Breast Cancer: Targets and Therapy

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REVIEW

From Pioneering Discoveries to Innovative Therapies: A Journey Through the History and Advancements of Nanoparticles in Breast Cancer Treatment

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Abstract: Nanoparticle technology has revolutionized breast cancer treatment by offering innovative solutions addressing the gaps in traditional treatment methods. This paper aimed to comprehensively explore the historical journey and advancements of nanoparticles in breast cancer treatment, highlighting their transformative impact on modern medicine. The discussion traces the evolution of nanoparticle-based therapies from their early conceptualization to their current applications and future potential. We initially explored the historical context of breast cancer treatment, highlighting the limitations of conventional therapies, such as surgery, radiation, and chemotherapy. The advent of nanotechnology has introduced a new era characterized by the development of various nanoparticles, including liposomes, dendrimers, and gold nanoparticles, designed to target cancer cells with remarkable precision. We further described the mechanisms of action for nanoparticles, including passive and active targeting, and reviewed significant breakthroughs and clinical trials that have validated their efficacy. Current applications of nanoparticles in breast cancer treatment have been examined, showcasing clinically approved therapies and comparing their effectiveness with traditional methods. This article also discusses the latest advancements in nanoparticle research, including drug delivery systems and combination therapy innovations, while addressing the current technical, biological, and regulatory challenges. The technical challenges include efficient and targeted delivery to tumor sites without affecting healthy tissue; biological, such as potential toxicity, immune system activation, or resistance mechanisms; economic, involving high production and scaling costs; and regulatory, requiring rigorous testing for safety, efficacy, and long-term effects to meet stringent approval standards. Finally, we have explored emerging trends, the potential for personalized medicine, and the ethical and social implications of this transformative technology. In conclusion, through comprehensive analysis and case studies, this paper underscores the profound impact of nanoparticles on breast cancer treatment and their future potential.

Keywords: Nanoparticles, Breast Cancer, Targeted Therapy, Drug Delivery, Immunotherapy

Introduction

Breast cancer (BC) is a complicated disease marked by the uncontrolled proliferation and spread of abnormal cells in breast tissue. Breast cells have tightly controlled cycles of growth, division, and death. However, genetic changes can interfere with this normal process, resulting in unregulated cell proliferation and tumor growth.[1] Breast cancer originates from breast tissue cells. It is most commonly initiated in the ducts of the breast (ductal carcinoma) or the lobules (lobular carcinoma). Breast cancer can manifest in various forms, ranging from noninvasive (confined within the ducts or lobules) to invasive (spreading beyond the initial site into the surrounding breast tissue).[2] As reported by Cancer Research UK, breast cancer is the most frequently diagnosed cancer among women, with approximately 56,400 new cases identified

Received: 17 October 2024
Accepted: 3 January 2025
Published: 21 January 2025

annually (2017–2019)[3] In the United States, the number of new breast cancer cases diagnosed annually is projected to increase from 283,000 in 2011 to 441,000 in 2030, a more than 50% increase[4]

BC is caused by a complex interaction between genetics and the environment. It originates often from mutations that disrupt regulatory processes in normal breast cells, driven by both hereditary and non-hereditary influences. Known risk factors include genetic predispositions, hormonal changes, and environmental exposures. These mutations can lead to benign or malignant tumor formation, with malignant tumors able to invade nearby tissues and metastasize. The development of molecular subtyping has revealed distinct genetic profiles, emphasizing the necessity of precision medicine to treat BC effectively[5,6]

Building on this foundational understanding, current research has mapped a more intricate genetic landscape of breast cancer. The BRCA1 and BRCA2 genes are the most common inherited gene mutations known to increase the risk of breast cancer. Beyond these two, large-scale studies have identified 40 driver mutations, with PIK3CA and TP53 among the most common.[7] Moreover, moderate-penetrance genes like CHEK2 and ATM have also been linked to increased breast cancer risk.[8] Insights into the dynamics of breast cancer reveal that some key mutations, such as der (1;16), emerge during adolescence and evolve into distinct cancerous and non-cancerous clones by early adulthood, contributing to tumor heterogeneity.[9]

Further studies highlight the discovery of novel pathogenic mutations, including alterations in BRCA2, ERBB2, and TP53, emphasizing the global and region-specific variability in genetic profiles. For instance, a study in Jordan revealed both recurrent and newly detected mutations, with recurrence rates at 14.5% and novel mutations at 3.5%, showcasing the evolving landscape of breast cancer genetics.[10,11] These findings enhance our understanding of the disease's progression and inform the development of more targeted therapeutic approaches.

Current BC research aims for the development of innovative therapeutic strategies, including cell therapies, antitumor vaccines, and targeted treatments. The introduction of monoclonal antibodies and immune checkpoint inhibitors has substantially improved survival rates and enhanced the quality of life for patients with cancer, with some documented instances of complete tumor remission.[12,13]

In BC treatment, recent advances have led to more personalized approaches based on molecular subtypes and genetic alterations. For BRCA1/2 mutation carriers, PARP inhibitors have shown promise, with olaparib approved for HER2-negative metastatic breast cancer patients with BRCA1/2 mutations.[14] The OlympiAD trial demonstrated improved progression-free survival and health-related quality of life for olaparib compared to chemotherapy in this patient population. Similarly, talazoparib® was approved following the EMBRACA trial, which showed comparable benefits. PARP inhibitors target tumors with DNA repair defects, particularly those with homologous recombination deficiencies such as BRCA1/2 mutations. Recent research has expanded their applications; for instance, the OlympiA trial led to olaparib's approval for high-risk early HER2-negative breast cancer with germline BRCA mutations.[15,16] However, challenges remain, as resistance to PARP inhibitors occurs in almost all patients with metastatic breast cancer. The ongoing research is investigating novel therapeutics and combination strategies to overcome this resistance, including PARP1-selective inhibitors that may reduce hematological toxicities associated with PARP2 blockade.[17]

Nano-drug delivery systems have emerged as revolutionary platforms for improving drug bioavailability and enabling precision medicine, particularly in cancer treatment. Key types include liposomes, polymeric nanoparticles, dendrimers, micelles, and solid lipid nanoparticles, each with distinct advantages. Liposomes, spherical vesicles composed of phospholipid bilayers, enhance the solubility and stability of chemotherapeutic agents, facilitating targeted delivery to tumors while reducing systemic toxicity. Polymeric nanoparticles offer controlled and sustained drug release, essential for maintaining therapeutic levels over extended periods. Dendrimers, with their highly branched structures, enable multivalent drug loading and targeting capabilities. Micelles, formed from amphiphilic molecules, improve the solubility of hydrophobic drugs, while solid lipid nanoparticles provide a biocompatible and stable delivery matrix. These systems are particularly valuable in breast cancer therapy, especially for resistant breast cancer, by overcoming multidrug resistance (MDR) mechanisms such as efflux pumps and poor tumor penetration. NPs can overcome these barriers through their small size, enhanced permeability, and retention (EPR) effect, allowing them to accumulate selectively in tumor sites. Functionalized NPs, such as those coated with antibodies or ligands, enable targeted delivery to cancer cells expressing specific markers, such as HER2 or EGFR. Furthermore, NPs can be engineered to carry multiple therapeutic

agents, including chemotherapeutics and gene-silencing molecules like siRNA, to simultaneously target drug resistance mechanisms and tumor growth pathways. For instance, liposomal formulations of doxorubicin have demonstrated increased intracellular drug concentrations by bypassing efflux pumps like P-glycoprotein. Similarly, polymeric NPs loaded with paclitaxel have been shown to improve therapeutic efficacy in resistant BC by enhancing drug stability and tumor penetration. Additionally, stimuli-responsive NPs release their payload in response to tumor-specific conditions, such as acidic pH or elevated enzyme activity, ensuring drug activation at the target site while minimizing systemic toxicity. These innovations highlight the potential of NPs to revolutionize the treatment landscape for resistant BC by overcoming the limitations of conventional therapies.[18–20] For instance, nanoparticles functionalized with antibodies or ligands enable targeted delivery of drugs to specific cancer cell receptors, sparing healthy tissues and enhancing efficacy. Studies have demonstrated that nanoparticles loaded with doxorubicin or paclitaxel significantly improve therapeutic outcomes in resistant breast cancer by ensuring higher intracellular drug concentrations and reducing adverse effects.[21] These advances highlight the potential of nanocarriers in addressing the challenges of traditional therapies and improving patient outcomes.

At present, with extensive knowledge and technological advancements, we continue to strive for an improved understanding, prevention, and treatment of cancer BC. Our ongoing efforts aim to transform BC from a distressing illness into a conquerable challenge. This paper aimed to comprehensively explore the journey and advancements of nanoparticles (NPs) in BC treatment, highlighting their transformative impact on modern medicine. The article initially provides an overview of the historical context of BC therapy and the advent of nanotechnology. It then delves into the mechanisms by which NPs target cancer cells, followed by a detailed discussion of the development and current applications of NP-based therapies. Advancements in research, challenges faced, and future directions in NP therapy have been examined to offer a holistic understanding of this field. The article concludes by exploring the ethical, regulatory, and social considerations supported by case studies to underscore the profound therapeutic potential and real-world impact of NPs in BC.

