial pyruvate carrier (MPC) and is converted by pyruvate dehydrogenase (PDH) to acetyl-CoA, fueling the tricarboxylic acid cycle (TCA). Key intermediates include citrate, isocitrate, α-ketoglutarate, succinyl-CoA, succinate, fumarate, malate, and oxaloacetate, coupled to redox cycling of nicotinamide adenine dinucleotide (NAD^+/NADH) and flavin adenine dinucleotide (FAD/$FADH_2$), and adenosine triphosphate/diphosphate (ATP/ADP) generation. Succinate dehydrogenase complex subunit C (SDHC) links the TCA cycle and electron transport. Citrate export supports lipid biosynthesis *via* ATP-citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC), producing sterols and fatty acids, while amino acid metabolism (glutamine, glutamate, proline, aspartate, and arginine) replenishes TCA intermediates. Excess lactate is exported by the monocarboxylate transporter (MCT). Signaling through mTOR (mechanistic target of rapamycin) integrates nutrient availability with growth and biosynthesis (Authors' own art work).

TP53, a critical component that stops cells from executing the DNA repair mechanism. In TNBC, there are limited frequently observed mutations, such as changes in TP53 and PI3KCA, alongside a substantial array of unique, infrequent mutations. The combined impact of genetic changes causes TNBC development.[26] TNBC possesses a distinctive genetic profile, marked by recurrent TP53 mutations (about 80% of cases) and a comparatively low occurrence of PIK3CA mutations (around 9%).[27] Mutations in the TP53 gene may cause genomic instability and a reduction in heterozygosity. The level of p53 protein expression is influenced by the specific type of mutation present. Many studies have explored how TP53 mutations affect the prognosis of TNBC. Nonetheless, the variability in p53 expression has made it difficult to determine the definitive role of TP53 status as a reliable prognostic marker. Since TP53 is commonly altered in most TNBC cases, it represents a promising target for the design of anticancer treatments. Recently, chemicals have been developed that target mutant TP53, previously considered non-druggable.[28] The anti-apoptotic protein BCL2 is significantly over-expressed in numerous cancers relative to normal cells, positioning it as a valuable target for cancer treatment strategies. Approximately 41% of TNBCs and 19% of basal-like tumors exhibit increased expression of BCL2.[29] Previous studies indicate that BCL2 could function as a successful predictive biomarker, particularly in HR-positive breast cancer.[30] Patients with BCL2-positive breast cancer have a better prognosis in terms of overall survival and relapse-free survival.[31] Positive BCL2 expression correlates with improved prognosis in both metastatic and early-stage breast cancer patients undergoing hormone therapy or chemotherapy.

The underlying cause of the variations in outcome predictions is still uncertain; however, since BCL2 expression is influenced by estrogen receptor status, its differing roles seem to be determined by the specific molecular subtype of breast cancer.[30]

2.1. Metabolic pathways in TNBC

The need for energy and biosynthesis of cancer cells is met by enhancing the metabolism of glucose and glutamine.[32] TNBC follows this trend, displaying increased glucose uptake and a gene expression profile characteristic of enhanced glycolysis.[33] Additionally, TNBCs exhibit greater sensitivity to glutamine deprivation and consume more glutamine compared to other breast cancer subtypes, indicating an upregulation of glutaminolysis.[34] The transcriptional mechanisms underlying elevated glucose metabolism in TNBC are not fully understood, but the MYC oncoprotein (also referred to as c-Myc) is believed to be a key contributor. TNBCs commonly exhibit Myc overexpression and Myc-associated gene signatures; Myc is recognized for promoting the expression of glycolytic genes, enhancing glucose uptake, and driving aerobic glycolysis.[35] Additionally, transporters, including glucose transporter (GLUT) and monocarboxylate transporter (MCT), as well as vital glycolytic enzymes like lactate dehydrogenase (LDH), are also over-expressed in TNBC. When GLUT4 is silenced, glucose uptake and lactate generation are decreased, and glycolytic activity is shifted toward oxidative phosphorylation (OXPHOS), which decreases cell survival and proliferation in low-oxygen environments.[36]

2.1.1. Mitochondrial oxidative metabolism. According to the Warburg effect, when oxygen and nutrients are few, cancer cells transition from OXPHOS to glycolysis. However, in TNBC cells, both increased and decreased OXPHOS activity have been observed. Reduced OXPHOS function may be attributed to mutations in mitochondrial DNA (mtDNA) or a lower amount of mtDNA, which encodes subunits of the OXPHOS protein complexes I through V.[37] OXPHOS produces ROS, and TNBC cells are notable for having higher ROS levels than other forms of breast carcinoma.[38] As elevated concentrations of mitochondrial ROS may trigger apoptotic, moderate ROS concentrations can serve as potent signaling molecules that aid cells in adjusting to the harsh circumstances of the tumor microenvironment.[39]

2.1.2. Amino acid metabolism. To survive in a nutrient-deficient environment, cancer cells require an abundant supply of amino acids.[40] An example is glutamine, an amino acid that becomes essential under certain conditions, but this amino acid is not needed in healthy cells. Tumor cells consume it more quickly than any other amino acid, making it the most common amino acid in plasma.[41] Firstly, glutamine serves as a carbon donor by generating 2-oxoglutarate, an intermediate that feeds into the tricarboxylic acid cycle (TCA) cycle. Secondly, it supplies nitrogen necessary for the production of non-essential amino acids and nucleotides. Thirdly, glutamate produced through glutaminolysis acts as a precursor for glutathione, which is crucial in preserving cellular redox balance.[35] Furthermore, glutamine can be internally produced by tumor cells through the conversion of glutamate to ammonia. To maintain their rapid proliferation, cancer cells exhibit substantial upregulation of glutamine synthetase. It is intriguing to note that glutamine synthetase can promote cell proliferation by interacting with nuclear pore proteins alone, regardless of its enzymatic activity.[41]

2.1.3. Fatty acid metabolism. Lipid metabolism is one such metabolic pathway, encompassing lipid synthesis, lipid breakdown, and catabolism, as well as fatty acid oxidation.[42,43] Besides glucose and amino acids, tumor cells utilize fatty acids as an alternative fuel *via* fatty acid oxidation, a highly efficient energy-producing process, which can be either generated inside the cell or taken up from the extracellular matrix. Carnitine palmitoyl transferase (CPT) initiates fatty acid oxidation by converting fatty acids into acyl-CoA, which is subsequently carried into the mitochondria, marking the first committed step of the pathway. Targeted metabolomic studies reveal that TNBC cells with Myc overexpression exhibit elevated CPT activity and a greater reliance on the oxidation of fatty acids to provide energy.[44,45] Peroxisomes can also undergo fatty acid oxidation. The pace-setting enzyme that causes the β-oxidation of branched, long-chain fatty acids in this organelle is called acyl-CoA oxidase 2 (ACOX2). It has been demonstrated that estrogens control the production and translation of an alternative transcript, ACOX2-i9, in mammary carcinoma cell models exhibiting estrogen receptor expression. Silencing this enzyme leads to a reduction in cell viability.[46,47]

2.2. Altered metabolism pathway due to mutations

The limited number of approved molecularly targeted therapies for TNBC corresponds to the absence of frequently altered genomic targets. Chemotherapeutics are primarily used for the treatment of

TNBC. However, TNBC features have been associated with several distinct molecular pathways; the Ras-Raf-Mek-Erk (Ras/MAPK) signaling cascade is known to be carcinogenic and leads to the development of several cancers.[48] Multiple intracellular energy-generating pathways are closely associated with TNBC. Increased expression of glycolytic transporters and enzymes in malignancies greatly accelerates glycolysis and the metabolic pathways that follow. Furthermore, the hexosamine biosynthesis pathway (HBP) leads to increased protein glycosylation, while the serine synthesis pathway and the pentose phosphate pathway (PPP) boost the generation of NADPH.[49]

Compared to individuals with HER2-positive tumors, TNBC patients had altered glutamine metabolism in addition to alterations in glycolytic and mitochondrial oxidative metabolism. Increased glutamine absorption and utilization in TNBC cell line models results in epigenetic changes that trigger the expression of genes linked to tumor growth.[50] While these pathways involve metabolic reprogramming and cellular energy, the Ras/MAPK signaling pathway is activated through active mutations in KRAS, NRAS, HRAS, or BRAF, which are frequently seen in malignancies but are uncommon in primary breast tumors. Ras/MAPK signaling supports the development of stem cell–like properties in tumor cells, immunological evasion, metabolic changes, and progression/metastasis.[48]

The PI3K/AKT/mTOR pathway helps manage metabolism, growth, and cell death in healthy breast cells by activating receptor tyrosine kinases (RTKs) and G-protein-coupled receptors. One of the PI3K pathway's major effectors, AKT, is essential for mTOR activation. During cancer development, however, alterations such as PIK3CA and AKT mutations, RTK overexpression, and PTEN loss disrupt the normal functioning of this pathway.[49] In most human breast cancers, tumor cells express more KLF4 than the neighboring, uninvolved epithelium. KLF4 is a transcriptional regulator that is linked with tumor progression and proliferation. Therefore, increased expression of this protein, or demethylation of the KLF4 promoter, is indicative of a negative prognosis.[51]

A marked reduction of the cell cycle protein CDC14B was identified in breast cancer tissues, whereas its levels remained consistent in normal breast tissues. This decreased expression of CDC14B was associated with a poorer prognosis in patients with TNBC. When analyzing CDC14B alterations across various histological subtypes of breast cancer, it was found that amplification, deep deletions, and mutations were the most common types of genetic changes observed in patients.[52] Hence, it is evident that this metabolic heterogeneity is responsible for the variability of TNBC, and it can be utilized as a determinant of pharmacological sensitivity for treating patients.[50]

3. TNBC diagnosis

Early detection of breast cancer plays a pivotal role in improving survival rates and treatment outcomes. According to Coleman *et al.* (2017),[53] serial screening through quality digital mammography remains the most reliable and effective approach for identifying small, non-palpable tumors, which are associated with significantly reduced mortality. Mammography, when performed by trained professionals using certified equipment, can achieve an accuracy rate of 85–90%, contributing to a 30–50% reduction in mortality among screened women. Complementary methods, such as clinical breast examination and breast self-examination continue to play essential roles, particularly in low-resource or underserved settings where access to mammography is limited. Furthermore, emerging imaging technologies, like digital breast tomosynthesis (3D mammography) and breast magnetic resonance imaging (MRI), have enhanced diagnostic precision and detection rates.[53] Building upon these early detection strategies, recent advancements in cancer research have introduced the use of targeted NPs for both diagnosing and treating aggressive subtypes, such as TNBC. These targeted NPs hold immense potential for improving detection sensitivity and therapeutic precision. However, challenges related to the development of efficient and safe delivery mechanisms must be addressed to ensure their successful translation into clinical applications.

Ongoing developments in cancer studies have resulted in the creation of site-specific NPs for detecting, as well as for treating TNBC. By employing fourth-generation (G4) polyamidoamine (PAMAM) dendrimers functionalized with gadolinium 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (Gd-DOTA), a clinically approved MRI contrast agent, and a fluorescent dye, researchers have engineered multifunctional NPs capable of real-time tracking of tumour accumulation, targeting the tumour microenvironment, and inhibiting tumour growth. These NPs demonstrate promise for combined therapeutic delivery and imaging, while exhibiting minimal toxicity to healthy tissues and organs.[54]

By combining NPs with specific drugs for site-specific targeting, researchers have improved TNBC chemotherapy while minimizing adverse effects. Studies have identified promising molecular markers for treating TNBC, such as the transmembrane tumor necrosis factor (TNF) α (tmTNF-α) expression. Most TNBC patients express tmTNFα, making it an appealing target for therapy. Paclitaxel (PTX) NPs coupled with anti-TNF-α monoclonal antibodies (mAbs) have been developed to actively target TNBC, effectively reducing the viability of TNBC cells and improving therapeutic effectiveness.[55] Additionally, photodynamic therapy (PDT) is a promising and effective cancer treatment that uses photosensitizing agents and light to selectively target and destroy cancer cells. The developed cyclic arginine-glycine-aspartic acid (cRGD) peptide-decorated conjugated polymeric NPs with poly[2-methoxy-5-(2-ethyl-hexyloxy)-1,4-phenylenevinylene] (MEH-PPV) NPs have shown significant potential for imaging-assisted photodynamic treatment of TNBC by selectively targeting and destroying cancer cells when exposed to light, with no toxicity in the absence of light. This approach could lead to new and improved treatment approaches for TNBC.[56]

3.1. Application of nanoparticles in TNBC diagnosis

Medical imaging techniques such as MRI, fluorescence imaging, photoacoustic imaging (PAI), computed tomography (CT), ultrasound (US), single-photon emission CT, and positron

emission tomography (PET), and single-photon emission computed tomography (SPECT) are commonly used for a non-invasive approach to evaluate anatomical, functional, and molecular data for supporting the detection of abnormalities.[57] These techniques have been frequently combined with NPs for improved cancer diagnosis.

