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REVIEW ARTICLE

From scientific promise to clinical reality: Nanomedicine for breast cancer

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Abstract

Breast cancer is still one of the most important health burdens worldwide, with incidence and mortality rates increasing, especially in Asia and Africa. As conventional therapeutic approaches, including endocrine therapy, chemotherapy, surgery, and radiotherapy, have developed, their limitations were gradually identified from systemic toxicity to therapeutic resistance. Nanomedicine has emerged as a revolutionary approach where nanotechnology is exploited for precise drug delivery, improving bioavailability while reducing adverse effects. The passive and active targeting mechanisms are involved in the nanoparticle-based drug delivery systems (DDS), which enhance the therapeutic outcomes. Passive accumulation of nanoparticles in tumours is facilitated by the enhanced permeability and retention (EPR) effect, while active targeting is enhanced by the use of ligand-functionalised nanocarriers. Stimuli-responsive nanomedicines further optimise drug release, with triggers from the tumour microenvironment, including pH and reactive oxygen species. Furthermore, nanomedicine has been playing an important role in overcoming radio-resistance and improving immunotherapy efficacy. Nanomedicine, though very promising, has its problems: high expenditure for research and development, legislative barriers, and public scepticism. Overcoming these issues requires resolving nanotoxicity and making the processes capable of large-scale manufacturing. Because cancer nanomedicine is well on its course toward precision medicine, interdisciplinarity at work, and strong policy support should be seen for the fullest deployment of this concept in the treatment of breast cancer.

Keywords: Breast Cancer Treatment, Cancer Nanomedicine, Clinical Translation of Nanomedicine, Nanoparticle-Based Therapy, Targeted Drug Delivery

INTRODUCTION TO CANCER NANOMEDICINE - ENTERING THE EQUATION

Breast cancer is a major global health concern, with nearly two million new cases diagnosed annually.[1] As of 2022, it had the highest crude incidence rate (58.7 per 100,000) and ranked second in mortality (17.0 per 100,000) worldwide. Projections indicate continued increases, particularly in Asia and Africa.[2] Given these trends, there is an urgent need for improved therapeutic strategies.

Breast cancer risk factors include sex, age, hormonal influences, genetic predisposition, and lifestyle factors. Mutations in *BRCA1* and *BRCA2* disrupt DNA repair, increasing susceptibility.[3] Diets high in processed foods and alcohol consumption further elevate risk.[4,5] Obesity contributes by promoting chronic inflammation and immune modulation.[6,7]

Standard treatments include endocrine therapy, chemotherapy, surgery, and radiotherapy. While effective, these approaches have significant limitations. Endocrine therapy requires prolonged administration and may cause thromboembolic complications.[8] Chemotherapy, particularly

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for triple-negative breast cancer (TNBC), has improved survival rates but is associated with severe systemic toxicity.[9] Surgical interventions enhance relapse-free survival but can have psychological and cosmetic consequences.[10] Radiotherapy reduces local recurrence but faces resistance mechanisms such as hypoxia-inducible factor 1-alpha (HIF-1α) and cancer stem cells.[11] These challenges necessitate novel approaches such as nanomedicine.

Nanomedicine applies nanotechnology to healthcare, offering advancements in drug delivery, diagnostics, and immunotherapy. Currently, over 100 nanomedicine formulations are in development, with 53% focused on oncology.[12] Nanostructured drug delivery systems (DDS) enhance therapeutic precision while minimising systemic toxicity.

Cancer nanomedicine relies on passive and active targeting mechanisms. Passive targeting exploits the enhanced permeability and retention (EPR) effect, allowing nanoparticles to accumulate in tumours due to leaky vasculature.[13] However, rapid systemic clearance can limit efficacy, which polyethylene glycol (PEG) modifications help address.[14] Active targeting enhances specificity through ligand-functionalised nanoparticles, such as folate-conjugated systems that bind to overexpressed tumour receptors.[15]

Targeted drug release is crucial for efficacy. Stimuli-responsive "smart" nanomedicines exploit tumour-specific environmental cues like pH, reactive oxygen species (ROS), and temperature to trigger drug release.[16] For example, ROS-sensitive nanoparticles encapsulating mitoxantrone selectively degrade within the oxidative tumour microenvironment.[17] Immune cell-derived nanovesicles, such as T-cell-derived vesicles, also enhance cancer immunotherapy by directly targeting tumour cells.[18]