Early History of Breast Cancer Treatment

The history of cancer dates back thousands of years, with evidence of the disease found in ancient civilizations, such as ancient Egypt.[22] The Edwin-Smith Papyrus, an ancient text dating back to approximately 3000 BCE, is one of the earliest known descriptions of tumors resembling cancerous growths.[23] This papyrus describes treatments for various injuries, including cauterization, which involves the destruction of tissues using heat; however, it does not explicitly mention the treatment of breast tumors.[23] Although specific treatments for cancers like those of the stomach and uterus are not well documented, other Egyptian medical texts detail various remedies, such as the use of barley and dates.[24]

In ancient Greece, Hippocrates postulated that cancer was caused by an imbalance of bodily fluids, specifically an excess of black bile.[25] He also recognized the differences between benign and malignant tumors.[22] Hippocrates' theories were widely accepted until the 19th century, when scientists unraveled the cellular and genetic basis of cancer.[26] This led to the development of modern cancer treatments such as chemotherapy and radiation. These revolutionary treatments were much more effective at treating cancer than Hippocrates' methods. His theories, however, remain an important milestone in cancer research history.[26]

Traditional Treatments: Surgery, Radiation, and Chemotherapy

Considerable advancements in cancer treatment were achieved in the 20th century through the introduction of various modalities, including surgery, radiation therapy, chemotherapy, and improved diagnostic techniques.[27] Established as the foundation for cancer management, surgery plays a vital role in driving progress. With prolonged practice, surgical tumor resection remains a fundamental approach, substantially strengthened by advancements in techniques and anesthesia, leading to improved patient outcomes.[28] Surgical intervention immediately reduces the cancer burden and potentially provides curative outcomes, particularly in early-stage cancers. Often combined with complementary therapies, such as chemotherapy and radiation, surgery ensures a comprehensive approach to cancer treatment.[29] The evolution of minimally invasive techniques, including laparoscopic and robot-assisted surgery, has refined precision and safety, offering patients minor incisions, reduced trauma, shorter hospital stays, and faster recovery times.[30]

Following surgical intervention, adjuvant therapies, such as chemotherapy and radiation, may be recommended to target residual cancer cells. Chemotherapy, known for its ability to target rapidly dividing cells, has become the cornerstone of cancer management. Its efficacy is often heightened postoperatively to address any remaining cancerous cells that may have metastasized beyond the primary tumor site.[27,29]

Subsequently, radiation therapy emerged as a significant advancement in cancer management. This non-invasive treatment utilizes high-energy lasers to target and eradicate cancer cells within a tumor, thus minimizing damage to the surrounding healthy tissue.[31] Radiation therapy is particularly valuable when chemotherapy is not viable; it has become an integral adjuvant treatment, strengthening the efficacy of cancer care.[32,33]

Moreover, diagnostic capabilities have undergone a revolutionary transformation with the introduction of imaging tools, such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans.[32,33] These technological advances have facilitated early detection and precise diagnosis, thereby providing a basis for precision treatments. Enhanced diagnostic accuracy significantly improves treatment decisions and patient outcomes. These breakthroughs continue to enhance modern cancer care and stimulate ongoing research to refine and improve cancer treatment modalities.[27]

Limitations and Challenges of Early Treatments

The early stages of cancer treatment pose several restrictions and challenges. Historically, techniques such as cauterization and herbal remedies have often been damaging and ineffective.[34] Radiation treatment was first introduced with the discovery of radium and X-rays in the late 19th and early 20th centuries. However, its use in deep tumors was initially limited, and it was mainly used to treat superficial cancers.[35]

Before the development of surgical procedures and the exploration of metastasis, surgery was inefficient in treating cancer.[36] Despite the development of anesthetics in the 19th century, surgery was still frequently performed in a drastic and multilateral manner.[37] Emotional damage caused by breast removal during cancer surgery can be profound and long-lasting. It can affect a person's body image, self-esteem, and overall sense of femininity, leading to feelings of grief, loss, and anxiety.[38] Until the late 19th and early 20th centuries, the concept of metastasis was unclear, which limited the effectiveness of early cancer surgery.[39] Early cancer surgery was often radical and mutilating, leading to considerable morbidity and mortality.[37]

The biological effects of radiation were unclear until the late 19th and early 20th centuries, which limited the efficacy of early radiation therapy.[40] The biological mechanisms underlying cancer were not elucidated until the mid-20th century, which limited the effectiveness of early chemotherapy. Early chemotherapy agents were often toxic and had significant side effects such as neutropenia, infection, mucositis, and diarrhea.[41]

The understanding that the combination of chemotherapy and radiation therapy is more effective than either alone has led to the development of combination therapies.[42] The introduction of imaging tests, such as ultrasound, CT, MRI, and PET scans, has replaced exploratory surgery and enabled a more accurate diagnosis of cancer.[43]

These limitations have led to the development of more efficient modern oncology procedures. Understanding metastasis has improved the overall therapies applied to eradicate cells that have spread throughout the body following surgery.[44] The discovery of the p53 gene and the development of CAR T-cell therapy have opened new avenues for targeted therapy.[45,46] The approval of DNA sequencing tests and the use of genetic information to guide treatment plans have enabled precision medicine approaches.[47] These advances have contributed to the development of more effective and targeted cancer treatments, which greatly improve patient outcomes and survival rates.

Initial Exploration of Alternative Therapies (Tumor Microenvironment and Role of T Cell Immunotherapy)

A complicated tumor microenvironment (TME) is key to cancer development. It comprises various components, including pericytes, endothelial cells, immune cells, and cancer-associated fibroblasts. Although initially presumed to be non-functional, these noncancerous cells are now known to notably impact cancer pathogenesis. Factors such as the

tumor organ of origin, nature of cancer cells, tumor stage, and patient-specific features may affect the cellular composition and functional state of the TME.[48]

Unveiling the Immune Orchestra: Natural Killer, CD4, and CD8 Cells in Breast Cancer Defense

Breast cancer is a complex and multifaceted disorder that requires a comprehensive understanding of the role of the immune system in its development and progression. Dendritic cells (DCs) are key players in the immune response against breast cancer. These antigen-presenting cells are pivotal in initiating and orchestrating immune responses against cancer cells. DCs capture antigens from breast cancer cells and present them to other immune cells, such as T cells, initiating an immune response. They also secrete cytokines and chemokines, which attract other immune cells to the tumor site, leading to an antitumor immune response (Figure 1).[49,50]

Additionally, DCs can activate natural killer (NK) cells, which directly kill cancer cells and enhance the immune response against breast cancer. In breast cancer, DCs are found in various tissues, including the TME, where they interact with tumor-associated antigens and initiate antitumor immune responses by presenting these antigens to T cells, which then recognize and attack cancer cells. This process plays a crucial role in the body's defense against breast cancer.[51]

The immune response against breast cancer also includes highly essential NK cells. According to[52] NK cells are innate immune cells that grow and mature in secondary lymphoid organs and bone marrow. They possess the remarkable ability to rapidly respond to infected or malignant cells without prior sensitization. Equipped with diverse activating and inhibitory receptors, NK cells distinguish between healthy and abnormal cells, including tumor cells, and initiate cytotoxic processes to eliminate these cells.[52] NK cells exert their antitumor effects through various mechanisms, including the direct killing of cancer cells and cytokine secretion, which modulate the TME. However, breast cancer cells evade NK cell-mediated immune surveillance via strategies such as the downregulation of activating ligands and

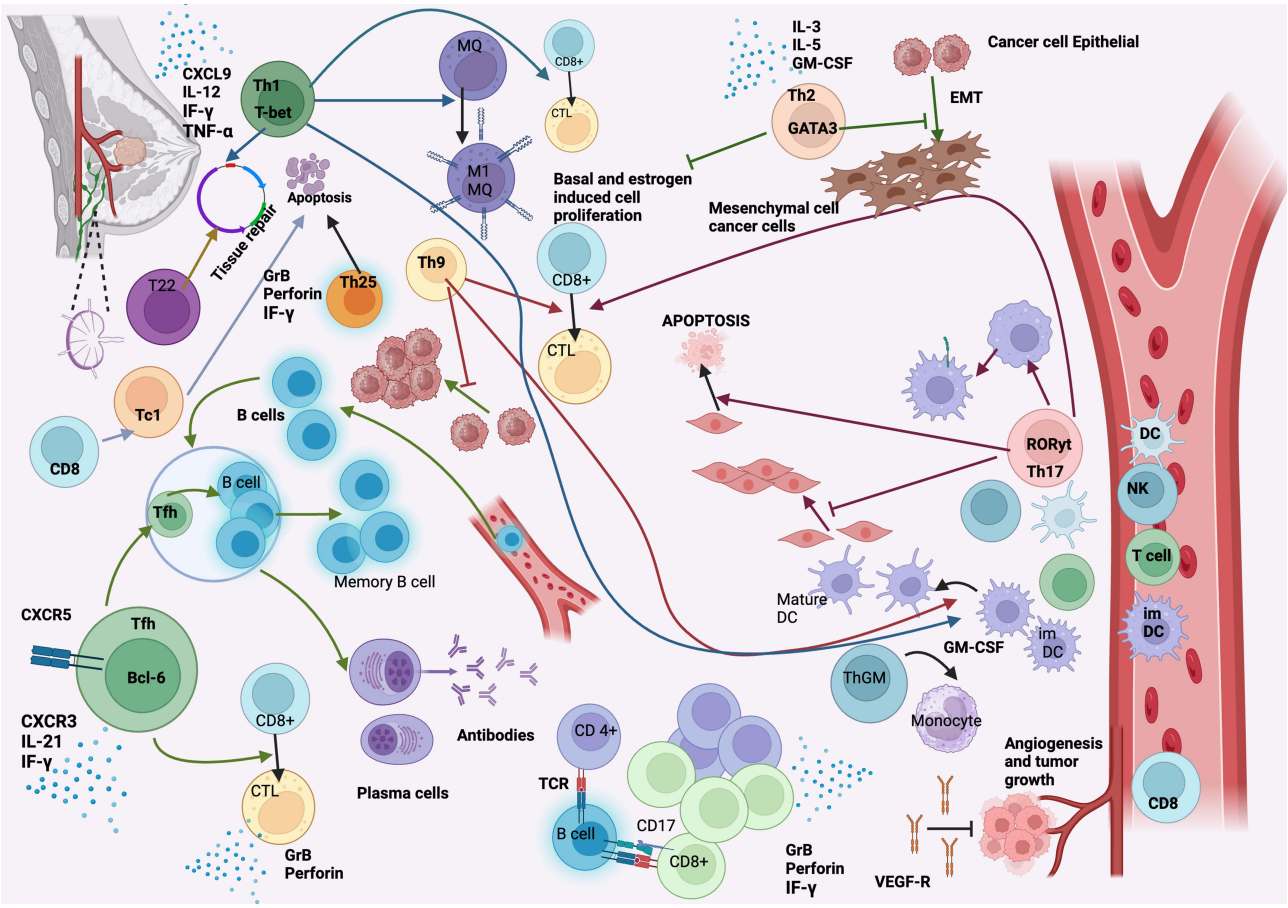

Figure 1 Illustrates the immune response against breast cancer. The figure is created at https://BioRender.com.