3.1.1. Computed tomography. Ongoing improvements in medical imaging have supported the design of innovative contrast enhancers for CT imaging, such as barium or iodine compounds and targeted NPs. For CT imaging, low-density lipoprotein (LDL)-based iodinated NPs targeting specific receptors have been explored. These innovations hold promises for improving the visualization of anatomical structures and organs while also minimizing toxicity to normal cells during radiotherapy. Additionally, TNBC is linked to a heightened immune response due to overexpression of the mucin 1 (MUC1) gene, which is a marker of malignancy in various cancers. Therapeutic strategies targeting MUC1 include immunoglobulins, immunization treatments, and nucleic acid-based aptamers, which are synthetic oligonucleotides with high affinity and specificity to their targets.[58] This study demonstrated that nano-radiopharmaceuticals incorporating the anti-MUC1 aptamer have the potential to function as imaging agents for TNBC.[58] The potential of utilizing these innovations to target specific molecules, such as MUC1 in TNBC, opens new doors for improving imaging approaches and developing effective therapeutic strategies.

3.1.2. Positron emission and single photon emission computed tomography. Advancements in nuclear imaging methods, specifically PET and SPECT, have paved the way for extensive research in medical applications involving NPs. The combination of these imaging methods with NPs has shown the potential to significantly enhance image contrast by labeling NPs with multiple radionuclides. Additionally, NPs linked with unstable radioisotopes for PET and SPECT imaging exhibit high sensitivity, suggesting their efficacy for successful imaging.[58] The relevant results from PET/CT images, revealing characteristics such as prolonged circulation in the bloodstream, minimal kidney excretion, increased accumulation in tumors, and decreased liver load, highlight the promising role of NPs as novel agents for PET imaging (Fig. 3).[59]

3.1.3. Magnetic resonance imaging. MRI technology has rapidly evolved, becoming a pivotal tool in both preclinical research and clinical practice for visualizing physiological processes and anatomical structures. In this context, various advanced techniques, including functional MRI (fMRI), dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-sensitive MRI (DW-MRI), have been instrumental in enhancing contrast and providing detailed images.[59] Tumor-homing peptides, like the LyP-1 peptide,

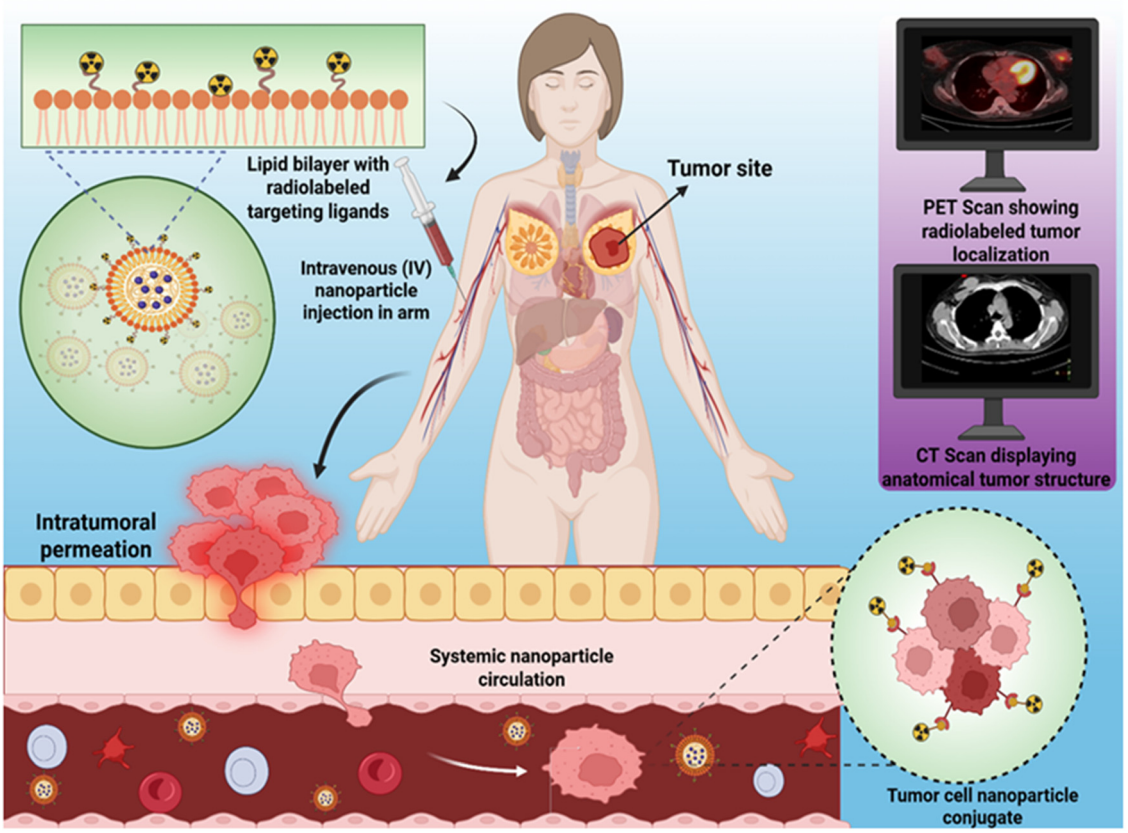

Fig. 3 Schematic diagram illustrating tumor-targeted imaging with radiolabeled nanoparticles. Following intravenous injection, the nanoparticles accumulate at the tumor site, bind to cancer cells, and enable non-invasive imaging *via* Positron Emission Tomography (PET) and Computed Tomography (CT). This approach integrates targeted delivery with diagnostic imaging, enhancing early detection and treatment monitoring in breast cancer and other solid tumors (authors' own artwork).

have been identified for their specific localization to tumors and are being used in advanced imaging technologies for the non-invasive quantification of tumor biomarkers. Magnetic iron-oxide NPs are also being used in medical imaging due to their detectability using standard MRI techniques.[60] These NPs can be conjugated with tumor-specific biomolecules for targeted imaging of TNBC. Molecular imaging techniques are being developed to diagnose TNBC at early stages and monitor the effectiveness of treatments, ultimately improving the prognosis for TNBC patients.[61]

Efforts are being made to develop NPs, such as antibody-conjugated gadolinium-doxorubicin-loaded poly(ethylene glycol)-poly(ε-caprolactone) copolymers (PEG-PCL) (anti-Gd-DOX@PEG/PCL) NPs, to enhance treatment effectiveness while minimizing the overall toxicity of chemotherapeutic drugs, like DOX.[62] Furthermore, ICAM1, a cell adhesion molecule, is being explored as a prospective indicator for selective imaging and therapeutic applications for TNBC. Studies have shown that biocompatible NPs targeting ICAM1 have enhanced diagnostic and therapeutic efficacy for TNBC without causing significant damage to major organs, indicating the potential for effective TNBC management[62]

4. TNBC theragnostics

Engineered NPs with the dual function of therapy and diagnosis leads to a new, powerful tool in TNBC treatments. Thecodelivery of imaging agents, chemotherapeutics, siRNA/miRNA, and immune-stimulatory agents is expected to achieve synergistic cytotoxic and immunomodulatory effects in preclinical TNBC models.[63] By remodeling the immunosuppressive tumor microenvironment and promoting immunogenic cell death, NPs can sensitize TNBC to immune checkpoint blockade and other immunotherapies.[64] Biomimetic and ligand-targeted NPs (*e.g.*, hyaluronic acid natural targeting ability to bind to overexpressed CD44 receptors on cancer cells, and peptide conjugates on the NPs' surface that identify cancer cell receptors) increase uptake by TNBC cells and tumor stromal targets, improving the therapeutic index and reducing off-target effects.[65]

Various types of NPs, including lipid, inorganic, polymeric, and carbonaceous, have been studied for their theragnostic use in TNBC. Lipid NPs offer biocompatibility due to their composition in *e.g.*, phospholipids, fatty acids, and cholesterol. Inorganic NPs, like gold, iron oxide, and quantum dots, serve as multifunctional agents for diagnostic and therapeutic purposes because of their exceptional opto-magnetic characteristics. Polymeric NPs enable controlled drug release and immune evasion by tuning their physical and chemical properties. The anti-cancer agent is protected within the NPs and is released at a target site, avoiding systemic clearance and reducing side effects.[66] Polymeric nanoparticles such as micelles, dendrimers, and polymersomes enable controlled drug release through their tunable architectures and stimulus-responsive polymer matrices that release payloads in response to pH, enzymes, or redox conditions.[67] Their surfaces can be modified (*e.g.*, PEGylation), which minimizes protein adsorption and immune recognition, thereby prolonging circulation time and enhancing tumor-selective delivery.[66] Carbon-based nanomaterials, such as graphene and carbon nanotubes, contribute to enhanced drug loading, membrane penetration, and imaging sensitivity. Beyond composition, the surface electrical charge (zeta potential) of NPs plays a pivotal role in their performance, influencing cellular uptake, tumor targeting, colloidal stability, and cytotoxicity. By carefully tuning both the type and surface charge, these nanocarriers can maximize therapeutic delivery, improve imaging sensitivity, and achieve integrated diagnosis and treatment strategies in TNBC.[68–70]

4.1. Organic nanoparticles in cancer theragnostics

Fattahi *et al.* (2024)[71] developed poly-ε-caprolactone (PCL) NPs incorporated with DOX and 5-fluorouracil (5-FU), which induced the reduction of Bcl2 and Bax expression levels in NPs' treated cells.[71] Liposomes are undoubtedly the most recognized and versatile lipid NPs accessible today, owing to their distinct features. They consist of phospholipid bilayers surrounding an aqueous core and provide several benefits, such as excellent biological compatibility, biological degradation, simple fabrication, controlled drug release, minimal toxicity, and the capacity to carry both water-soluble and fat-soluble anticancer agents. Furthermore, their exterior can be tailored for site-specific delivery in oncology treatment.[72] Liposomes are among the few NPs that are thought to be suited for a variety of drug delivery applications, including the transfer of functional compounds into cellular systems.[73,74]

Liposomes can gather in malignant tissues *via* two mechanisms: passive uptake mediated by the enhanced permeability and retention (EPR) effect and selective binding to malignant cells or an angiogenic signal. Liposomes are a valuable platform for delivering anti-tumor medicines *in vivo*, such as PTX, DOX, oligonucleotides, and other cytotoxic agents. DOX-loaded liposomes (Doxil) were described to be more effective and absorbable in breast cancer patients compared to free DOX.[75] Doxil is an FDA-approved nanomedicine, and more than twelve nanomedicine formulations utilizing polymeric micelles are undergoing therapeutic trials.[76] Tahmasbi Rad *et al.* (2019)[77] described that spherical nanomedicines with a diameter of 20–100 nm are more effective for tumor progression due to their EPR effect, although distinct EPR effects were proven to be due to nonspherical nanostructures (*i.e.*, nanorods).[78,79]

Bahrami Parsa *et al.* (2023)[80] developed a co-delivery liposomal system encapsulating cisplatin and DOX (Fig. 4A) to enhance treatment efficacy and reduce toxicity in ovarian cancer therapy. Cytotoxicity studies showed that the dual-drug liposomes were more biocompatible with normal cells and significantly more cytotoxic to ovarian cancer cells (A2780) than free or combined drugs. Additionally, the formulation promoted apoptosis and cell cycle arrest in cancer cells[80]

Vári *et al.* (2023)[81] compared traditional CREKA-modified liposomes with newly designed SREKA-liposomes, where the N-terminal cysteine was replaced with serine to enhance conjugation efficiency and stability (Fig. 4B). Both peptides target the

tumor-associated extracellular matrix present in primary and metastatic sites. The results showed that SREKA-liposomes exhibited comparable tumor targeting ability to CREKA-liposomes but offered higher production yield, improved conjugation stability, stronger inhibition of tumor growth and metastasis, and enhanced survival in tumor-bearing mice.[81]

While a large range of polymers and lipids are accessible for the creation of theragnostic platforms, proteins also offer great promise as a carrier material because of their enhanced biological compatibility, biodegradability, and low risk of inducing adverse effects.[82] Unlike synthetic polymers, they possess natural targeting ability through proteins, such as albumin, ferritin, and transferrin, enabling selective tumor delivery and co-loading of drugs and imaging agents.[83] Their abundant reactive groups allow easy surface modification for precise targeting and multimodal imaging.[82] Moreover, their mild synthesis conditions preserve biomolecule activity while reducing toxicity and immune responses.[83]

Proteins are naturally amphipathic, allowing the hydrophobic domains of the NPs to bind to a variety of non-polar anti-cancer medicines, which increases their drug loading capacity. Certain proteins inherently tend to target cancer cells, and specific ligands can be modified on the protein–NP surface to enhance tumor targeting.[84,85] Because of their low toxicity and efficient therapeutic loading ability, protein NPs employed for loading drug molecules can achieve increased intratumoral drug levels.[86] Protein NPs break down into amino acids during metabolism, which are harmless and safe for human use.[82] Albumin-associated NPs (~130 nm) represent a protein-derived technology used in cancer therapy. Albumin has shown high tumor uptake[87] establishing it as a possible vehicle for targeted anticancer medicines. The clinical adoption of Abraxane (albumin-PTX) for progressive breast cancer by the FDA points to the translational potential of albumin-mediated nanomedicine.