Nanoparticle-based DDS offers several advantages over conventional therapies. They improve drug solubility, bioavailability, and tumour penetration while reducing systemic toxicity.[9] Nanovaccines, which enhance dendritic cell activation and T-cell responses, represent another breakthrough in immunotherapy.[19,20] Additionally, nanotechnology addresses radiotherapy resistance. Fe-engineered polyethylene glycol (PEG)-modified hollow mesoporous silica nanoparticles (FHPA) enhance oxidative stress within tumour cells, improving radiosensitivity.[21]

With increasing evidence supporting nanotechnology's role in oncology, cancer nanomedicine stands at the forefront of precision medicine. By enhancing specificity, reducing toxicity, and overcoming resistance mechanisms, nanomedicine offers a transformative approach to breast cancer treatment. Continued research and clinical translation will be key to maximising its potential in improving patient outcomes.

NANOMEDICINE'S IMPACT ON CONVENTIONAL CANCER TREATMENT

Nanomedicine is revolutionising cancer therapy by overcoming the limitations of conventional treatments, particularly in drug delivery and tumour targeting. The impermeable tumour vasculature and dense extracellular matrix (ECM) hinder effective drug penetration, leading to suboptimal therapeutic outcomes.[22] Hybrid nanomedicine, such as the "small-in-large" nanoparticle (NP) approach, addresses these challenges by enhancing circulation and penetration. Wong *et al.* (2011) demonstrated this with gelatin-coated 100 nm NPs encapsulating 10 nm NPs, facilitating deeper tumour infiltration and improved bioavailability.[23]

A key advantage of nanomedicine is its enhanced specificity, minimising off-target effects. Conventional drugs like Tamoxifen exhibit unintended binding, leading to adverse reactions.[24] In contrast, ligand-functionalised nanocarriers selectively target overexpressed receptors in cancer cells. For instance, folate-decorated nanocarriers significantly improved curcumin delivery to HER2-positive breast cancer cells, resulting in higher intracellular accumulation and therapeutic efficacy.[25] This precision paves the way for personalised cancer therapy, particularly in aggressive subtypes like triple-negative breast cancer.[26]

Despite its promise, nanomedicine presents challenges, particularly nanotoxicity. Toxicity risks stem from NP size, surface properties, and composition. Large NPs may accumulate in non-target tissues, while smaller ones can penetrate unintended physiological barriers. For example, mesoporous silica nanoparticles (MSNPs) of 600 nm cause membrane deformation, whereas 100 nm MSNPs are readily internalised by red blood cells.[27] Additionally, lipid-based nanoparticles induce DNA strand breaks[28] and metallic nanoparticles trigger oxidative stress, potentially leading to renal toxicity.[29]

While nanomedicine holds immense potential

in optimising cancer treatment, addressing safety concerns is paramount. Future research should focus on refining nanoparticle design and biocompatibility to maximise therapeutic efficacy while minimising adverse effects, ensuring its successful clinical translation.

SMALL PARTICLES, BIG CHALLENGES

Despite its promising potential in revolutionising cancer treatment, nanomedicine faces substantial challenges, including high research and development (R&D) costs and public scepticism.

Hefty Research and Development Costs

The high cost of scaling up nanomedicine production is a significant barrier. While small-scale production is manageable, large-scale manufacturing introduces complexities, as minor changes can alter nanoparticle properties.[30] Nanomedicine production requires specialised equipment, highly trained personnel, and extensive research funding, making it more expensive than conventional anticancer drugs.[31] The estimated cost of pivotal trials for 35 nanomedicines reaches $1.4 billion, with a median cost of $233.6 million per product.[32] In comparison, conventional anticancer drugs have a median annual cost of $194,000, while gene and virus therapy drugs can cost up to $448,000.[33] Investments such as the EU Framework Program and Horizon 2020 (€430 million across 84 projects) and the U.S. NIH's $445 million investment illustrate the substantial funding required.[34] Moreover, scaling up necessitates advanced manufacturing technologies, further increasing costs. Regulatory approval, particularly from the FDA, adds another financial burden, with clinical trials (phases I–III) comprising 50–70% of total development costs and extending over 15–20 years, pushing total expenses to approximately $2 billion.[35]