https://doi.org/10.2147/BCTT.S501448

upregulation of inhibitory signals. In breast cancer, NK cells play a significant role in tumor surveillance and control. These cells infiltrate breast tumors, and their presence within the TME correlates with prognosis and treatment outcomes[53] Excessive NK cell infiltration into breast tumors has been associated with improved patient survival rates and better responses to therapy.[54]

To examine immune surveillance systems, analyzing T cells comprehensively elucidates immune responses against pathogens and specific cells. White blood cells (T cells), commonly known as T lymphocytes, are crucial for adaptive immune responses. They originate in the bone marrow and mature in the thymus gland. T cells are critical players in cell-mediated immunity; they directly attack cells infected with viruses or bacteria. They also help to regulate immune responses by releasing cytokines. T cells recognize specific antigens presented by other cells, allowing them to target and eliminate pathogens and abnormal cells, including cancer cells. Various types of T cells, such as regulatory T, cytotoxic T, and helper T cells, have specific roles in the immune system.[55] Stated that helper T cells (CD4 cells) and cytotoxic T cells (CD8 cells) are essential elements of the immune system, each having a unique function in the body's responses against diseases such as cancer.

CD4+ cells orchestrate immune responses by releasing cytokines and coordinating the activities of other immune cells.[55] In breast cancer, the presence and function of CD4+ cells within the TME have been associated with prognosis and treatment outcomes.[56] Higher levels of CD4+ cell infiltration into breast tumors are linked to improved patient survival rates and enhanced responses to therapy. In contrast, CD8+ cells directly target and kill cancer cells.[57] These cells recognize antigens present on cancer cell surfaces and release toxic molecules to destroy them.[58] In breast cancer, tumor-infiltrating CD8+ cells are crucial determinants of antitumor immune responses and patient outcomes. Elevated levels of CD8+ cell infiltration into breast tumors are linked to improved survival rates and an excellent response to treatment.[59] Although CD4 and CD8 cells play complementary roles in the immune response against breast cancer, tumor cells often develop mechanisms to evade their surveillance.[60] These include the downregulation of antigens recognized by CD8 cells and the induction of immunosuppressive signals, which dampen CD4 cell activity.[61] Overcoming these immune evasion strategies represents a significant challenge in the development of effective immunotherapies for breast cancer.[62]

Distinctive Features of Nanotechnology in Oncological Applications

In oncological applications, nanotechnology offers several distinct features that potentially enhance cancer treatment and diagnosis. These include enhanced drug efficacy with fewer side effects and targeted drug delivery to specific cells or tissues, which minimizes damage to healthy cells. Nanotechnology enhances the stability and solubility of therapeutic molecules, allowing for controlled drug release mechanisms.[63] It facilitates the delivery of large biomolecules, such as DNA and RNA, and enables the co-delivery of multiple drugs to combat resistance.[64] Nanotechnology enables drugs to cross biological barriers more effectively, thereby improving tumor access.[65] Moreover, it enhances cancer diagnosis and imaging precision, provides real-time drug delivery and efficacy visualization, and aids in the development of synthetic vaccines.[66] Furthermore, significant advancements in the field include miniaturized medical devices for diagnosis and therapy and exploring the inherent therapeutic properties of nanomaterials.[67]

The Advent of Nanotechnology in Medicine

Definition and Basic Principles of Nanotechnology

Nanotechnology, which involves manipulation of matter at the molecular level, holds significant potential for advancing cancer research and treatment. This technology can potentially improve diagnostic test accuracy, the development of targeted therapies, and the design of personalized cancer vaccines, thereby revolutionizing the fight against cancer.[68] By creating materials with specialized properties, nanotechnology can target cancer cells, deliver drugs directly to tumors, and develop treatments that are less invasive and more effective than the existing approaches. Its unique properties, such as high surface area and diverse functional groups, make it the best platform for targeted therapy and molecular imaging.[69]

The small size of nanomaterials enables them to navigate through the body and reach specific targets, such as tumors, with greater ease and accuracy than those by conventional therapies. Pharmaceutical nanocarriers have been developed to

improve disease diagnosis and prognosis.[70] Recent studies have demonstrated promising developments in the use of nanotechnology in cancer treatment. To minimize damage to healthy cells, reduce side effects, and ensure precise drug delivery, NPs can be engineered to carry chemotherapeutic drugs directly to cancer cells and release their payload in response to particular triggers within the body[64].

Nanotechnology has enabled the development of advanced imaging techniques for early tumor detection. NPs can be used as contrast agents in imaging technologies, such as MRI, providing more precise and detailed images of tumors than those using traditional contrast agents.[68] This early detection capability is crucial for improving treatment outcomes as it allows for the identification and treatment of cancer at its earliest and most treatable stages.

Furthermore, innovations such as nano vectors and high throughput nano sensor devices have introduced more effective cancer therapies. Nano vectors can carry multiple therapeutic agents simultaneously, targeting different pathways involved in cancer progression and leading to more comprehensive treatment strategies.[71] High-throughput nano sensors can rapidly analyze large volumes of biological data, aiding in identifying cancer biomarkers and developing personalized treatment plans.[71] Researchers are also exploring the potential of nanotechnology to create precision vaccines against cancer. These vaccines use NPs to deliver tumor antigens directly to the immune system, stimulating a robust immune response targeting cancer cells.[72] These advancements enable earlier cancer detection and more effective treatments, ultimately improving patient care and outcomes. As nanotechnology research progresses, its integration into oncology promises a new era of precise and personalized cancer treatment.

Historical Milestones in the Development of Nanotechnology

The history of NPs dates back to the 1950s when Jatzkewitz pioneered the design of a polymer-drug conjugate,[73] followed by Bangham's landmark discovery of liposomes in the mid-1960s.[74] In 1972, Scheffel et al reported the development of albumin-based NPs, laying the foundation for albumin-bound paclitaxel (Abraxane®), which received approval for breast cancer treatment in 2005, from the US Food and Drug Administration (FDA).[75,76] Notably, Abelcet, an amphotericin B lipid complex approved by the FDA in 1995 for the treatment of invasive fungal infections, has since been widely used in patients with cancer.[77] During the 1980s, Maeda et al noticed enhanced NP accumulation in tumors attributed to the altered structure of tumor vasculature, leading to the conceptualization of the "enhanced permeability and retention (EPR) effect.[78] This phenomenon, characterized by a leaky tumor vasculature and reduced lymphatic drainage, facilitates NP accumulation in tumors, enhancing therapeutic efficacy while mitigating side effects;[78] Figure 2).

Cancer nanotechnology has emerged as an interdisciplinary endeavor with promising advancements in cancer detection, diagnosis, and treatment.[68] Nanotechnology offers many innovative techniques and methodologies for characterizing tumors, detecting micro metastases, and ensuring complete tumor removal. In cancer therapy, nanomaterial-based approaches, including photodynamic, molecular, and targeted therapy, along with NP-based chemotherapy and chemodynamic treatment can potentially improve drug efficacy and overcome drug resistance.[66]

The advantages of nano-based drugs over conventional therapies include enhanced target selectivity, improved pharmacological properties, and reduced off-target effects.[79] Various types of NPs such as metal NPs, polymer-based NPs, and nanovesicles, including liposomes and dendrimers, have been developed and investigated for their ability to overcome chemoresistance in cancers. However, challenges such as particle size optimization, stability enhancement, and immune system evasion remain pivotal areas for further research to optimize NP-based drug delivery systems.[79]

Early Experiments and Findings Related to NPs in Medical Research

Early experiments and findings related to NPs in medical research marked pivotal moments in the evolution of nanomedicine.[80] At the nascent stages of exploration, scientists have conducted foundational experiments to understand the behavior, interactions, and potential applications of NPs in medicine. One landmark discovery in the early days of NP research was the development of gold nanoparticles (AuNPs) as contrast agents for biomedical imaging.[81] This breakthrough, pioneered by Van Duyne and El-Sayed in the late 20th century, demonstrated the unique optical properties of AuNPs, particularly their ability to enhance contrast in imaging modes such as surface-enhanced Raman spectroscopy and photoacoustic imaging. These early experiments laid the groundwork for the use of NPs in diagnostic imaging, offering a non-invasive method for visualizing biological structures with unprecedented sensitivity and resolution.