Ma *et al.* (2021)[88] developed a tLyP-1-functionalized ferritin nanocarrier (tLyP-1-HFtn) (Fig. 4C) for targeted delivery of PTX to tumor cells.[88] The tumor-penetrating peptide tLyP-1 was fused to the N-terminal of human ferritin, and PTX was encapsulated *via* a pH-mediated assembly method. The resulting NPs showed enhanced cellular uptake, cytotoxicity, and anti-migration effects in MDA-MB-231 and SMMC-7721 cells compared to non-targeted ferritin-PTX. N-terminal tLyP-1

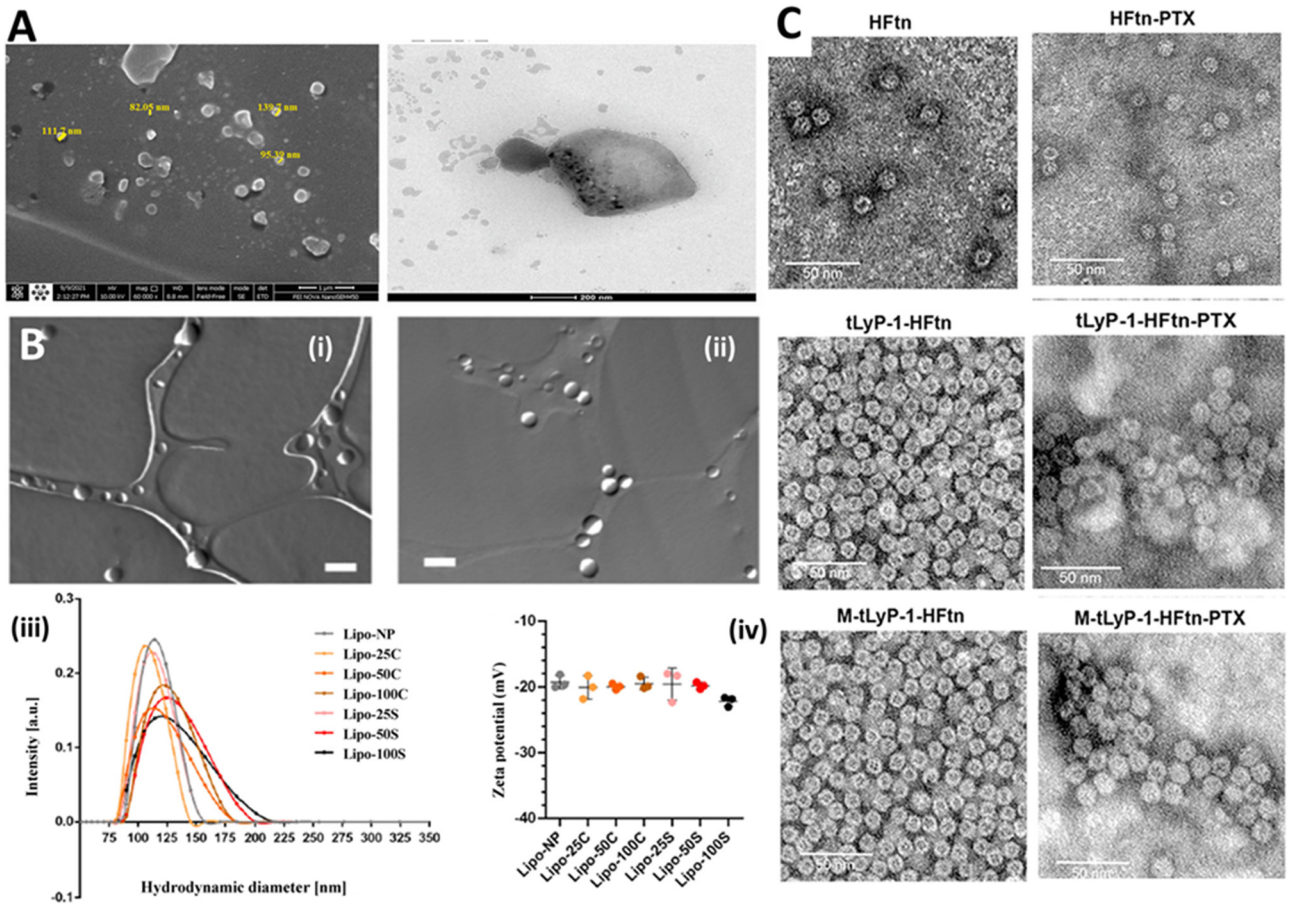

Fig. 4 (A) Field emission scanning electron microscopy (FE-SEM) and transmission electron microscopy (TEM) images of cisplatin and doxorubicin-loaded liposomes [Lipo (CIS + DOX)][80] reproduced under open access Creative Common CC BY NC ND license). (B) (i) TEM images of liposomes. (ii) TEM image of liposomes Lipo-100C. (iii) Hydrodynamic mean diameter and (iv) zeta potential of liposomes composed of different amounts of DSPE-PEG-CREKA and DSPE-PEG-SREKA[81] (reproduced under open access Creative Common CC BY license). (C) TEM micrographs of HFtn, tLyP-1-HFtn, and PTX-loaded NPs.[87] (Reproduced under open access Creative Common CC BY license).

modification effectively enhanced ferritin-based targeted PTX delivery and antitumor performance.[88]

Bioengineering techniques can be used to manufacture proteins without using chemical synthesis or harmful substances[85,89] Because proteins have various epitopes and microstructures on their surfaces, modifying and producing NPs to improve their functionality is possible. Advanced bioengineering technology could be employed in antigenic epitopes or surface groups on protein NPs for anticancer applications.[90–93]

In recent decades, metal–organic frameworks (MOFs) have garnered a great deal of attention for cancer theragnostics.[87] MOFs have variable structures with a broad spectrum of morphologies, chemical characteristics, sizes, and compositions, making them ideal as multifunctional moieties for triggered drug release. MOF-based materials maintain predictable size, homogeneity, and shape.[87] Their enhanced pore density and broad surface areas provide MOFs a maximum payload capacity; besides, their labile bonds make MOFs biodegradable.[94]

Despite these inherent advantages, MOFs are especially promising for breast cancer treatment because their tunable three-dimensional architecture allows for precise customization of pore size, surface chemistry, and metal–ligand composition to suit the specific demands of tumor microenvironments. These properties allow them to be tailored to the acidic, redox-imbalanced, enzyme-rich breast tumor microenvironment, enabling precise drug delivery, controlled release, active targeting, and multimodal therapy, features that are difficult to achieve simultaneously with conventional NPs.[95] Their exceptionally high porosity and surface area enable high loading and efficient delivery of chemotherapeutic agents, imaging moieties, and immunomodulators, thereby integrating therapy with diagnostics.[96] Furthermore, the stimuli-responsive degradability of MOFs triggered by tumor-specific conditions, such as low pH or elevated glutathione, ensures controlled release inside tumor sites and rapid clearance from the body, reducing systemic toxicity and improving biocompatibility.[97]

Large quantities of drugs with various chemical and physical characteristics can be encapsulated in MOF-based NPs.[98,99] The most widely utilized subtype of MOFs, zeolitic imidazolate framework-8 (ZIF-8), is consistent with 2-methylimidazole and zinc ions. Remarkably, ZIF-8 has strong biodegradability and pH-sensitive degradation characteristics, enabling the release of encapsulated medications in the endosomal and/or lysosomal environment of tumor cells and high stability in circulation.[100]

Wu *et al.* (2024)[99] designed self-targeted MOF-based NPs to form methotrexate-PEG conjugates (MTX-PEG@TPL@ZIF-8) for metastatic TNBC therapy by synergistically enhancing chemotherapy efficacy and tumor microenvironment modulation. The NPs exhibited an average size of 132.0 ± 4.3 nm and a surface electrical charge of 11.9 ± 2.5 mV. The encapsulation efficiency reached values above 75%, and the loading capacity was around 10%. The NPs' pH-triggered release enabled efficient tumor accumulation and deep tissue penetration through MTX-mediated self-targeting.[99]

Kulkarni *et al.* (2025)[101] developed transferrin-functionalized, PEGylated DOX-loaded Zn-MOF-74 NPs to overcome the limitations of conventional chemotherapy. The highly porous MOF structure ($\sim$1680 m^2 g^{-1}) enabled exceptional high encapsulation efficiency ($>$90%) while maintaining nanoscale dimensions ($\leq$100 nm) and structural integrity. The PEGylated DOX-loaded Zn-MOF-74 NPs exhibited pH-responsive degradation, endorsing selective drug release in acidic tumor microenvironments and minimizing systemic toxicity. Extensive hemocompatibility and chorioallantoic membrane (CAM) assays demonstrated excellent biocompatibility. *In vitro* studies using 4T1 cells, along with *in vivo* pharmacokinetic, pharmacodynamic, and biodistribution analyses, revealed enhanced tumor targeting, prolonged circulation, and superior therapeutic efficacy, highlighting strong translational potential for breast cancer treatment.[101]

Carbon nanomaterials have significantly enhanced the diagnosis and treatment of cancer.[102] Carbon nanomaterials possess remarkable characteristics, including extensive surface coverage with adaptable pore dimensions and chemically inert yet easily functionalizable surfaces, rendering them highly suitable for biomedical applications, especially in cancer detection. These features pave the way for enhanced therapeutic approaches. Carbon nanomaterials include fullerene (0-D), carbon nanotubes (1-D), and graphene (2-D).[103] These nanomaterials possess suitable dimensions, electrical properties, surface characteristics, molecular makeup, tendency to cluster together, and solubility, which can have a significant impact on their interactions with biomolecules and cells, making them ideal candidates for establishing new antineoplastic systems.[57,104,105]

Carbon nanotubes (CNTs) are innovative synthetic nanomaterials characterized by their tubular shape. Graphene scroll formation produces CNTs. CNTs have exceptional chemical, electrical, and structural properties. Modifying CNTs with biological components enhances their potential for biocompatible drug delivery strategies aimed at selectively targeting and destroying cancer cells.[110,111] The π–π interactions and functionalizable surface groups in multiwalled carbon nanotubes (MWCNTs) facilitate covalent or non-covalent attachment of drugs, targeting ligands, and biomolecules, enhancing tumor specificity and minimizing systemic toxicity.[112] Komane *et al.* (2018)[106] synthesized vertically aligned MWCNTs for delivering dexamethasone to ischemic brain tissue (Fig. 5A). CNTs were PEGylated and loaded with dexamethasone after optimizing conditions for high yield. The developed CNTs showed strong potential for controlled dexamethasone delivery to improve ischemic stroke treatment, with ongoing studies aimed at targeted delivery using atrial natriuretic peptide antibodies in stroke models.[106] Asadipour *et al.* (2024)[113] investigated the therapeutic potential of carboxylated MWCNTs as a novel nanotherapeutic strategy for TNBC. Using MDA-MB-231 cells, CNTs revealed dose-dependent cytotoxicity, significantly reduced spheroid formation, and inhibited epithelial–mesenchymal transition–associated tumorigenic behavior *in vitro*. *In vivo* evaluation in TNBC xenograft mouse models revealed a marked reduction in tumor volume following intratumoral CNT administration, confirming antitumor efficacy. The findings highlighted CNTs as promising nanomaterials for TNBC treatment, while emphasizing the need for mechanistic, pharmacokinetic, and long-term safety studies to support clinical

translation.[113] Similarly, in one of the most recent studies done by Nabawi *et al.* (2025),[114] a folic acid–targeted, sorafenib-PEGylated CNT was developed for TNBC, demonstrating threefold higher cytotoxicity, enhanced apoptosis, and superior molecular inhibition compared with the free drug. *In vivo*, the formulation achieved eightfold increased bioavailability and prolonged half-life, highlighting improved pharmacodynamic and pharmacokinetic performance for targeted TNBC therapy.[114]