Public Scepticism and Reluctance

Public scepticism and reluctance also hinder nanomedicine adoption. Concerns regarding the unpredictability of nanoparticle interactions with biological structures persist, especially as even well-established cancer drugs like paclitaxel and doxorubicin exhibit toxicity when paired with novel nanocarriers.[36] Limited public knowledge about nanotechnology contributes to uncertainty, with studies showing that individuals with higher education levels generally hold more positive views due to greater access to scientific information.[37] An online survey by Joubert *et al.* (2020) found that while many respondents had neutral attitudes, more than half believed nanotechnology had a positive impact.[38] However, safety concerns remain, particularly among women, who expressed both greater apprehension and interest in learning more. While nanomedicine is more accepted in medical applications than in other domains, misinformation from mass media and social platforms fuels public hesitation. Figure 1 summarises the impact and challenges of nanomedicine in breast cancer treatment.

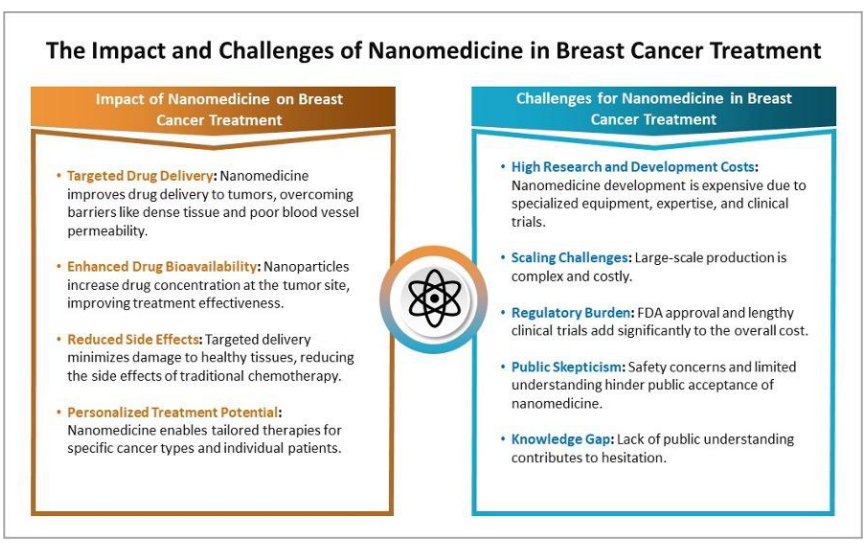

Figure 1. The impact and challenges of nanomedicine in breast cancer treatment.

Beyond scientific advancements, fostering public trust is crucial for the successful integration of nanomedicine in healthcare. Public health experts play a vital role in bridging the knowledge gap, addressing concerns, and ensuring informed acceptance of nanotechnology-based therapies.

IMPACT ASSESSMENT

This section assesses the impact of nanomedicine on breast cancer treatment, focusing on the main stakeholder, breast cancer patients, and the potential for reduced healthcare costs.

The Main Stakeholder - Breast Cancer Patients

Cancer nanomedicine offers the potential for more effective breast cancer treatment, leading to increased chances of remission without recurrence. This is supported by its higher potential to achieve pathological complete response (pCR), reducing the need for invasive procedures like mastectomy and surgery. Robidoux *et al.* (2010) demonstrated that albumin-bound paclitaxel (similar to nab-paclitaxel) was well-tolerated by breast cancer patients (including those with HER-2+ breast cancer), achieving high pCR rates with minimal toxicity.[39] While some grade 3 adverse effects were reported, they were manageable and did not necessitate discontinuation of the trial. This aligns with findings from a phase II clinical trial by Roy *et al.* (2009), which utilised nab-paclitaxel to treat adult patients with invasive breast cancer and evidence of metastasis.[40] The study showed substantial efficacy of nab-paclitaxel with manageable side effects, particularly when compared to standard paclitaxel, known for its poor solubility and hypersensitivity reactions. Out of 50 patients treated, only 8 experienced grade 3 neurotoxicity, highlighting nanomedicine's potential to reduce toxicity while maintaining therapeutic effectiveness. The targeted nature of nanomedicine, as discussed above, suggests that breast cancer patients may experience fewer and shorter durations of adverse effects. Harbeck *et al.* (2017) reported that pegylated liposomal doxorubicin (PLD) demonstrated equivalent efficacy and Quality of Life (QoL) to conventional capecitabine but with fewer serious adverse events (SAEs).[41] This positions nanomedicine as an effective alternative to conventional therapies for breast cancer patients.