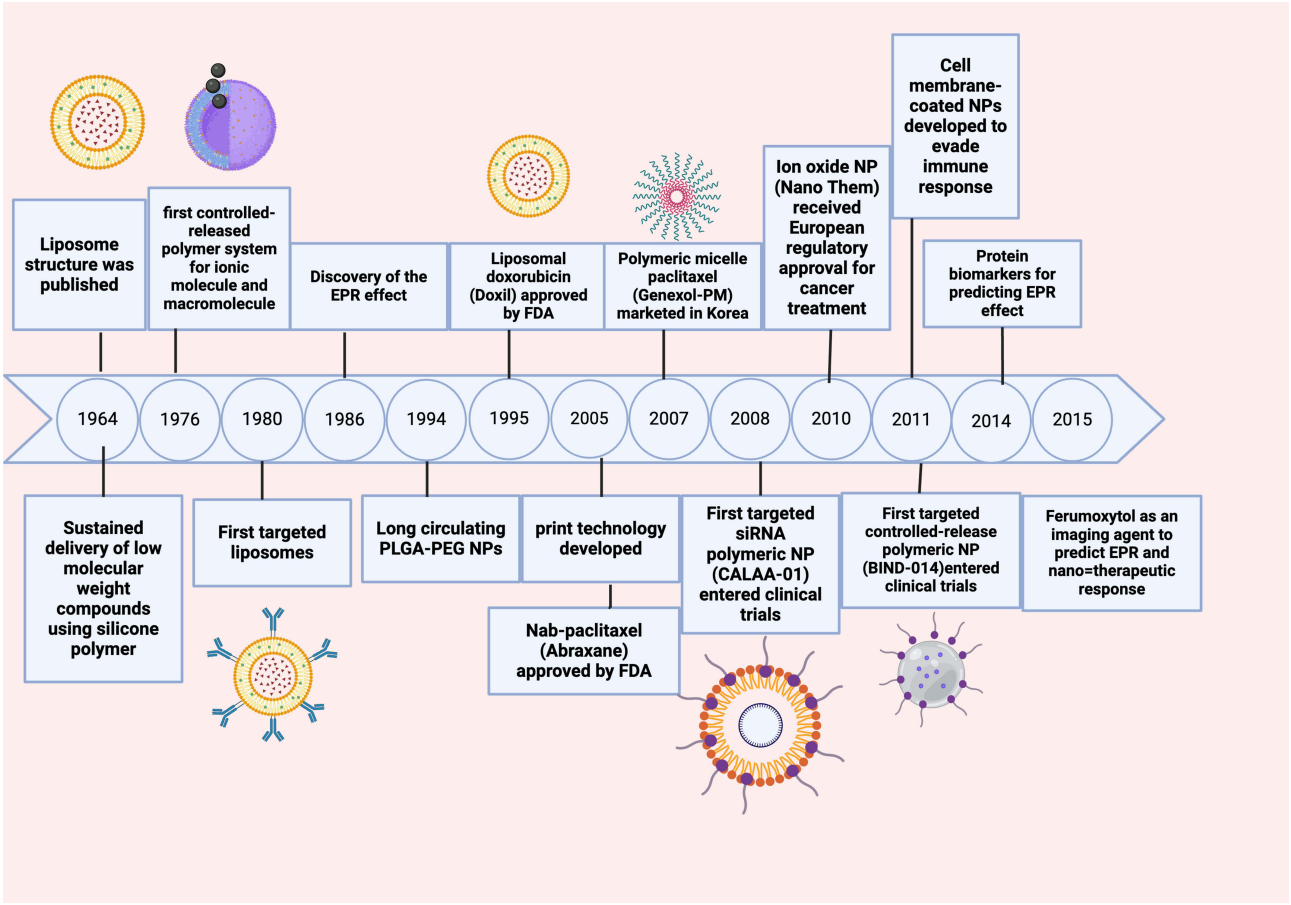

Figure 2 Milestone of significant Nanoparticle development. The figure is created at https://BioRender.com.

Another significant area of early research focused on the therapeutic capabilities of NPs, particularly in drug delivery. In the late 20th and early 21st centuries, researchers explored various NP formulations for targeted drug delivery to improve the efficacy and safety of conventional therapeutics.[82] Notable is the development of liposomal formulations for delivering chemotherapy drugs, such as Doxil® (pegylated liposomal doxorubicin), which gained FDA approval in 1995.[83] This pioneering study demonstrated the ability of NPs to encapsulate and deliver drugs to specific tissues or cells, thereby lowering systemic toxicity and enhancing therapeutic outcomes.

In addition, the multifunctionality of NPs has also been highlighted. NPs may be engineered to target certain cells or tissues, elude immune detection, deliver therapeutic payloads, and even interact with biological molecules for therapeutic or diagnostic purposes.[84] These discoveries have led to the development of multifunctional NPs with customized features for targeted drug delivery, cancer therapy, gene therapy, and regenerative medicine.

Building upon the insights gained from early research remains essential for realizing the full potential of NPs in improving human health and well-being as nanomedicine continues to evolve. Early findings related to NPs in medical research have inspired innovative NP-based technologies that have the potential to revolutionize the diagnosis, treatment, and prevention of various diseases.[85]

Functional Mechanisms and Types of NPs Mechanism of NPs

Molecular Functioning of NPs

NPs, typically ranging from 1 to 100 nm in size, are small enough to interact closely with biological structures at the molecular level, including proteins and DNA.[86] This scale allows them to interact with biomolecules in unique ways, including electrostatic interactions, surface adsorption, and receptor-ligand binding. These interactions affect the

conformation, activity, and stability of the biomolecules, thereby aiding biomedical applications, such as targeted drug delivery and biosensing. Owing to their small dimensions, NPs have a surface area larger than their volume, analogous to a tiny ball with a vast absorbent, sponge-like surface. This extensive surface area allows them to interact with considerably more molecules, making them ideal for drug delivery or accelerating chemical reactions.[87]

Tunability is a key feature of NPs, wherein their size, shape, and composition can be precisely controlled during manufacturing.[88] This allows for the design of NPs with specific properties tailored to their intended purpose. For instance, AuNPs can be engineered to efficiently absorb light, making them ideal for photothermal therapy.

Drug delivery is a key application, where NPs can deliver drugs directly to diseased cells and act as miniaturized carriers. Owing to their size, medications are delivered to precise locations since NPs can travel through the body and target particular cell surface molecules.[89] Imaging is another potential application of NPs. Designing NPs that bind to specific molecules in the body can aid in molecular imaging of biological processes thus allowing comprehensive understanding of disease progression and treatments.[90] NPs can also act as catalysts to accelerate chemical reactions at the molecular level. Nanotechnology has significant applications in various fields ranging from the development of clean energy sources to streamlining industrial processes. They can facilitate faster and more efficient chemical reactions than those using conventional techniques.[91]

Moreover, NPs can be used as biosensors to detect specific biomolecules. NPs bind to these targets and generate signals, allowing sensitive detection methods.[92] The unique ability of NPs to interact with molecules at their level, coupled with their customizable properties, makes them powerful tools with vast potential in medicine, diagnostics, and engineering.[93]

Types of NPs

Liposomes, dendrimers, gold, and polymeric NPs are the most prominent NPs, owing to their distinct structures and functionalities (see Table 1 and Figure 3). Liposomes are spherical particles with diameters ranging from 50 to 1000 nm and comprising one or more phospholipid bilayers.[93] These phospholipids may be of natural or synthetic origin and are generally combined with cholesterol to enhance their stability. The primary advantage of liposomes is their biocompatibility because their composition mimics that of cell membranes, thereby reducing their toxicity and immunogenicity.[94]

Table 1 Properties of Different Nanocarrier Types

Type of Nanocarrier	Properties	Advantages	Disadvantages	Citation
Liposomes	Spherical structures with a phospholipid bilayer membrane	High biocompatibility, controlled drug release, targeted delivery	Limited stability, potential for leakage, expensive production	[97]
Polymeric Nanoparticles	Made of synthetic or natural polymers	Versatile, tunable properties, high drug loading capacity	Potential for immune response, complex manufacturing process	[98]
Micelles	Self-assembled structures formed by amphiphilic molecules	High drug solubilization, enhanced bioavailability	Limited drug loading capacity, rapid drug release	[99]
Solid Lipid Nanoparticles	Solid lipid core surrounded by a stabilizer	Improved drug stability, sustained drug release	Lower drug loading compared to liposomes, potential for physical changes during storage	[100]
Dendrimers	Highly branched, synthetic polymers with a well-defined structure	High drug loading capacity, targeted delivery capabilities	Potential for toxicity, complex design and synthesis	[101]
Nanogels	Three-dimensional networks of cross-linked polymers	High drug loading capacity, controlled drug release, biocompatibility	Potential for aggregation, complex design and synthesis	[102]