Carbon quantum dots are promising nanomaterials with broad application potential in cancer treatment. Carbon quantum dots exhibit lower cytotoxicity compared to conventional quantum dot counterparts, primarily because the former lack heavy metals in their composition. Their extensive surface area enables interaction with a wide range of chemical substances, making them particularly advantageous in drug delivery systems (DDSs), especially for carrying multiple anticancer agents.[57,115] Azizi *et al.* (2024)[116] reported the development of a carbon dot–based theragnostic nanoplatform conjugated with anti-PD-L1 antibodies (anti-PD-L1-CD) for targeted immunotherapy and bioimaging of TNBC. Ethylene glycol-stabilized carbon dots aided efficient antibody conjugation, cellular internalization, and fluorescence-based imaging in PD-L1–overexpressing MDA-MB-231 cells. The anti-PD-L1-CD bioconjugate showed significantly improved cytotoxicity, reduced colony formation, and augmented apoptosis compared with free anti-PD-L1 antibody, while maintaining high biocompatibility in normal fibroblasts. The findings advocated carbon dot–antibody conjugates as promising immuno-theragnostics for precision TNBC treatment.[116] Similarly, Kumar *et al.* (2024)[117] designed luminous blue carbon quantum dots using *Anisomeles indica* (Catmint) with imaging and therapeutic effects on MDA-MB-231 cells. The carbon quantum dots generated from catmint showed excitation-dependent emission, near-spherical shape with size ranging between 5 and 15 nm. The carbon quantum dots induced cytotoxicity with a lethal concentration (LC50) of 3.22 ± 0.64 μg mL^{-1} in MDA-MB-231 cells. Additionally, the carbon quantum dots promoted apoptosis by increasing ROS and decreasing the mitochondrial membrane potential. Moreover, the carbon quantum dots remarkably up-regulated pro-apoptotic gene expression levels such as caspases-8/9/3. The results demonstrated catmint-derived carbon quantum dots as prospective theragnostics to improve cancer targeting and imaging.[117]

Graphene is defined as a 2-D nanoscale sheet composed of a monolayer of carbon atoms organized in a six-sided lattice structure, representing a finite fragment of graphite placed at the vertices of a hexagonal network.[118,120] The 2-D configuration of graphene and the delocalized π-electrons distributed across the surface promote effective drug attachment through hydrophobic forces and π–π stacking. Additionally, the extensive surface area of graphene enables high-capacity biofunctionalization through both covalent and non-covalent surface alteration methods. Several investigations on graphene's *in vivo* performance and therapeutic activity demonstrate that NPs engage with cellular membranes and are internalized through endocytic pathways.[121–123]

The graphene-modified NPs have been seen as promising materials for the theragnostics of TNBC. The study done by Itoo *et al.* (2023)[119] reported multifunctional graphene oxide-based poly-L-lactic acid (PLA) NPs loaded with DOX (DOX@GO(m-PEG-PLA) NPs) for synergistic chemo-photothermal therapy of TNBC. The optimized NPs showed a particle size of approximately 161 nm, a zeta potential of −28 mV, a drug loading of 6.3%, and an encapsulation efficiency of 70%. Under 808 nm NIR irradiation, the NPs enhanced ROS production, caused mitochondrial depolarization, induced G2/M cell-cycle arrest, and triggered apoptosis in MDA-MB-231 and 4T1 cells, surpassing the effects of free DOX. In 4T1-Luc tumor-bearing mice, laser-activated DOX@GO(mPEG-PLA) NPs significantly suppressed tumor growth and lung metastasis, demonstrating strong potential for translational application in combined TNBC therapy.[119] Another study done by Basu *et al.* (2024)[120] demonstrated that folic acid-functionalized PEGylated graphene oxide (FA-PEG-GO) efficiently suppresses MDA-MB-231 cell migration through targeted delivery. FA-PEG-GO disrupts actin dynamics and lamellipodia formation by inhibiting NF-κB-mediated miR-21, thereby upregulating PTEN gene and downregulating pFAK, pAkt, and pERK1/2. *Ex ovo* chick embryo assays confirmed its strong antimigratory potential, highlighting FA-PEG-GO as a promising anti-metastatic nanotherapeutic strategy.[120]

4.2. Inorganic nanoparticles in cancer theragnostics

Inorganic NPs feature a metallic or metal oxide center enclosed within an organic outer layer, which stabilizes the core in the biological milieu and allows functionalization sites to incorporate biomolecules for targeted drug delivery.[121] Inorganic NPs exhibit unique physicochemical characteristics, like easy synthesis, extensive surface compared to their volume, and customizable surfaces to improve their binding ability and specificity towards target molecules.[122,123] Inorganic NPs offer greater drug-loading potential, enhanced stability, and adjustable degradation rates when compared to their organic counterparts.[124–128] Because of their unusual physicochemical properties, inorganic NPs such as gold, silver, silica, rare earth oxides, iron oxides, and zinc oxide, have been widely utilized in numerous biomedical fields, including cancer theragnostics, biosensing, bioimaging, and the transport of therapeutic agents and genetic material.[129,130]

Oliveira *et al.* (2023)[107] developed PTX-loaded lipid-coated manganese ferrite magnetic NPs as synthetic magnetosome analogs for combined chemotherapy and magnetic hyperthermia treatment (Fig. 5B). This approach drastically reduced the drug's half-Maximal Inhibitory Concentration (IC_{50}), demonstrating high therapeutic efficiency with minimized systemic toxicity.[107]

Green chemistry biosynthesis of inorganic NPs has attracted significant interest owing to several benefits over traditional chemical synthesis methods.[131] Biosynthesis is usually fast and simple, offering an environmentally friendly alternative by eliminating the use of harmful chemicals; it utilizes a wide range of readily available biological reducing agents (*e.g.*, algae, plants, and bacteria) and employs water as a generally accepted solvent. Montazersaheb *et al.* (2024)[108] explored the use of green-synthesized AgNPs as radiosensitizers for TNBC.[108] AgNPs were synthesized using pumpkin peel extract, offering a low-

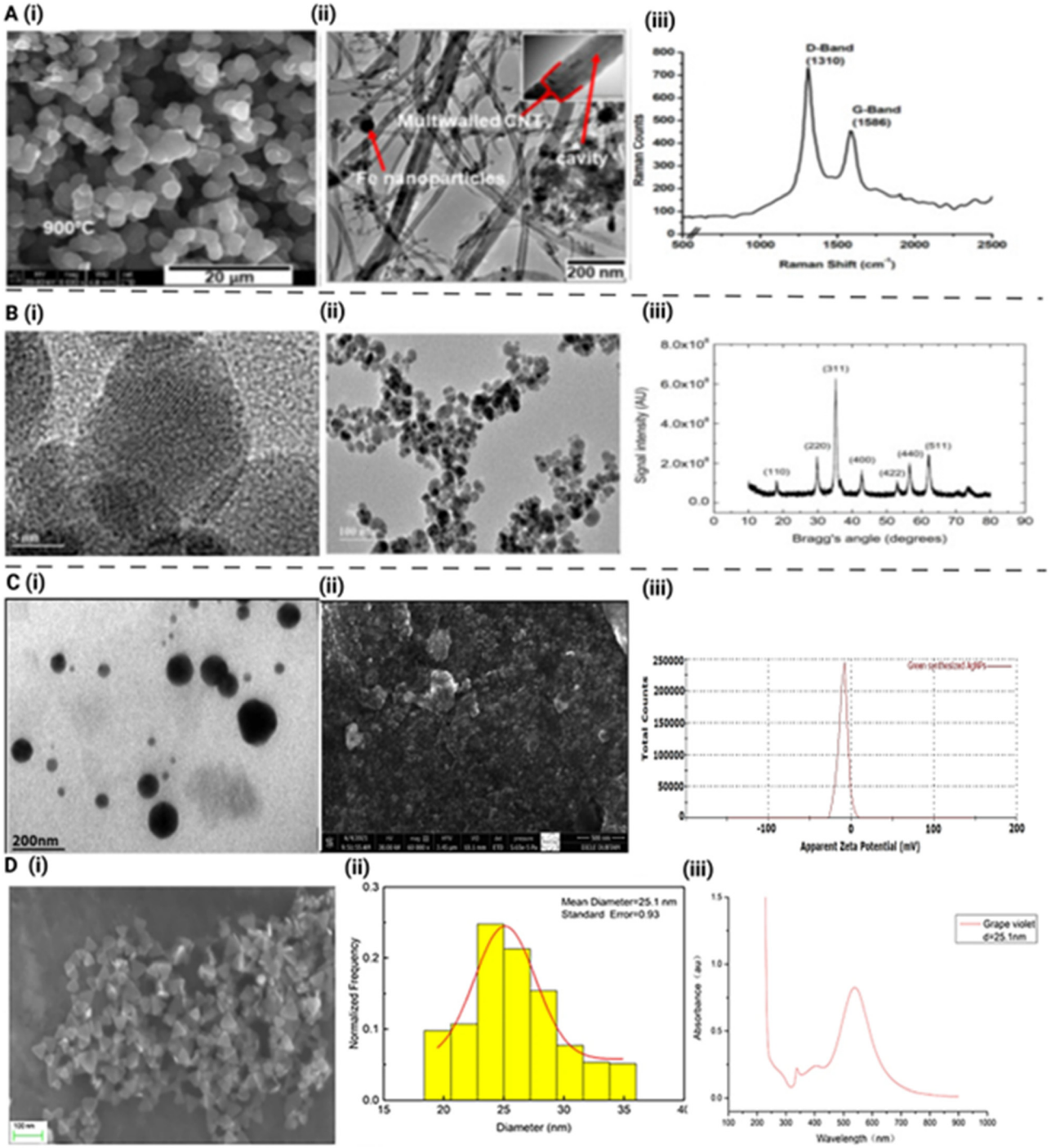

Fig. 5 (A) (i) Scanning electron microscopy (SEM) image of carbon NPs formed at 900 °C; (ii) transmission electron microscopy (TEM) image of multi-walled carbon nanotubes (MWCNTs); (iii) Raman spectrum showing graphitic carbon[106] (reproduced under open access Creative Common CC BY license). (B) (i) TEM and (ii) high-resolution TEM (HR-TEM) images of the passivated manganese ferrite magnetic NPs; (iii) X-ray diffraction pattern confirming crystallinity[107] (reproduced under open access Creative Common CC BY license). (C) (i) TEM image of AgNPs; (ii) SEM image showing aggregated AgNPs; (iii) zeta potential of AgNPs.[108] (D) (i) SEM image of triangular AgNPs (tAgNPs) clusters; (ii) average diameter of tAgNPs; (iii) UV-Vis absorbance spectrum of tAgNPs[109] (reproduced under open access Creative Common CC BY license).

toxicity and eco-friendly approach (Fig. 5C). The research aimed to assess how these green Ag-NPs enhance the sensitivity of MDA-MB-231 cells to radiation therapy, potentially improving treatment outcomes while minimizing side effects.[108] Krishnaraj *et al.* (2014)[109] investigated the cytotoxic effects of biologically synthesized AuNPs on MDA-MB-231 cells. NPs were successfully synthesized as confirmed by ultraviolet-visible (UV-Vis) spectroscopy, field emission scanning electron microscopy (FE-SEM), transmission electron microscopy (TEM), and X-ray diffraction (XRD) analyses (Fig. 5D). At 100 μg mL^{-1}, the NPs showed strong

anticancer activity, inducing apoptosis *via* caspase-3 activation and DNA fragmentation. These findings suggest that plant-derived AuNPs have potential as breast cancer therapeutics, pending further clinical validation.[109]

4.2. Nanoparticles as drug delivery systems

Controlled DDSs alleviate the impact of drugs on healthy tissues and reduce side effects by transporting them directly to the site of action (Fig. 6), *via* the EPR effect. DDSs shield the drug from rapid degradation, leading to increased concentration in target tissues. By regulating drug delivery, NPs may improve site specific drug delivery and reduce off-target effects. The properties and biological effects of different types of NPs in the delivery of standard chemotherapeutic drugs are summarized in Table 1.