Reduced Cost of Healthcare

Cancer patients, in general, face a higher risk of financial burden. Breast cancer patients and their families are associated with significantly high out-of-pocket costs (OOPCs) and substantial financial toxicity compared to those with other cancer types.[42,43] Mennini *et al.* (2021) revealed that hospital costs alone for breast cancer treatment exceed 280 million euros annually, contributing to a total financial burden of 2.5 billion euros.[44] While the incorporation of cancer nanomedicine may initially increase treatment costs, its targeted delivery to tumour cells could ultimately reduce these costs. This potential cost reduction stems from a decreased need for lengthy hospital stays, follow-up treatments, and management of side effects. Furthermore, nanomedicine could decrease indirect costs associated with lost productivity, missed workdays, morbidity, and premature death.[45] However, the high cost of research and development of nanomedicines remains a challenge. Bosetti and Jones (2019) highlight that most innovations in nanomedicine are driven by small-medium enterprises (SMEs), not large pharmaceutical companies, which typically bear the major costs of research, development, and validation.[31] While SMEs drive innovation, they often face high financial pressures, and larger pharmaceutical companies tend to invest only after innovations have proven successful.[46] This can lead to diseconomies of scale, potentially reinforcing high selling prices for nanomedicine. This pricing burden is further compounded by the reluctance of many insurance companies to provide coverage for nanomedicine treatments due to their nascent stage of development, placing additional financial strain on patients.

POLICIES AND RECOMMENDATIONS

Key policy recommendations for advancing nanomedicine focus on standardisation, government support, public awareness, and the integration of emerging technologies.

The Need for a Gold Standard

To foster public trust and acceptance of nanomedicine, addressing safety concerns is paramount. Establishing Good Laboratory Practice (GLP) protocols is crucial to prioritise nanoparticle safety and assure the quality and integrity of non-clinical studies, creating a more consistent standard for evaluating nanomedicine safety. While the FDA has issued

guidelines for nanotechnology development, these are not legally binding.[36] Therefore, a "gold standard" is urgently needed to streamline and harmonise regulatory guidelines globally. This would facilitate the mutual recognition of nanomedicines approved in different countries, reducing delays in bringing treatments to market and enhancing public confidence.

Government - One of the Key Players

Governments play a critical role in supporting nanomedicine development through increased funding for research, innovation grants, and clinical trials. This can stimulate innovation while mitigating financial barriers for institutions and pharmaceutical companies. This support can take the form of direct funding for SME pharmaceutical companies and/or facilitating partnerships with established pharmaceutical companies to support drug innovation and development. The Public-Private Partnership (PPP) model, successfully implemented in Malaysia for nearly 40 years across various public health initiatives (e.g., dialysis funding, methadone maintenance therapy, HIV interventions, and mammogram screening subsidies)[47], can be adapted for breast cancer nanomedicine research and development. Government involvement can also incentivise research scientists to reformulate proven drugs into nanotherapeutics, potentially shortening approval timelines due to the established efficacy of the original drugs. Furthermore, government funding can support the optimisation of nanotherapeutic manufacturing processes, including covering the costs of continuous flow manufacturing machinery to ensure efficiency, consistency, and product quality. A collaborative effort involving the government, large pharmaceutical companies, and SMEs can facilitate the generation of long-term clinical trial data demonstrating the effectiveness and safety of these nanomedicines.