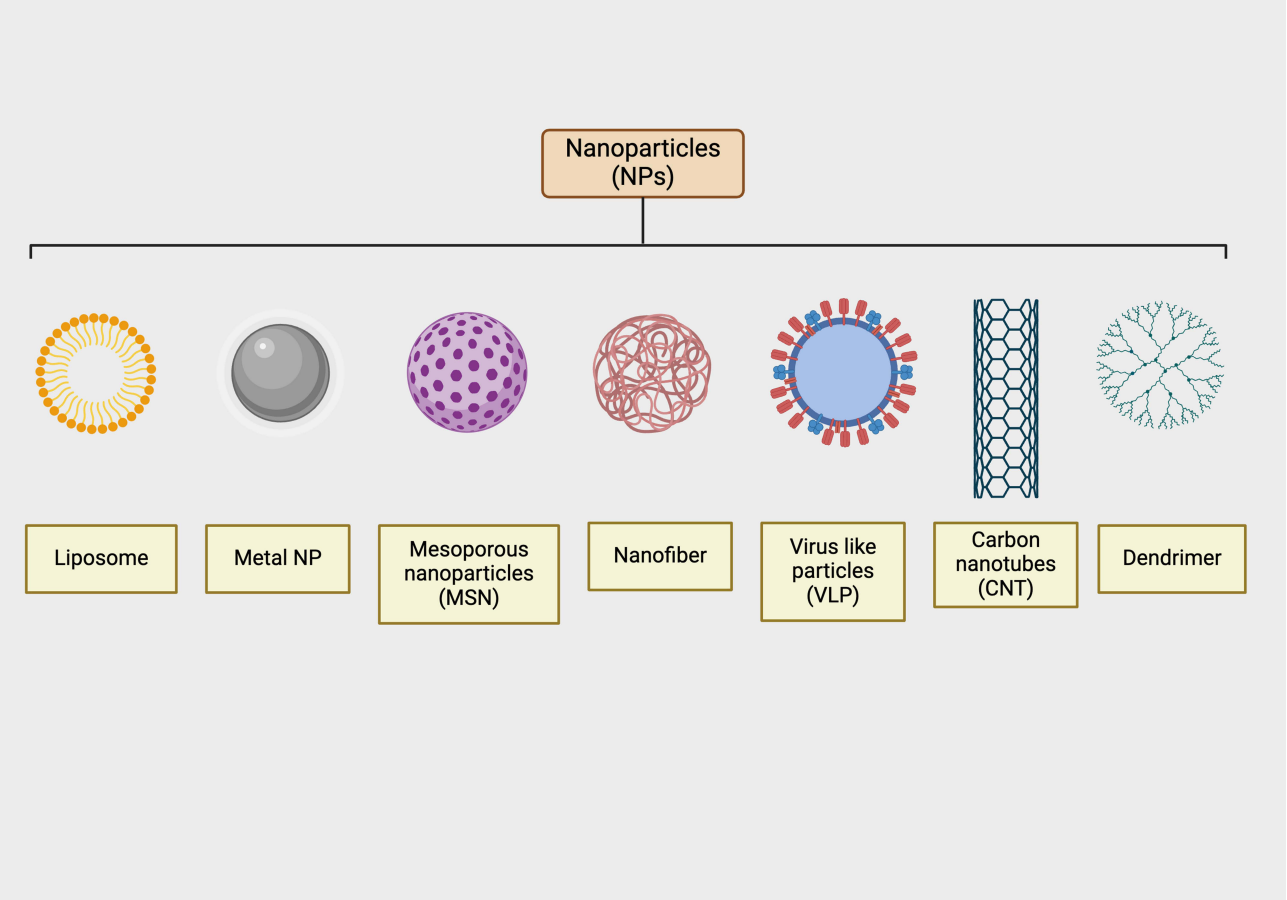

Figure 3 Types of nanoparticles. The figure is created at https://BioRender.com.

Liposomes exhibit high encapsulation efficiency, can carry both hydrophilic and hydrophobic drugs, and offer controlled release properties which can prolong the therapeutic effect of the encapsulated drug.[95] Furthermore, the surface modification of liposomes enables targeted drug delivery and enhances treatment efficacy for specific tissues or cells. However, liposomes face stability challenges and are prone to degradation and fusion over time, necessitating careful storage conditions. In addition, their production costs are relatively high, which limits their widespread application.[96]

In contrast to the vesicular, monodisperse structure of liposomes, dendrimers resemble heavily branched trees. These NPs are synthesized in layers called generations, which increases the size and surface functionality of the molecule.[103] Dendrimers offer several advantages, including a high degree of surface functionality, which allows the attachment of multiple drug molecules to a single dendrimer. These properties make them ideal for drug delivery and diagnostic applications.[104] Dendrimers also possess precise molecular weights and sizes, which enhance their predictability and reproducibility in biological systems. However, dendrimers can be expensive and complex to synthesize, and their toxicity is a concern, particularly with higher-generation dendrimers, which may require surface modifications to improve their biocompatibility.[105]

AuNPs differ significantly from liposomes and dendrimers in their composition and properties. AuNPs are colloidal gold particles ranging from 1 to 100 nm in size. They exhibit unique optical properties such as surface plasmon resonance, which makes them ideal for imaging, diagnostics, and photothermal therapy.[106] AuNPs are biocompatible and can be easily functionalized with various molecules, including drugs, antibodies, and peptides, to enhance targeting and therapeutic efficacy[107] They are also relatively easy to synthesize and modify. However, the long-term toxicity and environmental impact of AuNPs are still under investigation. Additionally, their stability in biological environments is a concern, necessitating careful surface modification to prevent aggregation and ensure consistent performance[108].

Polymeric NPs represent a distinct approach to NP design and application. These NPs consist of biodegradable and biocompatible polymers, such as polylactic acid, polyglycolic acid, and copolymers. Polymeric NPs can be designed for controlled drug delivery, improved therapeutic outcomes, and reduced side.[109] In turn, polymeric NPs offer a high drug-loading capacity and can be engineered to release drugs in response to specific biological stimuli, such as pH or temperature changes.[110] Moreover, surface modifications can be performed to further enhance targeting capabilities. However, their synthesis can be complex and requires precise control over the polymerization processes. Additionally, potential issues with polymer degradation and the release of toxic byproducts must be carefully managed to ensure clinical safety and efficacy.[111] In summary, each type of NP has unique benefits and limitations, underscoring the importance of continued research in this dynamic field.

Mechanisms of Targeting Cancer Cells: Passive and Active Targeting

The effective targeting of cancer cells is crucial for successful cancer therapy. Two primary targeting mechanisms are employed for this purpose: passive and active targeting. Each mechanism uses distinct strategies to direct therapeutic agents toward cancer cells. Passive targeting exploits the unique properties of the TME to accumulate therapeutic agents at tumor sites.[112] The Enhanced Permeability and Retention (EPR) effect is the most significant feature of passive targeting. Tumors have a leaky vasculature owing to rapid and abnormal angiogenesis, allowing NPs and macromolecules to penetrate and accumulate within the tumor tissue more readily than that in normal tissues[113]. Additionally, poor lymphatic drainage in tumor tissues helps retain these particles at the tumor site for extended periods. This method is advantageous because it does not require modification of therapeutic agents with targeting ligands and exploits the natural differences between the tumor and normal tissue vasculature, thus reducing systemic toxicity.[112] However, passive targeting has limitations. The EPR effect can vary considerably between patients and even within different regions of the same tumor, leading to inconsistent drug accumulation. Additionally, passive targeting provides less control over the distribution and concentration of therapeutic agents within the tumor tissue.[114]

In contrast, active targeting involves the modification of therapeutic agents with specific ligands that bind to receptors or antigens overexpressed on the surface of cancer cells. These ligands can include antibodies, peptides, small molecules, or other moieties with a high affinity for tumor-specific markers.[85] Therapeutic agents can be selectively delivered to cancer cells by binding to these markers, thereby enhancing their specificity and uptake through receptor-mediated internalization. Active targeting offers significant advantages such as high specificity and minimal effects on normal cells, thus reducing side effects.[115] Additionally, ligand-receptor interactions facilitate the uptake of therapeutic agents into cancer cells, thereby improving their efficacy. However, active targeting requires modification of therapeutic agents with targeting ligands, which can be technically challenging and costly. Moreover, the introduction of foreign ligands can trigger immune responses, potentially reducing the efficacy of the therapy and causing adverse reactions.[112] The heterogeneous expression of target receptors within the tumor or changes during disease progression can also affect the targeting efficiency.[116]

The integration of passive and active targeting mechanisms can enhance the effectiveness of cancer therapies. A synergistic approach can be achieved by using passive targeting to exploit the EPR effect and active targeting to refine the delivery to specific cancer cells. This integrated strategy aims to maximize drug accumulation at the tumor site, while ensuring precise delivery to cancer cells, thereby improving therapeutic outcomes and minimizing side effects.[116]

Development of NP-Based Therapies for Breast Cancer

Timeline of Fundamental Discoveries and Technological Advancements

Recently, substantial research has focused on the development of innovative breast cancer treatments using NPs, following its initiation in the 1980s.[117] This innovation was influenced by the fact that NPs can be engineered to target certain cells or tissues, enabling more focused and efficient therapies.

In the 1990s, researchers initiated the development of NPs from various materials, including lipids, polymers, and metals.[117] These early NPs were primarily used to deliver chemotherapeutic drugs and effectively reduce tumor size and improve patient outcomes. However, research was limited owing to uncertainties regarding the pharmacokinetics and

toxicity of NPs. Since then, considerable effort has been devoted to developing safer and more effective NPs for cancer treatment. The development of NPs continued in the 2000s, with considerable progress in their design and fabrication.[79]

In the 2010s, clinical trials using NP-based therapies against breast cancer were initiated.[118] Regulatory organizations, such as the FDA, authorized several such treatments.[119] These approvals were a remarkable milestone in the development of NP-based breast cancer therapies. Researchers have continued to develop NP-based therapies for breast cancer.[79] These include the development of new materials and techniques for creating NPs and the integration of NPs with other therapeutic approaches, such as immunotherapy and gene therapy.[120] These advances can potentially improve the efficacy and safety of NP-based therapies for breast cancer.