Liu *et al.* (2022)[136] developed targeted NPs to enhance PTX delivery for TNBC treatment by exploiting the transmembrane TNF-α (tmTNF) biomarker (Fig. 7A). PTX-loaded NPs were conjugated with tmTNF-α monoclonal antibodies (tmTNF-α mAb-PTX NPs) using an emulsification–evaporation method. The proliferation of tumors in human MDA-MB-231 xenograft mice was markedly inhibited by tmTNF-α mAb-PTX NPs, which showed anti-tumor effects by enhancing apoptosis and modulating MAPK, PI3K – AKT – mTOR cascade, alongside the AMPK and NF-κB pathways. Nicolescu *et al.* (2023)[135] developed dual-targeted ECO/siDANCR NPs designed to silence DANCR by delivering siRNA using ionizable lipids (Fig. 7B). These NPs were engineered to target both extradomain B fibronectin (EDB-FN) in the tumor extracellular matrix and integrins on cancer cells, enhancing delivery specificity. *In vitro* treatment of Hs578T and MCF-7 cells led to marked downregulation of DANCR and EDB-FN, reducing cell invasion and 3D spheroid growth.[135] Mehta *et al.* (2024)[137] presented a novel targeted therapy for TNBC using lipid NPs loaded with siXBP1 and conjugated with an EGFR antibody (Fig. 8A). The NPs aimed to silence the XBP1 gene, which supports TNBC cell survival under hypoxic conditions. The EGFR-targeted siXBP1 NPs demonstrated strong potential for precise and effective TNBC therapy, laying the groundwork for future preclinical and clinical studies.[137]

Liu *et al.* (2022)[138] found that coating liposomes with PEG and dibenzocyclooctyne (DBCO) (Fig. 8B) significantly enhanced their internalization both *in vitro* and *in vivo*. Liposomes decorated with DBCO achieved about 50% tumor uptake, compared to ~20% for unmodified liposomes. Using 4T1, MDA-MB-231, and MDA-MB-436 breast cancer models, the DBCO-coated liposomes (L-PEG2000-DBCO) showed greater accumulation in tumors, regardless of the size, type, location, or receptor expression.

Dey *et al.* (2022)[139] investigated the therapeutic potential of AgNPs against MCF-7 cells. The AgNPs were found to localize within mitochondria, causing mitochondrial membrane depolarization (Fig. 8C), ROS generation (Fig. 8C), and loss of mitochondrial stability. They also induced endoplasmic reticulum stress, which was closely linked to disrupted mitochondrial dynamics. Together, these effects triggered apoptosis in MCF-7 cells. The

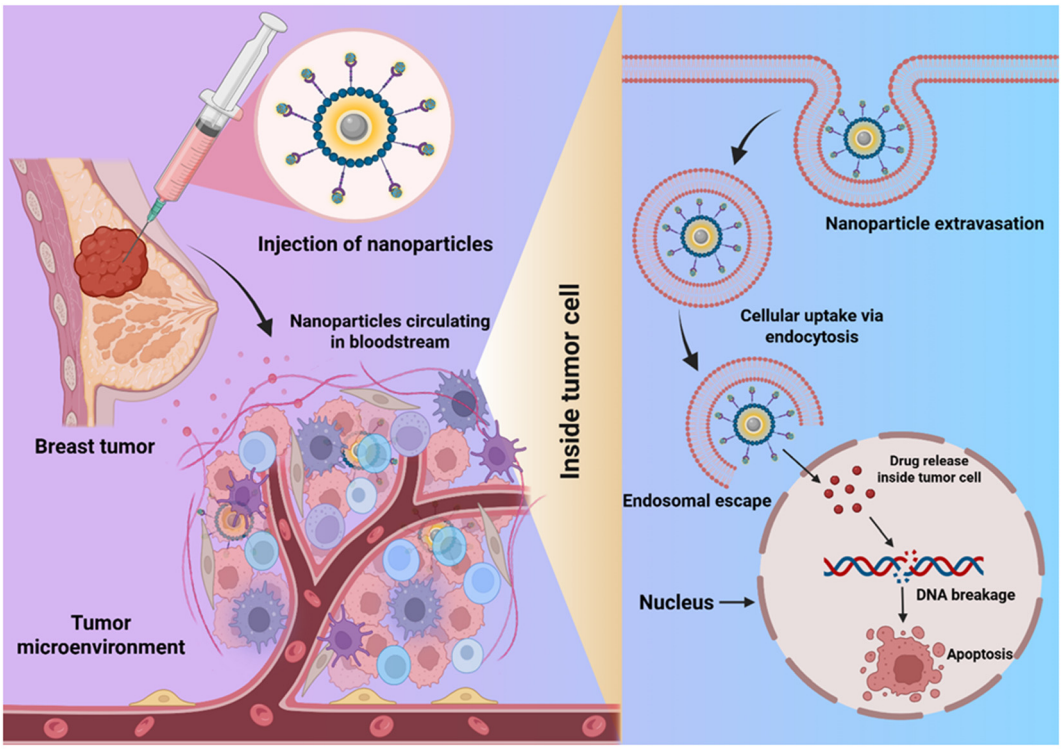

Fig. 6 Schematic representation of drug delivery to breast tumor: after administration, NPs accumulate at tumor sites through the enhanced permeability and retention (EPR) effect. They enter tumor cells *via* endocytosis, escape endosomes, and release their therapeutic payload, causing DNA damage and apoptosis. This process enhances the efficacy of treatment in breast cancer (authors' own artwork).

Table 1 Properties and biological effects of different types of nanoparticles loaded with chemotherapeutic drugs

Nanoparticles	Properties	Therapeutic drug	Drug loading	Biological effects	Ref.
Polymeric NPs	Spherical, branched, or core–shell in nature, biodegradable, and possess diameters between 10 and 100 nm	5-Fluorouracil	The drug is encapsulated during the polymerization process	It increases the amount of time drugs remain in the bloodstream	132
Liposomes	Artificially derived biodegradable spherical vesicles, with a hydrophilic core and a hydrophobic bilayer for encapsulating therapeutic agents	Doxorubicin	It is encapsulated in the inner core of liposomes	The drug's distribution to the heart and renal system is reduced	133
Carbon nanotubes (CNTs)	Cylindrical carbon structures made up of benzene rings	Dexamethasone	The drug is encapsulated within the carbon nanotube	The delivery of the drug to the cells protects it from breakdown, and its release occurs only under specific conditions	134
Magnetic NPs	Core–shell structure	Paclitaxel	The drug can be conjugated through covalent binding, electrostatic interaction, adsorption, or encapsulation	Improved uptake by the target tissue results in efficient therapy at ideal dosage levels	132
Protein-based NPs (viral NPs)	Biocompatible and biodegradable, lacking a virus genome and bearing similarities to the protein envelopes or capsids of viruses	Trastuzumab	NPs are conjugated with the trastuzumab monoclonal antibody	NPs inhibit the proliferation of cells and obstruct the transmission of signals	133

findings reveal that AgNPs can induce cancer cell death by modulating mitochondrial-endoplasmic reticulum interactions, highlighting their promise as a novel chemotherapeutic agent for breast cancer.

Surapaneni *et al.* (2018)[140] explored how the surface charge of AuNPs influences their cytotoxic effects in TNBC cells (Fig. 8D). Both negatively charged (citrate-capped) and positively charged (cysteamine-capped) AuNPs induced dose-dependent cell death in MDA-MB-231 and MDA-MB-468 cells through oxidative stress–mediated disruption of the Wnt signaling pathway. This study reveals that the surface charge of AuNPs critically determines their mechanism of cytotoxicity and potential for combination cancer therapy.[140]

Studies have emphasized the modification of NPs to enhance their biocompatibility (Table 2 and Table 3). A study used special pH-responsive linkages to fabricate DOX-conjugated PEG NPs on a β-L-malic acid. The pH-sensitive conjugates remained stable at physiological pH and released the encapsulated drug. The effective hindered growth of the MDA-MB-468 and MDA-MB-231 cancer cell lines was observed *in vitro*, as shown in Fig. 8D[140] Lectin-conjugated pH-responsive mesoporous silica NPs loaded with DOX showed targeted uptake and controlled release *in vivo*. In osteosarcoma models, these NPs achieved high tumor inhibition with minimal toxicity to healthy tissues, confirming excellent biocompatibility and therapeutic efficiency.[141]

Researchers developed gold-DOX nano-conjugates (Au-PEG-SS-DOX) for cancer therapy. These particles demonstrated efficient tumor targeting and drug delivery, and exhibited acceptable toxicity profiles in HepG2 cells, supporting their biocompatibility.[142] DOX-loaded solid lipid nanoparticles (DOX–SLNs) were designed to overcome multidrug resistance in cancer by co-delivering DOX and GG918 (Elacridar), a P-gp inhibitor. In MCF-7/ADR breast cancer cells, the NPs enhanced intracellular drug retention, apoptosis, and cytotoxicity compared to free drugs. In xenograft mouse models, they significantly inhibited tumor growth and metastasis with minimal toxicity. Histological analysis confirmed their biocompatibility and safety, highlighting the developed polymer-lipid hybrid NPs as a promising nanomedicine for MDR cancer therapy.[143] HER2-positive breast cancer cell lines (BT474 and SK-BR-3) showed efficient binding, internalization, and photothermal ablation when treated with a nanocomplex made up of gold nanorods, porphyrin, and trastuzumab plus near-infrared (NIR) laser irradiation, while normal mammary epithelial cells (MCF10A) exhibited minimal toxicity.[144] In *in vivo* studies using nude mice bearing BT474 (HER2-positive) xenograft tumours, systemic injection of the developed nanocomplex followed by NIR laser irradiation led to significant tumour growth inhibition compared to control groups. Biodistribution and toxicity analyses demonstrated that the nanocomplex accumulated preferentially in tumor tissue and organs, such as liver, kidneys, heart, spleen, revealed no significant alterations in biochemical markers (*e.g.*, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen and creatinine) or histopathological changes, supporting favorable biocompatibility of the nanoplatform.[144]

Zuo *et al.* (2021)[145] reported self-assembled nanodrugs made from PTX and curcumin for improved TNBC chemotherapy (Fig. 9A). Prepared *via* a simple reprecipitation method, these nanodrugs showed good water solubility, biosafety and pH-responsive drug release.

Anusha *et al.* (2023)[146] explored the anticancer potential of ginger-derived exosome-like NPs against TNBC cells (Fig. 9B). Ginger-derived exosome-like NPs were found to significantly reduce the viability of MDA-MB-231 cells in a concentration-dependent manner while sparing normal cells. They induced apoptosis through mitochondrial damage, ROS generation, nuclear fragmentation, membrane disruption, and activation of apoptotic proteins and caspases. The study revealed a novel anticancer role of ginger-derived exosome-like NPs and