Health Campaigns and Awareness

Effective public engagement and communication strategies are essential to address scepticism and reluctance towards nanomedicine. As previously discussed, disseminating accurate information from scientific sources is crucial. Education across all segments of society is a key tool. The COVID-19 pandemic demonstrated the power of public health education in reducing community transmission and peak mortality rates.[48] A 40% increase in education rates was associated with a 54.8% reduction in peak mortality by December 8, 2020. Post-pandemic, Chinese citizens anticipate increased public health education and training from policymakers.[49] Public health education can extend beyond traditional methods (e.g., educational institutions) to include innovative approaches like serious educational games to effectively convey information and raise awareness about nanomedicine.[50]

Artificial Intelligence and Organ-on-a-chip

A significant challenge in drug development is the low translatability of animal models to humans. A substantial percentage of drugs that pass animal studies and are approved by the FDA are later withdrawn due to unforeseen side effects in humans, and many licensed medications have limited response rates.[51] The Vioxx case, where a seemingly safe anti-inflammatory drug (based on extensive animal studies) caused numerous deaths due to cardiovascular problems, exemplifies this issue.[52] Other examples suggest that animal models may not fully capture the complex interactions of nanomedicine in humans. Artificial intelligence (AI) and organ-on-a-chip technologies offer promising solutions.[53,54] Organ-on-a-chip systems replicate human tissue models in physiologically relevant microenvironments, enabling the study of drug metabolism and organ-related diseases.[55,56] Integrating AI tools (e.g., Deep Chem, Deep Tox, ORGANIC) can further enhance this by assisting in nanoparticle design, predicting drug activity, and assessing potential interactions between drugs and target cells/proteins.[57] While AI-designed drugs are still in early stages of development and single-organ-on-chip models have limitations, the field is rapidly advancing.[58] Researchers are developing multiple-organ-on-chip systems for more holistic drug screening. The combined use of AI and organ-on-a-chip technologies has the potential to significantly accelerate the development of safe and effective nanomedicines. Table 1 summarises the future recommendations for the application of nanomedicine in breast cancer.

CONCLUSION

This review has explored the transformative potential of nanomedicine in breast cancer treatment, highlighting its mechanisms, impact on conventional therapies, and associated challenges. Nanomedicine offers significant advantages, including enhanced drug delivery, improved tumour targeting, reduced toxicity, and

TABLE 1. Future Recommendations for Application of Nanomedicine in Breast Cancer

Recommendation	Remarks	Reference
Need for a gold standard in nanomedicine	• Establish good laboratory practice protocols for nanoparticle safety. • Develop global regulatory standards. • Streamline approvals and enhance public trust.	Zhang *et al.*[36]
Government Support in Nanomedicine Development	• Increase funding for research and clinical trials. • Support SMEs through public-private partnerships. • Optimise manufacturing processes for efficiency.	Hamzi *et al.*[47]
Public Health Campaigns and Education	• Raise awareness through health campaigns. • Use serious educational games for public engagement. • Improve acceptance of nanomedicine.	Sharifzadeh *et al.*[50]
Alternative drug testing methods to animal models	• Animal models often fail to predict human responses. • Many drugs pass animal tests but fail in humans. • Alternative testing methods are needed.	Pippin[51]; Keen[52]
AI and Organ-on-a-Chip in Drug Development	• AI improves nanoparticle design and drug predictions. • Organ-on-a-chip mimics human tissue for better testing. • Reduces reliance on ineffective animal models.	Ma *et al.*[55]; Paul *et al.*[57]

the ability to overcome resistance. Nanocarriers navigate the tumour microenvironment, delivering payloads precisely and minimizing off-target effects. Furthermore, nanomedicine is enabling innovative immunotherapies and radiotherapies, offering hope for patients with aggressive or resistant cancers.

However, challenges remain. High R&D costs, complex manufacturing, and stringent regulations create financial barriers. Public scepticism and limited understanding of nanotechnology also pose obstacles. Addressing these requires a multi-pronged approach. Harmonised regulatory standards, increased government funding, and public education campaigns are crucial for fostering trust and accelerating nanomedicine's development and implementation. Integrating AI and organ-on-a-chip platforms offers immense promise for improving preclinical testing and optimising nanoparticle design, leading to safer and more effective nanomedicines.

While challenges persist, nanomedicine's progress in breast cancer is undeniable. This review underscores its potential to significantly improve patient outcomes and transform cancer care. Continued research, collaboration, and a focus on addressing existing challenges are essential to fully realise nanomedicine's promise and benefit all those affected by breast cancer. The future of breast cancer treatment lies in precision, and nanomedicine stands at the forefront of this revolution.

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