Case Studies of Significant Breakthroughs

An important success in NP-based treatments for breast cancer has been the development of liposomal doxorubicin under the trade name Doxil®. This formulation comprises PEGylated liposomes encapsulating the cytotoxic drug doxorubicin. The formulation in liposomes alters the pharmacokinetics and biodistribution of doxorubicin, which improves the efficacy and reduces cardiotoxicity relative to that of free doxorubicin.[121,122] These advantages make liposomal doxorubicin a promising NP-based therapy for breast cancer. Currently, Doxil® has been approved for the treatment of some breast cancer types, effectively reducing tumor size and improving patient outcomes. It is also being assessed for potential treatment of other cancer types.[123] Another critical development is the use of NP albumin-bound paclitaxel, under the trade name Abraxane®. This formulation is a solvent-free version of paclitaxel, where albumin NPs are used for drug delivery. This extends the activity of the drug by evading solvents such as Cremophor EL, which contribute to hypersensitivity reactions and other adverse effects related to the medications.[124]

Triple-negative breast cancer (TNBC) is a highly aggressive form of breast cancer that lacks the expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). Targeted NPs have demonstrated promise in the treatment of TNBC[125] and one example is paclitaxel-loaded, transferrin-targeted NPs. Transferring is overexpressed on many cancer cell surfaces, including those of TNBC cells. By targeting transferrin receptors, NPs can selectively deliver paclitaxel to tumor cells, potentially enhancing efficacy and reducing side effects. Hence, from the approval of liposomal doxorubicin and NP albumin-bound paclitaxel to the development of targeted NPs for specific breast cancer subtypes, additional breakthroughs are expected in this rapidly advancing field.[126]

Overview of Pioneering Research and Clinical Trials

NP-based therapies for breast tumors have shown great potential in improving treatment outcomes and reducing side effects. It has highlighted the development and clinical applications of various types of NPs, such as lipid and multi-functional NPs, in breast cancer therapy.[114] These NPs improve drug accumulation in tumors and restrict their harmful effects. Further,[116] studies have emphasized the clinical success of NP-based drug delivery platforms, such as doxorubicin and paclitaxel NP formulations, in improving patient tolerability and survival.[118] Additionally, research has discussed the use of NP-based platforms to penetrate biological barriers and enhance drug accumulation in tumors, thus providing a comprehensive overview of the current state of NP-based therapeutics for breast cancer.

Current Applications of NPs in Breast Cancer Treatment

Clinically Approved NP-Based Therapies

There has been a substantial increase in NP-based therapies, facilitating the enhanced delivery of drugs and reducing their side effects, dramatically increasing their therapeutic efficacy.[127] Several NP-based therapies have been clinically designed to treat various diseases, primarily breast cancer.[64] One successful application of NP-based therapy is the use of Doxil®, as discussed in Case Studies of Significant Breakthroughs.[83] In addition to avoiding immune detection, polyethylene glycol (PEG) coating prolongs the circulation time of these liposomes in the blood. The encapsulation of doxorubicin in liposomes enables its delivery to cancer sites via the EPR effect, which decreases drug uptake by healthy tissues.[115] Doxil® has been used to primarily treat multiple myeloma, ovarian cancer, and Kaposi's sarcoma.[128]

The complex of paclitaxel on albumin NPs in Abraxane increases the solubility and bioavailability of the drug, allowing the transport of paclitaxel across cell membranes and into cancer cells.[129] This formulation also harnesses the natural pathways of albumin transport and delivers higher concentrations of the drug to tumor sites. Abraxane is indicated for the treatment of pancreatic, non-small cell lungs, and metastatic breast cancers.[124] This NP formulation allows for the administration of higher doses of the chemotherapeutic agent, ie, paclitaxel, than those using traditional formulations, along with reduced hypersensitivity reactions.[130]

Onivyde® is a pegylated liposomal formulation of irinotecan, a topoisomerase inhibitor used in chemotherapy for metastatic pancreatic adenocarcinoma. Its liposomal encapsulation protects irinotecan from premature degradation and enhances its accumulation in tumors via the enhanced permeability and retention (EPR) effect.[131] Approved for use with other agents, Onivyde® improves irinotecan's pharmacokinetics and therapeutic index, leading to better clinical outcomes.[131] Similarly, Vyxeos® is a liposomal formulation that combines daunorubicin and cytarabine in a 1:5 molar ratio, enhancing drug delivery to leukemia cells while minimizing toxicity.[132] Both Onivyde® and Vyxeos® exemplify the advantages of liposomal drug delivery systems in oncology.

Mechanisms of NPs Within the Tumor Microenvironment (TME)

Understanding the improved effectiveness of nanoparticles (NPs) in breast cancer (BC) treatment requires an in-depth exploration of their interactions with the tumor microenvironment (TME) and the mechanisms driving their action. NPs enhance drug delivery by utilizing the enhanced permeability and retention (EPR) effect, allowing them to accumulate preferentially in tumor tissues due to the leaky vasculature characteristic of tumors. This accumulation not only increases the local concentration of therapeutic agents but also minimizes systemic toxicity, leading to improved treatment outcomes.[17]

Moreover, NPs can be designed in a way that they will specifically interact with the TME of the breast tumor by modifying their surface properties by targeting ligands binding to the overexpressed receptors on the surface of cancer cells, such as HER2. This targeted delivery enhances cellular uptake and promotes apoptosis in malignant cells while sparing normal tissues, as evidenced by recent advancements in targeted drug delivery systems for HER2-positive breast cancer.[133,134] The use of such strategies is crucial in improving therapeutic efficacy and minimizing off-target effects, thereby offering a promising approach for treating this aggressive subtype of breast cancer.[135,136] In addition, NPs can facilitate combination therapies through the co-delivery of multiple therapeutic agents, including chemotherapeutics and immunomodulators, which could further synergistically enhance antitumor efficacy.[137]

Recent studies have also highlighted the role of NPs in modulating immune responses within the TME. By delivering immune checkpoint inhibitors or stimulating agents directly to tumor sites, NPs can enhance local immune activation and promote a more robust antitumor response.[138]

Mechanisms and Efficacy of Current Treatments

Modern methods for drug delivery are highly effective, particularly for doxorubicin (Doxil®). This formulation encapsulates doxorubicin in PEG-coated liposomes, which are designed to be obscure to mononuclear phagocytes and cleared more slowly during the PEGylation process[127] Similarly, Abraxane leverages natural albumin transport pathways to enhance drug delivery to tumors. This formulation improves the solubility and bioavailability of paclitaxel, enabling its efficient transport across cell membranes into cancer cells. Clinical trials have demonstrated their superiority over traditional paclitaxel formulations, allowing higher doses with reduced hypersensitivity reactions, thereby improving patient outcomes.[139]

In addition, Vyxeos® (liposomal daunorubicin and cytarabine) combines daunorubicin and cytarabine at a fixed 5:1 molar ratio within liposomes. This ratio optimizes the synergistic action of these drugs, enhancing their targeting and uptake by leukemia cells, while minimizing systemic toxicity.[132] Vyxeos® has been approved for the treatment of newly diagnosed therapy-related acute myeloid leukemia (t-AML) and AML with myelodysplasia-related changes. Clinical trials have demonstrated improved overall survival and remission rates in aggressive forms of leukemia using Vyxeos®, compared with those using conventional chemotherapies.[132]

Lastly, Genexol-PM® (polymeric micelle paclitaxel) uses polymeric micelles to encapsulate paclitaxel, enhancing its solubility and stability. This formulation facilitates the delivery of paclitaxel to cancer cells while minimizing its exposure to healthy tissues, thereby reducing its adverse effects.[140] Genexol-PM® is used to treat metastatic breast, non-small cell lungs, and ovarian cancers. Genexol-PM® allows higher doses of paclitaxel to be clinically administered with fewer side effects than those using traditional solvent-based formulations, thereby improving the overall therapeutic efficacy.[140,141] These NP-based therapies leverage innovative mechanisms to enhance drug delivery and effectiveness while reducing toxicity.

Comparative Analysis with Conventional Treatment Methods

NP-based therapies offer distinct advantages over conventional treatment methods, primarily through improved drug delivery, enhanced efficacy, and reduced side effects. These therapies utilize advanced drug delivery systems, enhancing the pharmacokinetics and biodistribution of chemotherapeutic agents, unlike traditional drugs that affect both cancerous and healthy cells. By encapsulating drugs and targeting them specifically to tumor cells, NPs reduce off-target effects and allow for higher dosages, thereby enhancing therapeutic efficacy. NP formulations considerably enhance the pharmacokinetic and pharmacodynamic profiles of chemotherapeutic agents by improving their solubility, stability, and targeted delivery.[142] For instance, Abraxane utilizes albumin-bound paclitaxel NPs with a diameter of approximately 130 nm, allowing for high paclitaxel loading and enhanced tumor accumulation via the EPR effect.[139] Similarly, Onivyde® encapsulates irinotecan within 100-nm liposomes, providing a sustained release at the tumor site, leading to increased cytotoxicity compared to conventional formulations.[131]

NP-based delivery systems can also help overcome multidrug resistance (MDR) mechanisms. For example, vincristine-loaded solid lipid NPs (VCR-SLNs) efficiently deliver vincristine and temozolomide into U87MG glioblastoma cells, exhibiting higher cytotoxicity than single-drug SLNs.[143] The co-encapsulation of multiple chemotherapeutics within a single NP helps circumvent resistance pathways, such as efflux transporter overexpression and defective apoptotic signaling.