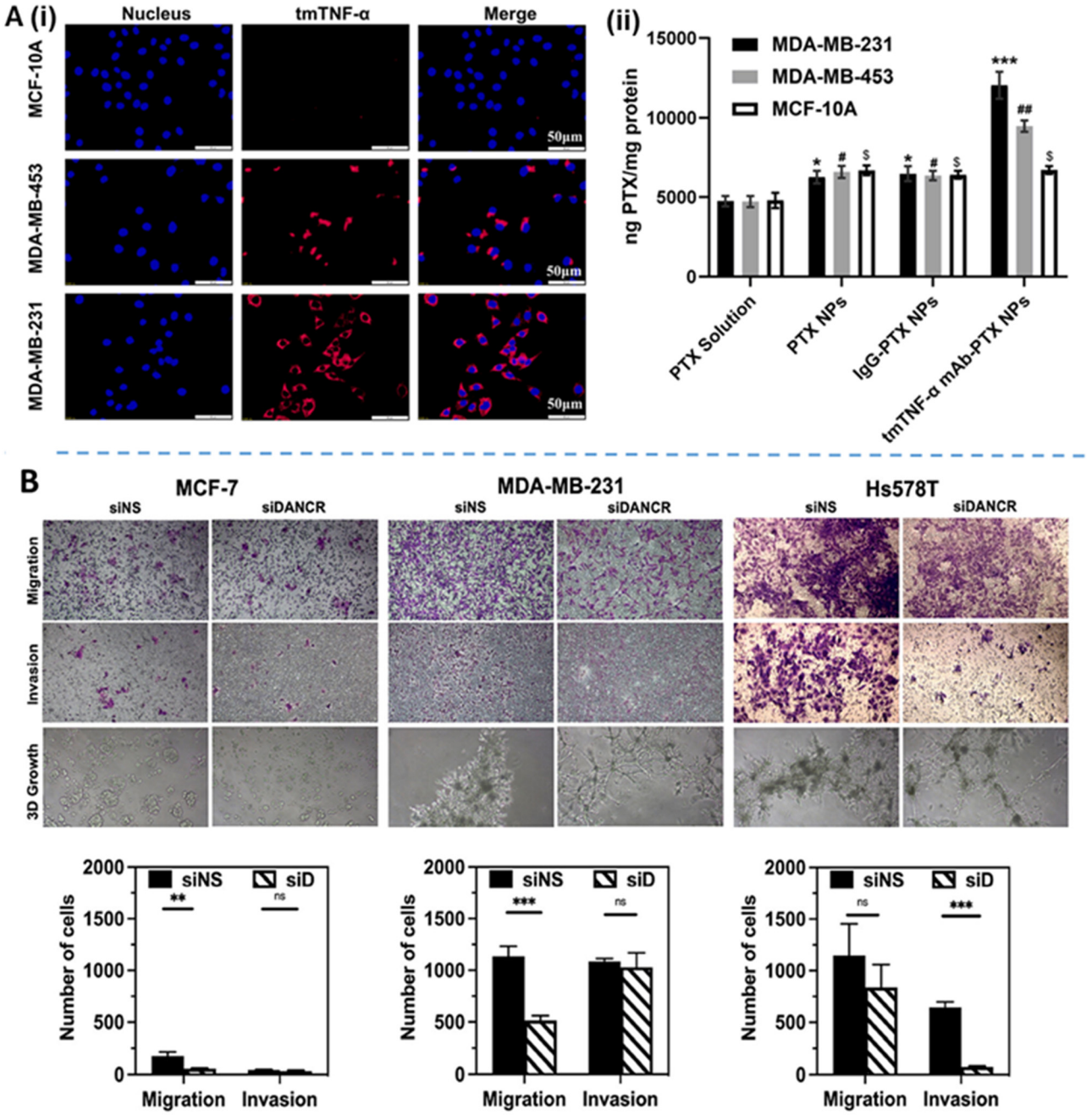

Fig. 7 (A) TNF-α is localized in the nuclei of MCF-7, MDA-MB-453, and MDA-MB-231 cells; enhanced PTX uptake is observed with PTX-loaded IgG@NPs. (i) Confocal microscopy images illustrate the expression of tmTNF-α (indicated in red) alongside 4′,6-diamidino-2-phenylindole (DAPI) nuclear staining (shown in blue) in the MCF-10A, MDA-MB-453, and MDA-MB-231 cell lines. Notably, MDA-MB-231 cells display the highest levels of tmTNF-α expression when compared to the other cell lines. The scale bar represents 50 μm; (ii) ELISA analysis quantitatively assesses the levels of PTX, tmTNF-α, and the complexes formed between PTX and tmTNF-α across the cell lines. The results indicate that MDA-MB-231 cells have significantly higher expression levels relative to both MCF-10A and MDA-MB-453 cell lines (***$p < 0.001$)[148] (reproduced under open access Creative Common CC BY license). (B) DANCR silencing reduces migration and invasion in breast cancer cells[135] (reproduced under open access Creative Common CC-BY-NC-ND license).

highlights their promise as natural, low-toxicity therapeutics for TNBC.[146]

Although NPs offer targeted delivery advantages, they can still cause off-target toxicity, harm normal cells when targeting precision is poor. Instability or premature drug release from NPs can lead to systemic toxicity, while physicochemical factors, such as particle size, charge, and surface coating significantly affect biodistribution and cytotoxicity.[147]

Lipid NPs can cause liver accumulation and hepatotoxicity, along with immune and inflammatory reactions such as cytokine release. Lipid peroxidation may lead to lipid byproducts that can trigger oxidative stress and membrane damage, while

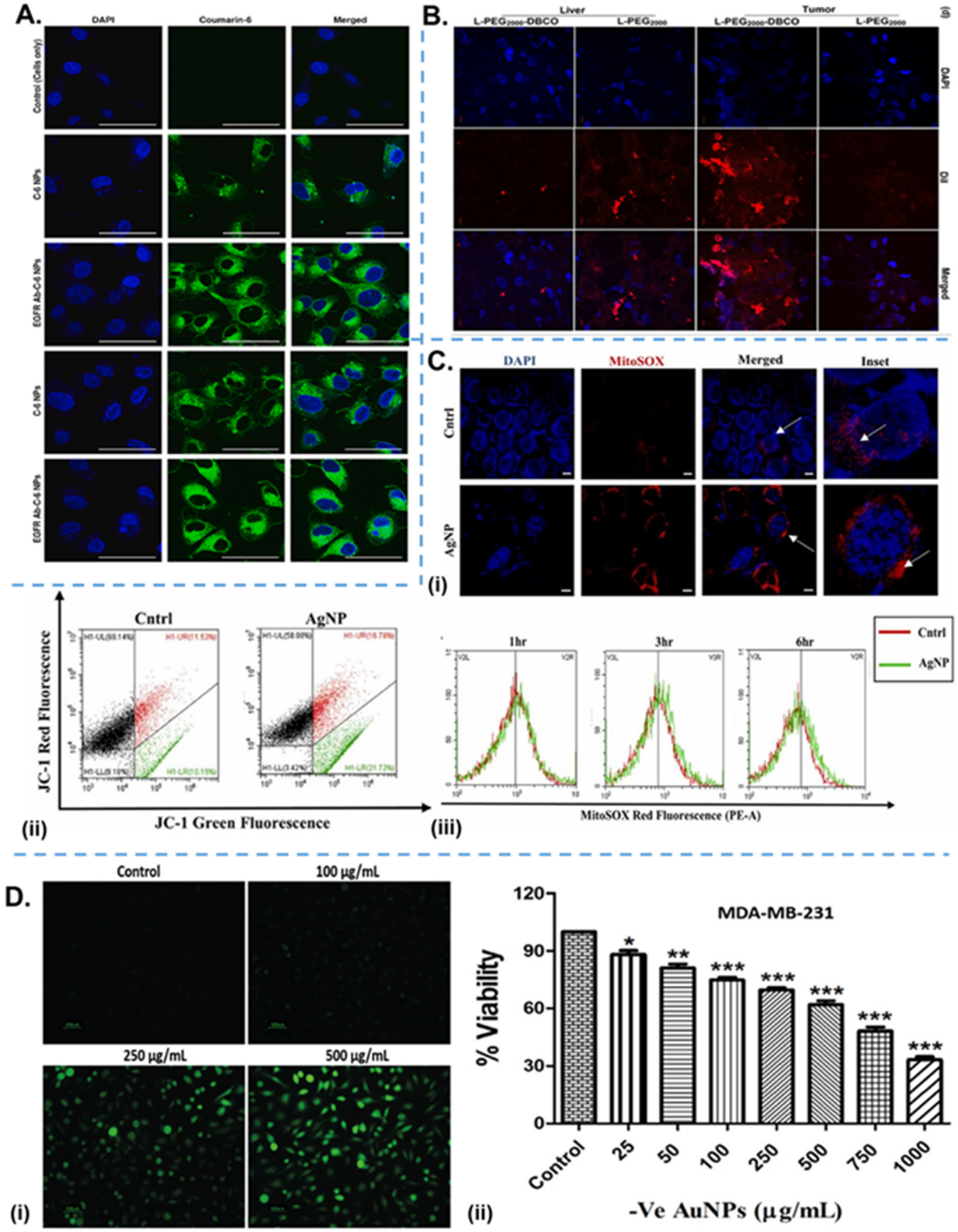

Fig. 8 (A) PEGylated liposomes show improved uptake and co-localization with endocytic markers in MDA-MB-231 cells. (B) Confocal microscopy image shows L-PEG$_{2000}$-DBCO and L-PEG$_{2000}$NP distribution in tumor spheroids, indicating 3D penetration and potential therapeutic benefits[138] (reproduced under open access Creative Common CC BY license). (C) AgNPs increase mitochondrial ROS and decrease the membrane potential in MDA-MB-231 cells. (i) Representative confocal microscopy images illustrate the staining of mitochondrial ROS using MitoSOX Red (shown in red) and nuclei marked with DAPI (shown in blue). Cells treated with AgNPs exhibit significantly elevated red fluorescence, indicating an increase in mitochondrial ROS production compared to the control group; (ii) Flow cytometric analysis assessed the mitochondrial membrane potential ($\Delta\Psi$m) through the use of the JC-1 dye. The treatment with AgNPs led to a reduction in the red/green fluorescence ratio, which indicates mitochondrial depolarization.

The accompanying quantitative bar graph clearly shows a significant decrease in the JC-1 ratio among the AgNPs-treated cells; (iii) The time-dependent accumulation of mitochondrial ROS levels was evaluated using MitoSOX Red fluorescence at 1, 3, and 6 hours following AgNP exposure. The results displayed a steady increase in fluorescence intensity with prolonged exposure duration, thereby affirming the buildup of ROS in the mitochondria[139] (reproduced under open access Creative Common CC BY license). (D) Negatively charged AuNPs induce dose-dependent cell death and reduce viability in MDA-MB-231 cells. (i) Fluorescence imaging of live and dead MDA-MB-231 cells treated with AuNPs at concentrations of 0 to 500 μg mL^{-1} shows reduced green fluorescence at higher concentrations, indicating decreased cell viability; (ii) (3-[5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) demonstrates a dose-dependent decline in cell survival, with significant cytotoxicity noted at 500 μg mL^{-1} and above[140] (reproduced under open access Creative Common CC BY license).

Table 2 Comparative summary of nanoparticle-based therapeutic systems targeting drug-resistant cancers

NP Type	Drug payload	Size	Cell/animal model	Key outcomes	Limitations	Ref.
PEG-coated gold NPs	None (radiosensitizer)	4.8, 12.1, 27.3, 46.6	Cancer cell lines and tumor-bearing mice	Enhanced radiation therapy efficacy; size-dependent radio-sensitization	Potential liver toxicity at higher concentrations	142
Lectin-conjugated mesoporous silica NPs	Doxorubicin	~100	Human osteosarcoma cell line (HOS) and preosteoblast cells (MC3T3-E1)	Selective targeting and internalization in cancer cells; higher cytotoxicity in tumor cells	Potential immunogenicity of lectin-conjugated NPs; challenges in large-scale synthesis	141
Gold-doxorubicin nano-conjugates	Doxorubicin	~20	Multidrug-resistant cancer cell lines	Enhanced intracellular drug delivery; significant reduction in cell viability in resistant cell lines	Limited *in vivo* validation; potential cytotoxicity in non-target cells	169
Branched poly(LAEMA) pro-drug self-assembled + encapsulated Akt inhibitor (capivasertib) and paclitaxel	Paclitaxel + Akt inhibitor	100-150 nm	MFC (mouse gastric tumor) *in vivo* + in vitro	Significant tumor growth inhibition vs single agents; suppression of the PI3K/Akt pathway; enzyme-responsive release in the tumor microenvironment	Limited number of *in vivo* models; longer-term toxicity/survival not deeply explored	142
Various nano-carrier types (liposomes, polymeric NPs, inorganic/hybrid NPs)	Many combinations: chemotherapy + MDR-reversal agents *etc.*	50–200 nm	Various cancer cell lines/animal models (breast, ovarian, lung, glioblastoma)	Demonstrated improved intracellular delivery, bypassing efflux pumps, improved targeting, enhanced efficacy in resistant models	Many are preclinical; heterogeneity in models and NP design; translation to clinic still limited	142
Mitochondrial-targeting lipid-polymer hybrid NPs (PLGA/CPT plus DOX) with pH-responsive shell	Doxorubicin (DOX)	~150 nm	MCF-7/ADR (doxorubicin-resistant breast cancer) *in vitro* + *in vivo*	Tumor inhibition rate (TIR) ~84.9%; improved lysosomal escape & mitochondrial targeting; overcame DOX-resistance	Specific to the DOX-resistant model; potential scale-up and safety in humans unknown	169
Porous gelatin nanocore functionalized with cetuximab-siRNA + gefitinib	Gefitinib (TKI) + siRNA for KRAS downstream	—	H23 KRAS mutant non-small cell lung cancer (NSCLC) cells in vitro	Knocked down the KRAS pathway, disrupted survival signaling (GAB1-SHP2), sensitized to TKI; minimal toxicity without TKI	No *in vivo* tumor model reported; translational hurdles (siRNA delivery, stability) remain	170

mild cardiotoxicity can occur with drug-loaded forms, like liposomal DOX. Long-term exposure may also disturb lipid metabolism and burden the liver and spleen.[148]

Some study shows non-specific cytotoxicity of AgNPs. MDA-MB-231 cells were damaged by oxidative stress and DNA damage in a dose-dependent manner. While they showed stronger toxicity toward cancer cells than normal ones, the same ROS-mediated pathways could also harm healthy tissues if exposure is high.[149]