These advancements in NP-based drug delivery systems translate into tangible clinical benefits. Enhanced tumor targeting and reduced systemic toxicity contribute to higher overall survival and improved progression-free survival rates in patients receiving NP-based chemotherapeutic treatments.[144] Traditional chemotherapy often causes severe side effects due to its nonspecific action on rapidly dividing cells, affecting not only cancer cells but also healthy cells in the bone marrow, gastrointestinal tract, and hair follicles. This results in common chemotherapy-associated toxicities such as myelosuppression, mucositis, and alopecia. In contrast, NP-based treatments offer a more targeted approach. For instance, Vyxeos®, which combines daunorubicin and cytarabine in liposomes, directly delivers these drugs to leukemia cells at an optimal ratio, reducing systemic toxicity and improving the safety profile of the treatment, making it more tolerable for patients, particularly older adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML).[132] Furthermore, With Genexol-PM®, high doses of paclitaxel can be administered with fewer side effects, improving therapeutic efficacy in non-small cell lung, metastatic breast, and ovarian cancer patients.[145]

Detailed Case Studies of Successful Treatments

The applications of NPs in breast cancer treatment have recently been very promising (Figure 4). Several case studies have demonstrated their potential to improve the current status of breast cancer treatment. In a clinical trial involving 509 patients with metastatic breast cancer whose prior therapy with anthracycline-based regimens had failed, Doxil® notably delayed the time to disease progression compared with that of conventional chemotherapy (6.9 vs 3.0 months). Moreover, it had a more favorable toxicity profile. The liposomal encapsulation of doxorubicin in Doxil® allowed for preferential drug accumulation in the tumor tissue by the EPR effect, reducing exposure in healthy tissues and mitigating the common cardiotoxicity of doxorubicin.[146]

In contrast, the use of NP albumin-bound paclitaxel was compared to that of solvent-based paclitaxel in a Phase III study including 460 patients with metastatic breast cancer. NP albumin-paclitaxel was associated with significantly improved progression-free survival (23 vs 16.9 months) and overall response rates (33% vs 19%) than those using

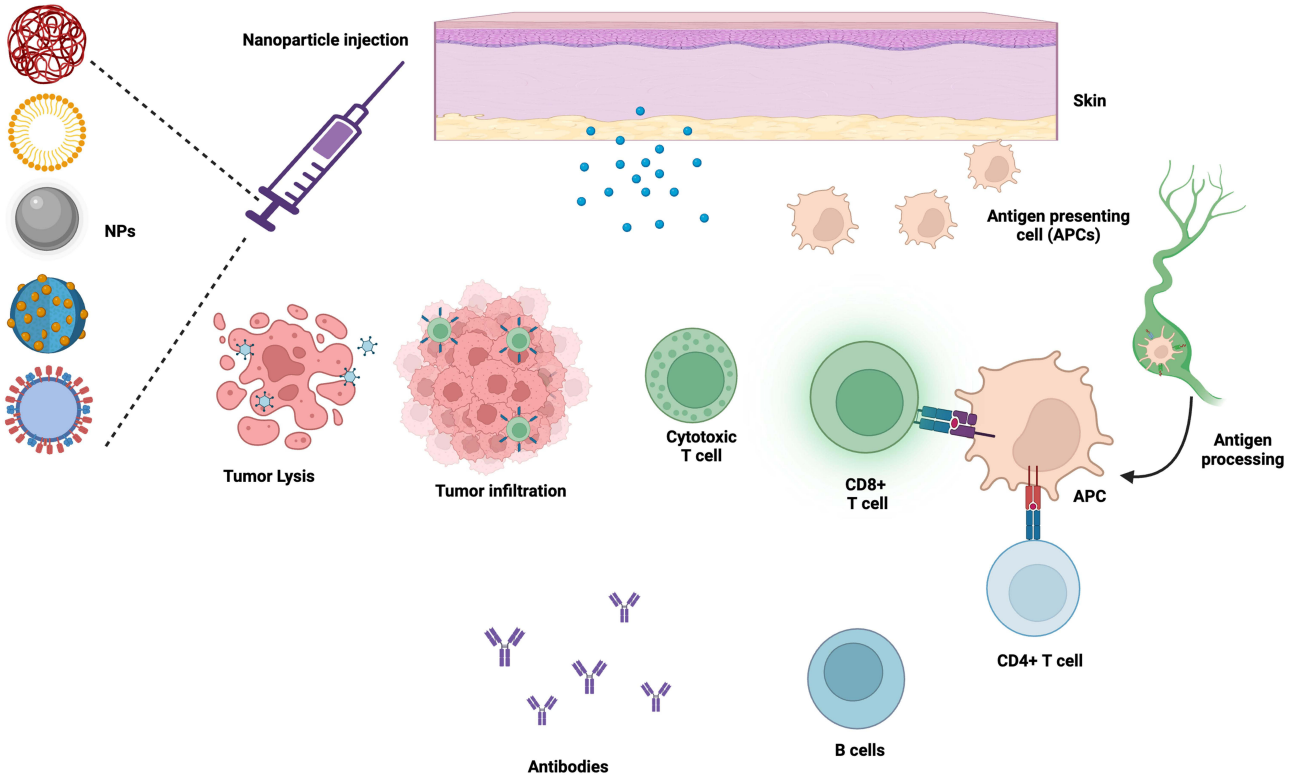

Figure 4 Nanoparticles' impact on Immune response. The figure is created at https://BioRender.com.

solvent-based paclitaxel. In addition, the NP formulation permitted more effective delivery of paclitaxel to the tumor without increasing neuropathy, which is a frequent dose-limiting toxicity related to solvent-based paclitaxel.[139]

Furthermore, polydopamine NPs loaded with both paclitaxel and trastuzumab have been developed to treat HER2-positive breast cancer. In mouse models of HER2-positive breast cancer, these NPs enhanced the accumulation of the drugs within tumors, thus improving their therapeutic efficacy, relative to that of unbound drugs. The NP platform was able to synergistically target and inhibit HER2+ breast cancer cells by combining a chemotherapeutic agent, paclitaxel, and a targeted therapy, trastuzumab.[147]

Finally, magnetic NPs were injected directly into the tumors of 14 patients with recurrent breast cancer, and an alternating magnetic field was applied. The results showed significant tumor regression in five patients without any major side effects[148] When exposed to an alternating magnetic field, magnetic NPs generate localized heat inside the tumor, thereby contributing to the selective ablation of cancerous cells and preserving healthy surrounding tissues.[149]

Advancements and Innovations in NP Research

Innovations in Targeted Therapy: Enhancing Specificity, Reducing Side Effects

Recent developments in NP research have ushered in a new age of targeted therapy, typified by the development of precise and relatively safe treatment approaches. For example, NPs have been ingeniously engineered for cancer therapy to target tumor cells while preserving healthy tissues.[150] An excellent example is the design of antibody-conjugated NPs that recognize and bind to the overexpressed surface receptors of cancer cells and deliver therapeutic payloads directly into the tumor site.[151] Targeted approaches improve the efficacy of treatment while reducing off-target effects, thereby notably reducing the chance of adverse reactions.[152]

NP-based drug delivery systems have been designed to cross these physiological barriers, and more importantly, the blood-brain barrier, so that neurological disorders can be treated effectively by reducing the associated toxicity in the systemic circulation. For instance, lipid-based NPs have been engineered to encapsulate therapeutic agents and deliver

them across the blood-brain barrier, making them an attractive strategy for the treatment of conditions such as brain tumors and neurodegenerative diseases.[153] This approach may potentially decrease systemic side effects and enhance therapeutic outcomes.

Moreover, targeted therapeutic strategies have been improved using a new subset of stimuli-responsive NPs. These NPs have been engineered to release therapeutic payloads in response to specific triggers present in the disease microenvironment, such as changes in pH or enzymatic activity.[150] Such precision-controlled drug release mechanisms increase treatment specificity and limit off-target effects, owing to the release of therapeutic agents only at the precise site of action. This tailored method offers enormous potential for reducing systemic toxicity and improving the therapeutic index of all classes of anticancer drugs and other therapeutics[154].

Integrating Nanotechnology with Other Treatment Modalities

The effective integration of nanotechnology with other treatment modalities, such as immunotherapy and gene therapy, is one of the most promising avenues for advanced medical interventions.[155] NPs can function in a versatile and efficient manner as carriers for therapeutic agents, leading to improved delivery at target locations and the minimization of off-target effects in immunotherapy.[151] For example, NPs functionalized to encapsulate immune-stimulating molecules can select immune cells and increase the immune response against diseases. In addition, nanocarriers in gene therapy provide an effective pathway for the delivery of genetic material to targeted cells, modulating gene expression with high precision.[155] Through the NP encapsulation of nucleic acids, cargo degradation is prevented, and their uptake by target cells is coordinated for optimal therapeutic effects. Upon NP encapsulation, gene editing tools like CRISPR-Cas9, enable the precise targeting of gene modifications related to immune function.[156] The application of immune checkpoint gene editing using CRISPR-Cas9 has succeeded in eliminating inhibitory signals which quench the immune response against cancer cells and in increasing the efficacy of immunotherapy.[157] In addition, a nanocarrier system for editing cargo within immune cells, including T cells, has been developed to engineer cargo with enhanced tumor recognition abilities and killing potential.[158] This approach may potentially increase the efficacy of immunotherapy and resistance mechanisms in cancer treatment. The strategic integration of nanotechnology with gene editing and immunotherapy has enabled researchers to develop medical interventions that best exploit the immune system's capabilities to fight diseases.