5. Multifunctional nanoparticles for cancer therapies

Current cancer therapeutics mainly target multiple tumor sites to deliver effective cancer detection and treatment. Multifunctional NPs have been found to be more effective than single-function NPs.[150] For greater precision, the synergistic NPs arise from their stimuli-responsive release behavior, where NPs respond to tumor-specific cues such as pH, temperature, or redox gradients, enabling controlled and localized drug release at the tumor site. Furthermore, NPs can serve as multifunctional theragnostics that combine chemotherapy, photothermal, and photodynamic therapies, and imaging capabilities, thereby allowing simultaneous treatment and real-time monitoring of therapeutic outcomes.[151] Additionally, temperature and pH play pivotal roles in enhancing the efficacy of nanoparticle-based nanomedicine for cancer therapy by enabling site-specific and stimuli-responsive drug release. The mildly acidic tumor microenvironment (pH ~6.5) and more acidic endo/lysosomal compartments (pH ~5.0–5.5) trigger pH-sensitive nanoparticle destabilization or bond cleavage, ensuring selective drug release within tumors while minimizing systemic toxicity. Similarly, localized hyperthermia (40–45 °C), induced by external

Table 3 Comparative overview of nanoparticle-based delivery systems and their mechanistic roles in TNBC therapy

NP	Mechanism of action	Advantages	Limitations	Toxicity	Clinical translational hurdles	Ref.
Liposomes	Lipid vesicles accumulate in TNBC *via* the EPR effect, entering tumor cells to release their therapeutic playloads	High biocompatibility, capable of carrying hydrophilic and hydrophobic drugs. Easily modified for targeted delivery to TNBC, minimizing off-target toxicity	Exhibit limited capacity for large biomolecules, face drug leakage and stability issues, and are cleared rapidly by the reticuloendothelial system (RES) without PEGylation, along with notable batch-to-batch variability	Generally low immunogenicity; PEGylated liposomes are well tolerated	Ensuring stable formulations, precise targeting in TNBC, and managing high manufacturing costs with strict regulatory requirements	171–173
Protein NPs	These carriers utilize natural uptake pathways, like albumin's gp60/SPARC receptor-mediated endocytosis, to enhance internalization into TNBC cells	Excellent biocompatibility and biodegradability with prolonged circulation. Intrinsic tumor targeting enhances TNBC uptake and allows easy co-delivery and ligand conjugation	Limited payload capacity, risk of protein denaturation, sourcing variability, and potential immunogenicity with non-human or modified proteins	Low protein breakdown produces non-toxic amino acids. Albumin-based NPs have minimal toxicity, but contaminants and surface modifications need testing	High manufacturing costs; challenges in protein stability; need for rigorous safety and immunogenicity testing; limited approved protein-based nanodrugs for TNBC	83 and 174
MOFs	Porous metal–organic frameworks release drugs in TNBC and combine therapies	High surface area and tunable pores allow ultra-high drug loading and combined imaging and therapy with MRI-active metals	Instability and complex synthesis challenge MOFs, leading to uncontrolled drug release and concerns about uniformity	Endogenous metal MOFs (Fe, Zn, Ca) are biocompatible; toxicity stems from harmful ions or linkers, but proper design can reduce risks	Challenges include biodegradability, safe clearance, *in vivo* stability, and regulatory safety	175 and 176
Carbon based	CNTs, graphene, and carbon dots are effective for photothermal therapy and imaging, and can target TNBC	CNTs/graphene provide effective photothermal therapy, and carbon dots offer bright fluorescence for TNBC tumor imaging. All are easily functionalized	Aggregation and solubility issues occur without functionalization; challenges include drug loading, release, and purification	Unmodified CNTs/graphene can be toxic; PEGylation reduces this. Carbon dots are low in toxicity, but their long-term effects are still being studied	Safety concerns over long-term toxicity hinder large-scale synthesis and clinical translation	177
Inorganic	Gold NPs convert NIR to heat and act as CT contrast/drug carriers; Fe_3O_4 NPs provide MRI contrast and heat in TNBC	Au enables NIR absorption; Fe_3O_4 is biodegradable and MRI-active, supporting multimodal imaging and drug conjugation	Limited biodegradability; aggregation risk. Au is costly; Fe_3O_4 may oxidize. Drug loading is surface-dependent	Au cores are mostly non-toxic; however, small Au NPs or coatings may trigger immune responses, and high doses of iron oxide can induce oxidative stress	Key challenges are organ retention, NP synthesis, and human safety. Few inorganic nanodrugs are in TNBC trials	176, 178 and 179
Polymeric	Biodegradable polymers like PLGA and PEG-PLA create NPs that release encapsulated chemotherapeutics in TNBC, triggered by pH or enzymes	Biocompatible and biodegradable, with targeted surfaces that enhance drug solubility and efficacy through sustained release	Lower drug loading than inorganic/MOF carriers; may show burst release and create acidic microenvironments, needing extra surfactants	Polymers are often FDA-approved and safer than free drugs, while cationic polymers like PEI are cytotoxic and avoided	Key challenges are scale-up and stability, with few polymeric theragnostic NPs for TNBC in clinical trials	180–183

stimuli such as near-infrared light or magnetic fields, increases tumor vascular permeability, enhances nanoparticle penetration and cellular uptake, and activates thermoresponsive drug release.

TNBC, being the most malignant type of breast cancer, has a heterogeneous tumor microenvironment due to the presence of M2-tumor-associated macrophages (M2-TAM). Multifunctional LyP-SA/AgNP@Dox NPs have been synthesized for site specific targeting of the p32 receptor, also referred to as gC1qR, that is located on the surface of breast cancer cells and macrophages associated with tumors.[152] tLyP-1-HA NPs with dual receptors have also been proposed for the targeting of highly metastatic TNBC.[153] Clinical research has shown that high expression of CD44 and neuropilins is positively correlated with cancer carcinogenesis, metastasis, and angiogenesis. The tLyP-1-HT NPs containing docetaxel were much more effective at stopping tumor growth and preventing it from spreading; the NPs reduced the size of primary tumors and lung metastases by 79.6%. Against post-pulmonary metastatic mice, the treatment demonstrated a metastasis suppression rate of 85.1% and a life extension rate of up to 62.5%.[153]

Liu *et al.* (2024)[152] designed multifunctional LyP-SA/AgNP@-Dox NPs to target TNBC cells and tumor-associated macrophages simultaneously. DOX was combined with AgNPs, which were coated with sialic acid and functionalized with the LyP-1 peptide for p32-mediated tumor and tumor-associated macrophages targeting. *In vitro* studies done with 4T1 cells and M2 macrophages demonstrated enhanced cellular uptake, mitochondrial damage, elevated ROS generation, and apoptosis,

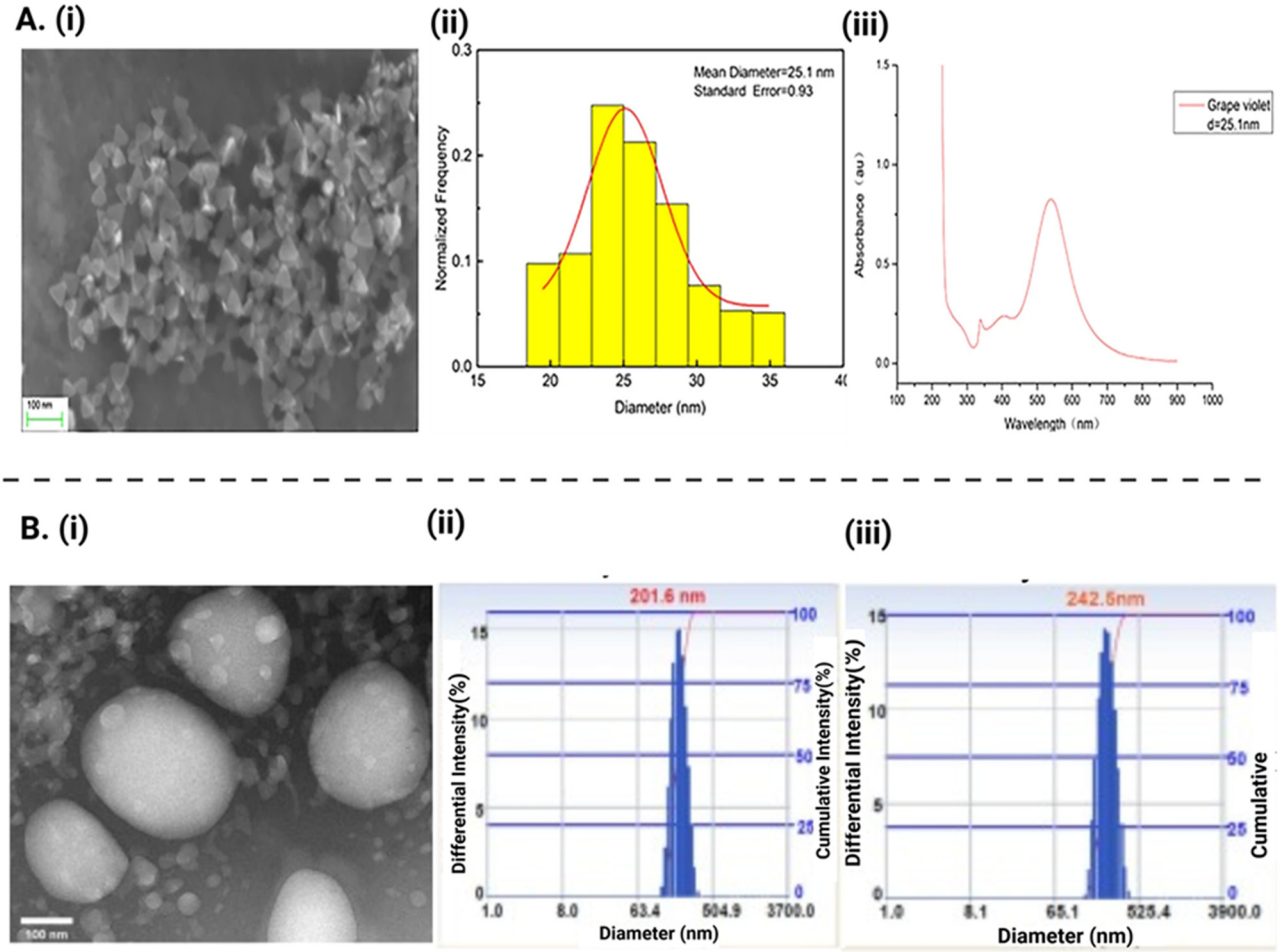

Fig. 9 (A) (i) TEM image of PTX-curcumin conjugate nanodrugs with a core–shell structure; (ii) SEM image of agglomerated PTX-curcumin conjugate nanodrugs on a rough surface; (iii) emission spectra of drug-loaded NPs indicating encapsulation[145] (reproduced under open access Creative Common CC BY license). (B) (i) SEM image of lipid vesicles; (ii–iii) mean diameter showing a narrow size distribution around 200–240 nm of PTX-NPs[146] (reproduced under open access Creative Commons CC-BY-NC-ND license).

while efficiently overcoming multidrug resistance. In orthotopic TNBC mouse models, the NPs showed greater tumor accumulation, significant tumor growth inhibition, and efficient biosafety.[152]

Elbialy *et al.* (2020)[154] created ALG-CasNFS-DOX1, in which tyrosine NPs were surface-modified to encapsulate DOX (CasNFS-DOX) with natural polysaccharide alginate (ALG). By facilitating the directed transport of DOX specifically to the tumor location, the NPs reduced the drug's toxicity to critical organs (*i.e.*, liver, spleen, kidneys, and heart) and enhanced its anti-cancer efficacy.[154]

Site-specific treatments are extensively performed to enhance the destruction of tumor tissues. Biocompatible, multifunctional lipid-coated calcium phosphate NPs were designed as an efficient delivery platform for combined gene and photothermal therapy, aimed at suppressing the growth of MDA-MB-468 both in laboratory settings and animal models.[155] Under 808 nm NIR laser illumination, MDA-MB-468 cells efficiently absorbed lipid-coated calcium phosphate NPs functionalized with bispecific antibody NPs loaded with siRNA and indocyanine green, which dramatically induced programmed cell death and inhibited cell growth.[155] Among other combinational therapy modalities, combining gene therapy and photothermal therapy has demonstrated enhanced therapeutic effectiveness through a synergistic approach *in vivo*.[155] Moreover, the conjugation of bispecific antibody to lipid-coated calcium phosphate NPs led to a significant enhancement in the accumulation of the therapeutic agents and penetration into the tumor tissues.[156]

In another study, block copolymer nanoflower capsules [(L-GluA-5-BE)-*b*-(L-AspA-4-BE)] were engineered to exploit TNBC's tumor microenvironment. Their thermosensitive (elevated temperatures commonly found in tumor tissues) and pH-responsive (slightly acidic conditions) drug release enables dual-triggered delivery, releasing drugs preferentially at tumor sites to enhance cytotoxicity while sparing healthy tissue. The nanoflower structure also allows high drug loading, stable circulation, and improved cellular uptake, collectively maximizing therapeutic efficacy and minimizing systemic toxicity.[157] The study designed self-assembled block copolymer [(BenzA)-*b*-(PCL)] micelles to arrange AuNPs into a hollow core–shell structure. This configuration

enhanced drug loading, photothermal efficiency, and cellular uptake, improving targeted cancer therapy with excellent biocompatibility and stability, making it a promising platform for future theragnostic use.[158]

A successful and improved therapeutic strategy for cancer treatment that blocks the tumor cells' ability to spread is to target many miRNAs. Devulapally *et al.* (2015)[159] created PLGA-*b*-PEG NPs for the encapsulation of antisense miR-21 and miR-10b. The dual loading inhibited growth of breast cancer cells *in vitro* and in living tumor models.

Researchers designed gold-decorated chitosan–L-arginine ([(CS)-*b*-(L-Arg)]) NPs capable of co-delivering gefitinib, a tyrosine kinase inhibitor, and miR-125b, a tumor-suppressor microRNA. This dual-delivery system enhanced tumor suppression by combining gene regulation and drug action, showing superior synergistic efficacy, stability, and biocompatibility compared to single treatments.[160] This approach can enhance chemotherapy outcomes with lower drug doses. Ongoing research is exploring the combination of therapeutic drugs with miRNA-loaded NPs in breast tumors.[160]

6. Regulatory issues and FDA-approved nanoparticles for TNBC

Developing a new drug is a long, expensive, and complex process that can take over a decade. Every new medicine must prove that its benefits clearly outweigh its risks before reaching patients. This strict regulation ensures safety and scientific accuracy from early lab research to large human trials. In the U.S., the Food and Drug Administration (FDA) oversees this entire process.[161] The FDA drug approval pathway involves preclinical testing, Investigational New Drug (IND) Application submission, three phases of clinical trials, and final FDA review. Through rigorous evaluation of safety, efficacy, and manufacturing data, FDA ensures only drugs with proven therapeutic benefits and acceptable risk profiles reach the market.[162] Among 207 oncology drugs approved by the FDA, 39 are indicated for breast cancer, the highest number for any cancer type. Most were initially approved for metastatic disease, with approximately 31% later granted adjuvant approval. From 2016 to 2021, the FDA approved 19 additional breast cancer therapies, primarily for advanced treatment lines.[163,164] FDA-approved liposomal formulations Lipodox, Evaset, Doxil/Caelyx, and Myocet are commercially available and widely used in breast cancer treatment.[165,166] Studies by Wissner and Mansour *et al.* (2008)[167] reported Doxorubicin Hydrochloride (Rubex) Phase II clinical evaluations of FDA-approved formulations, demonstrating their therapeutic efficacy and safety in patients. These trials provided essential clinical evidence supporting the optimized dosing, pharmacokinetic stability, and manageable toxicity profiles necessary for subsequent regulatory approval and clinical use. In combination with cyclophosphamide, vinorelbine has been shown to activate stem-like $CD8^+$ T cells and enhance anti-PD-1 therapy effectiveness in TNBC. It is marketed in both injectable and oral forms. Although novel formulations, such as liposomes[159] have been explored, the injectable form remains the only one commercially available. Abraxane (Nab-PTX), an albumin NPs formulation for injectable suspension, has been evaluated as a first-line treatment for TNBC in Phase II clinical trials (NCT00251472). Data from Lan *et al.* (2018)[168] and from ClinicalTrials.gov confirmed its safety and efficacy, providing pivotal evidence that supported FDA approval for this indication.

7. Conclusion and future perspectives

TNBC, being an extremely invasive type of breast cancer, has received an unusual amount of attention. This aggressiveness is attributed to alterations in multiple genes, with BRCA1/2 and TP53 being notable genes linked to TNBC. Patients with TNBC experience a greater likelihood of distant metastasis and face a worse overall outlook than those with other breast cancer subtypes. The TNBC tumor microenvironment is highly heterogeneous, presenting significant treatment challenges. Multifunctional NPs with theragnostic features show promise in precise cancer diagnosis, targeted treatment, and drug delivery for TNBC. Various treatment methods, including immunotherapy, chemotherapy, and NPs-assisted drug delivery, have been used, and there is potential for studying plant-based antioxidants combined with photosensitizers for TNBC treatment. Greater focus should be placed on customized treatments designed to address the specific needs of every individual patient.

The path forward in managing TNBC is rooted in comprehensive and personalized cancer care, combining molecular profiling, artificial intelligence (AI), and nanotechnology to tailor treatments for individual patients. Emerging tools such as single-cell sequencing, multi-omics integration, and spatial transcriptomics can unravel intratumoral heterogeneity and identify novel therapeutic targets. The advancement of stimuli-responsive NPs capable of drug release in response to pH, temperature, or enzymatic activity, will enhance selective tumor targeting. AI-driven predictive models are expected to optimize treatment strategies by analyzing patient-specific datasets and predicting therapeutic responses. Innovations in nanotechnology have given rise to immunotheragnostics, which combine aspects of nanomedicine and cancer immunotherapy to tackle challenges, such as immune evasion and the "cold" tumor microenvironment seen in TNBC.[184] Designed NP systems are now being employed to directly deliver immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti-CTLA-4, to tumor sites. This method enhances the accuracy of treatment while reducing systemic toxicity. These advanced nanocarriers also facilitate the co-delivery of immunostimulants, such as CpG oligodeoxynucleotides and STING agonists, as well as tumor antigens to promote dendritic cell activation and support effective antigen presentation.[185] Furthermore, liposomal and polymeric NPs are engineered to respond to the specific acidic or redox conditions of the tumor microenvironment, enabling localized release of immune agonists and decreasing systemic inflammation.[186] In addition, these NPs can shift the immune landscape by reprogramming tumor-associated macrophages from an M2 immunosuppressive phenotype to an M1

pro-inflammatory state, thereby increasing cytotoxic T-cell infiltration and enhancing anti-tumor immunity.[187] This comprehensive strategy, which combines tumor imaging, immune modulation, and drug delivery, emphasizes the vital role of immuno-theragnostic in converting ''cold'' TNBC tumors into ''hot'' immune-responsive forms, potentially leading to better clinical outcomes.

Simultaneously, AI and machine learning (ML) tools are transforming the field of TNBC nanomedicine by streamlining the design, characterization, and optimization of NPs. Contrary to traditional empirical methods, AI-driven approaches can predict optimal NP characteristics, such as size, surface charge, and composition, to maximize tumor uptake and biocompatibility.[188] Advanced algorithms, including random forests, support vector machines, and deep learning models, are utilized to simulate interactions between NPs and biological systems, forecast biodistribution, and predict therapeutic outcomes through *in silico* methods. These computational strategies are reshaping biomarker discovery within oncology by merging multi-omics datasets to uncover molecular signatures related to TNBC progression, metastasis, and treatment response. For instance, deep learning models have effectively identified pyroptosis-related gene networks that predict TNBC prognosis, thus opening avenues for selecting NP payloads and therapeutic targets.[189] The combination of AI-enhanced biomarker discovery with NPs mediated targeted therapy signifies a major advancement toward the development of intelligent, adaptive, and responsive nanomedicine.

Moreover, the genomic diversity inherent in TNBC presents opportunities for personalized nanotherapeutic approaches. By merging high-throughput genomic and proteomic analysis with NP-based treatments, therapies can be customized according to specific molecular signatures.[190] NPs can be tailored to deliver small interfering RNAs (siRNAs), microRNAs (miRNAs), or CRISPR/Cas gene-editing technologies aimed at targeting specific TNBC-related mutations, such as TP53, PIK3CA, and BRCA1/2. Additionally, researchers are investigating lipid or polymeric NPs for mRNA vaccines that encode patient-specific neoantigens to activate strong and precise anti-tumor immune responses. Moreover, biomarkers derived from liquid biopsies, such as circulating tumor DNA (ctDNA) and exosomal RNA, are being explored as noninvasive methods for monitoring treatment responses and dynamically adjusting nanotherapeutic strategies in real time.[191] These approaches reflect the principles of precision oncology, which emphasize adaptive, feedback-informed, and personalized nanomedicine for TNBC.

Tumor organoid models and patient-derived xenografts will further refine preclinical drug testing and bridge translational gaps. There is a growing interest in combining checkpoint inhibitors with anti-cancer-loaded NPs to enhance immunotherapeutic efficacy. Moreover, using plant-based materials for the green synthesis of NPs holds promise for safer and sustainable cancer therapies. The incorporation of circulating tumor DNA (ctDNA) and liquid biopsies into routine monitoring will offer real-time insights into treatment efficacy and resistance. Moving forward, a multi-pronged, patient-centered approach that integrates cutting-edge diagnostics and personalized therapeutics will be crucial in overcoming the therapeutic challenges posed by TNBC.

Author contributions

Soumya Sonalisha: writing – review & editing, writing – original draft, methodology, investigation, formal analysis, data curation, conceptualization; Apoorv Kirti: writing – review & editing, writing – original draft, methodology, investigation, formal analysis, data curation, conceptualization; SP. Asima: writing – original draft, validation, resources, methodology, conceptualization, writing – review & editing; Richeek Parashar: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing; Srijeeta Pal: writing – review & editing, writing – original draft, visualization, validation; Debidatta Barik: writing – review & editing, writing – original draft, visualization, validation; Shaikh Sheeran Naser: writing – review & editing, writing – original draft, visualization, validation; Eliana B. Souto: writing – review & editing, writing – original draft, visualization, validation, supervision, software, conceptualization, data curation, formal analysis, funding acquisition, investigation, resources. Suresh K. Verma: writing – review & editing, writing – original draft, visualization, validation, supervision, software, conceptualization, data curation, formal analysis, funding acquisition, investigation, resources.

Conflicts of interest

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

3PG	3-Phosphoglycerate
5-FU	5-Fluorouracil
ACOX2	Acyl-CoA oxidase 2
ACC	Acetyl-CoA carboxylase
ACLY	ATP-citrate lyase
ADP	Adenosine diphosphate
AI	Artificial intelligence
ALG	Alginate
ATP	Adenosine triphosphate
CNTs	Carbon nanotubes
CPT	Carnitine palmitoyl transferase
CT	Computed tomography
ctDNA	Circulating tumor DNA
DAPI	4′,6-Diamidino-2-phenylindole
DCE-MRI	Dynamic contrast-enhanced magnetic resonance Imaging
DDS	Drug delivery system
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
DW-MRI	Diffusion-sensitive magnetic resonance imaging
EDB-FN	Extradomain B fibronectin

EGFR	Epidermal growth factor receptor
EPR	Enhanced permeability and retention
$FAD/FADH_2$	Flavin adenine dinucleotide
FDA	Food and drug administration
FE-SEM	Field emission scanning electron microscopy
fMRI	Functional magnetic resonance imaging
Gd-DOTA	Gadolinium 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,N‴-tetraacetic acid
Gln	Glutamine
Glu	Glutamate
GLUT	Glucose transporter
GS	Glutamine synthetase
GSH	Glutathione
IC50	Half-maximal inhibitory concentration
HBP	Hexosamine biosynthesis pathway
HER-2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HR-TEM	High resolution transmission electron microscopy
HRR	Homologous recombination repair
LC50	Lethal concentration
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
M2-TAM	M2-tumor-associated macrophages
mAb	Monoclonal Antibody
MCT	Monocarboxylate transporter
MOFs	Metal–organic frameworks
MPC	Mitochondrial pyruvate carrier
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial DNA
mTOR	Mechanistic target of rapamycin
MTT	3-[5-Dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
MTX	Methotrexate
MUC1	Mucin 1 gene
$NAD^+/NADH$	Nicotinamide adenine dinucleotide
NPs	Nanoparticles
OXPHOS	Oxidative phosphorylation
PAI	Photoacoustic imaging
PAMAM	Polyamidoamine
PCL	Poly(ε-caprolactone)
PDH	Pyruvate dehydrogenase
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PET	Positron emission tomography
PLA	Poly-L-lactic acid
PLGA	Poly(lactic-*co*-glycolic acid)
PPP	Pentose phosphate pathway
PTX	Paclitaxel
ROS	Reactive oxygen species
RTKs	Receptor tyrosine kinases
SEM	Scanning electron microscopy
SPECT	Single-photon emission computed tomography
US	Ultrasound
UV-Vis	Ultraviolet-visible
TCA	Tricarboxylic acid cycle
TEM	Transmission electron microscopy
tmTNF-α	Transmembrane tumor necrosis factor alpha
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
XRD	X-ray diffraction

Data availability

No data were used in this work.

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