Breakthroughs in Imaging and Diagnostics Using NPs

Imaging and diagnostic breakthroughs with NPs have opened new avenues for medical diagnostics and testing methodologies, similar to rapid diagnostic tests for conditions such as coronavirus disease (COVID-19).[159] Moreover, the development of NP-based tests for early cancer detection employs NPs functionalized with specific ligands targeting cancer biomarkers, which provide sensitive and rapid detection of cancerous cells or tumor-associated molecules in patient samples.[160] In addition, NPs are increasingly used as contrast agents in various imaging modalities, such as MRI, CT, and fluorescence imaging, which allow for the precise visualization of tumors and metastases.[161] The working principle for NP-based cancer tests is similar to that used in COVID-19 antigen tests, whereby rapid and non-invasive screening can be performed in risk groups of patients for point-of-care diagnostics.[160] Researchers have attempted to determine the unique properties of NPs and combine them with portable detection devices to improve cancer screening and patient outcomes through early detection and intervention.[160]

Challenges and Limitations

Technical Challenges in the Development and Application of NP Therapies

The development and applicability of NP therapies face significant technical challenges, such as ensuring stability and preventing aggregation during storage and transportation. For example, lipid NPs used in mRNA vaccines require careful formulation to avoid aggregation, which can be managed by adding stabilizers such as sugars and employing freeze-drying.[162] Additionally, the complexity of NP synthesis and characterization, such as controlling the size, surface charge, and drug-loading efficiency, further challenges their applicability.[163] These challenges necessitate advanced analytical methods to ensure consistent quality and efficacy throughout the product life cycle.[164]

Biological Barriers: Toxicity, Immune Response, and Biodistribution

Therapies using nanoparticles (NP) face significant challenges that can limit their effectiveness in treatment of BC. One major issue is overcoming biological barriers, such as the ability to penetrate cell membranes, manage immune responses, and achieve predictable distribution throughout the body. For example, chitosan-based NPs, which are highly regarded for their biocompatibility and biodegradability, often struggle to cross biological membranes effectively without causing unwanted immune reactions.[163] Additionally, factors like aggregation, stability, and scalability directly affect the reproducibility and consistency of treatment outcomes, which poses a critical limitation in clinical applications.[164] To address these challenges, innovative strategies are needed, such as surface modifications and polymeric coatings that can improve stability and ensure targeted delivery.[165] Furthermore, the absence of standardized regulatory protocols hinders the widespread clinical adoption of NPs, making it essential to establish clear guidelines for safety and efficacy. Financial barriers also complicate access to these therapies, as high production costs limit their availability in resource-limited settings. Overcoming these limitations through interdisciplinary collaboration and robust regulatory frameworks is vital for optimizing NP design, enhancing therapeutic efficacy, and improving clinical feasibility.[162,165]

Regulatory Challenges: Approval Processes, Standardization, and Quality Control

Regulatory challenges for NP therapies include navigating complex approval processes, achieving standardization, and ensuring rigorous quality control. The need for specific regulatory guidelines for NP-based drugs implies that manufacturers must adapt to established frameworks, which can be time-consuming and uncertain.[162] Furthermore, ensuring consistent quality across batches through standardized production methods and thorough quality control testing is critical but challenging because of the intricate nature of NP formulations.[166] These regulatory hurdles can slow the translation of promising NP therapies from research to clinical use.[163]

Economic Factors: Cost of Development, Accessibility, and Scalability

Economic factors also significantly affect the development and application of NP therapies. The initial investment required for the research, development, and clinical trials of NP-based treatments is substantial, often resulting in high costs for end-users[167] Additionally, the sophisticated manufacturing processes required to produce NPs consistently and at scale pose further economic challenges. Ensuring that these therapies are accessible to a broad population, particularly in low-resource settings, remains a critical concern.[160] Addressing these economic barriers is essential to make NP therapies widely available and sustainable.[163]

Future Directions in NP Therapy for Breast Cancer

Emerging Trends and Future Research Directions

Future research in NP therapy for breast cancer involves the exploration of novel NP formulations and delivery systems to improve drug targeting and efficacy. For instance, researchers are investigating stimuli-responsive NPs which can release therapeutic agents in response to specific cues within the TME, such as pH or enzyme levels.[48] Additionally, there is growing interest in developing multifunctional NPs capable of simultaneous imaging and therapy, as exemplified by the integration of iron oxide NPs with anticancer drugs for MRI-guided therapy.[168]

Potential for New Therapeutic Applications and Combination Therapies

There is immense potential for new therapeutic applications and combination therapies using NP therapy for breast cancer. NPs can serve as versatile platforms for delivering various therapeutic agents, including chemotherapeutic drugs, small interfering RNAs, and immune checkpoint inhibitors, either alone or in combination, to overcome drug resistance and improve treatment outcomes. For example, NP-based combination therapies involving chemotherapeutic drugs and immunotherapeutic agents have shown promising results preclinically, demonstrating enhanced tumor regression and prolonged survival in animal models of breast cancer.[169]

Role of Precision Medicine and Treatments

Precision medicine and patient-specific treatments are becoming increasingly important in NP therapy for breast cancer. Clinicians can optimize treatment efficacy while minimizing adverse effects by tailoring NP formulations to individual patient profiles, such as tumor biomarker expression and genetic mutations. For instance, NP-based therapies can target specific dysregulated molecular pathways in individual tumors, offering a tailored approach to treatment.[65] Furthermore, advances in imaging technologies allow real-time treatment response monitoring, enabling therapy adjustments based on individual patient responses.[65]

Long-Term Outlook: Sustainability and Global Impact

Sustainable synthesis and biodegradable nanoparticle (NP) formulations are crucial for minimizing environmental impacts.[170] These NPs enable targeted drug delivery, reducing required dosages and side effects while enhancing efficacy against tumors.[171] By adopting sustainable NP practices, we can address inequalities and improve health outcomes for all. Innovative NP technologies not only enhance therapeutic effectiveness but also support global sustainability, ensuring that healthcare advancements do not compromise planetary health.[172]

Ethical, Regulatory, and Social Considerations

Ethical Issues in NP Research and Therapy

Ethical considerations in NP research and therapy include informed consent, privacy, and equitable access to treatment. Researchers face dilemmas in ensuring that participants understand the risks and benefits of NP therapies.[173] Transparency in reporting results and managing conflicts of interest are critical. Additionally, their long-term impacts on health and the environment need to be scrutinized to avoid unintended consequences, such as the environmental accumulation of NPs affecting ecosystems.[172]

Overview of Regulatory Frameworks and Their Evolution

Regulatory frameworks for NP-based therapies have evolved with technological advancements and complex medical interventions. Through rigorous testing, agencies such as the FDA and European Medicines Agency ensure the safety and efficacy of these therapies. These frameworks have been adapted to address unique challenges, such as NP characterization and biological interactions, to ensure patient safety.[174] The updated FDA guidelines reflect an understanding of NP behavior in biological systems.[175]

Balancing Innovation with Patient Safety and Ethical Standards

To develop NP-based therapies, it is essential to balance innovation with patient safety and ethical standards. Integrating ethical considerations throughout development is crucial. This includes clear guidelines for ethical research, decision-making transparency, and stakeholder collaboration. Robust safety protocols and ongoing monitoring help mitigate risks, such as unforeseen side effects.[176]

Social Implications and Public Perception of Nanotechnology in Medicine

Media, cultural attitudes, and public awareness campaigns influence the social implications and public perceptions of nanotechnology in medicine. Public concerns regarding safety, privacy, and environmental impact shape perceptions.[177] Addressing these issues requires proactive communication to educate the public about the benefits and risks of nanotechnology, foster informed dialogue, and promote trust in the regulatory processes. Transparency and clear communication are essential to gain public trust.[178]

Conclusion

NP technology has ushered in a new era of precision medicine, particularly in the treatment of breast cancer. Since the discovery of cutting-edge innovations, NPs have considerably enhanced the effectiveness and specificity of cancer therapies, addressing many limitations of traditional methods. This article traces the historical development of NP-

based treatments, elucidates their mechanisms of action, and highlights their current applications and clinical successes. We also explored recent advancements in targeted drug delivery systems and combination therapies, which promise to further revolutionize cancer treatment.

Despite these advancements, technical barriers, biological complexities, and regulatory hurdles must be addressed. Research and innovation continue to address these issues, paving the way for more accessible and effective treatments. The potential for precision medicine, wherein treatments are tailored to individual patient profiles, represents an exciting frontier in NP therapy.

Advances in nanoparticle-based combination therapies and targeted delivery have significantly improved breast cancer treatment by enhancing drug efficacy and minimizing side effects. Despite these advancements, challenges such as scalability, biocompatibility, and regulatory complexities remain. Future efforts should focus on addressing these issues to meet unmet clinical needs and ensure broader accessibility for patients.

Nanoparticles (NPs) have revolutionized the treatment paradigm for resistant breast cancer (BC), addressing critical challenges associated with drug delivery and therapeutic efficacy. By leveraging their small size, surface modifiability, and enhanced permeability and retention (EPR) effect, NPs enable precise targeting and accumulation in tumor tissues. Functionalized and stimuli-responsive NPs offer innovative solutions to bypass drug resistance mechanisms, such as efflux pumps and altered drug targets, while minimizing off-target effects. Through their ability to deliver combination therapies and enhance drug bioavailability, NPs provide a promising approach to overcoming treatment resistance, paving the way for improved outcomes in BC management.

The ethical, regulatory, and social implications of using NPs in medicine are profound and must be carefully managed to ensure patient safety and public trust. The integration of NPs in breast cancer treatment is a testament to the remarkable progress in medical science and its potential to transform healthcare. The journey of NPs from experimental concepts to life-saving therapies underscores their pivotal role in cancer treatment and in the broader field of medicine.

Acknowledgments

The authors are grateful to all the personnel associated with the references who participated in this review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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