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Targeted Nanomedicine in Oncology: Novel Mechanisms of Abraxane in Overcoming Resistance in Breast Cancer

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ABSTRACT

Breast cancer remains a major global health problem, and treatment resistance is a major barrier to successful therapy. Conventional paclitaxel has limitations such as poor solubility, solvent-related toxicity, and drug efflux–mediated resistance. Nanomedicine offers solutions to these problems, and Abraxane is one such clinically proven nano formulation that improves drug delivery and therapeutic outcomes. This review examines how Abraxane helps overcome paclitaxel resistance, summarizes key preclinical and clinical findings, and discusses future directions for nanotechnology-based treatments. A systematic search was conducted using PubMed, Google Scholar, and clinical trial databases to evaluate mechanisms related to nanocarrier function, tumour microenvironment changes, efflux avoidance, and clinical performance. Abraxane shows higher tumour uptake through gp60-mediated transcytosis, SPARC-based stromal binding, and enhanced vascular permeability. These mechanisms help the drug bypass P-glycoprotein efflux, increase intracellular paclitaxel levels, and favourably modify the tumour microenvironment. Clinical studies, including CALGB 40502 and IMpassion130, report better responses, improved progression-free survival, and reduced toxicity compared with solvent-based paclitaxel. Additionally, Abraxane enhances immune activity and improves response to checkpoint inhibitors. Abraxane demonstrates how nanomedicine can overcome drug resistance and improve outcomes in breast cancer. Continued development of multifunctional and biomarker-guided nanocarriers may further support personalized cancer therapy in the future.

Keywords: ***Abraxane, nanomedicine, breast cancer, immunotherapy, nanoparticle drug delivery, tumour microenvironment.***

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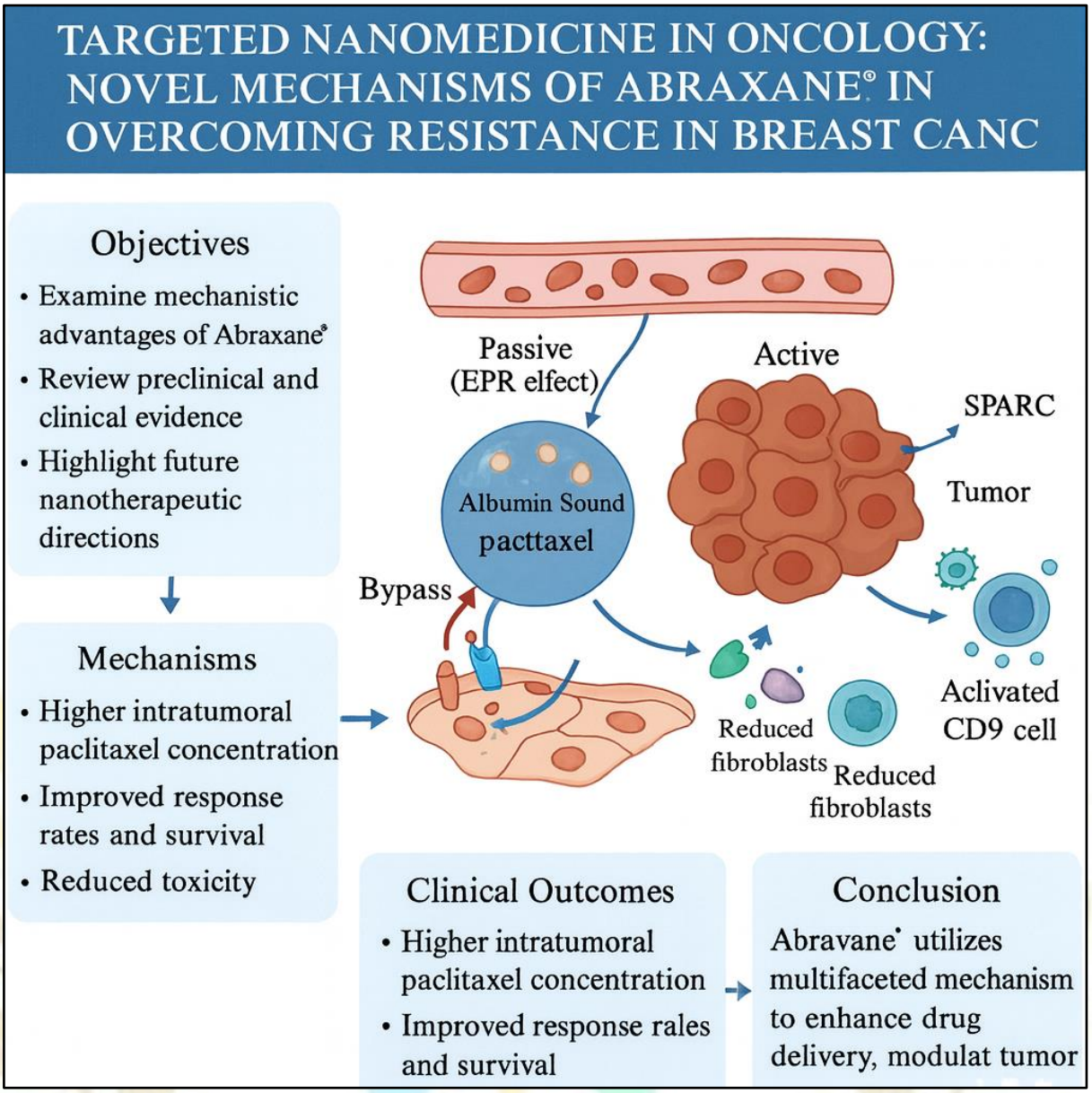
Graphical Abstract: Abraxane uses albumin nanotechnology to bypass resistance and improve breast cancer outcomes.



Introduction

Breast cancer is the most common cancer disease that is diagnosed in women and a major cause of cancer-related deaths across the world. In spite of considerable progress in early diagnosis and multimodality treatment, the recurrence, metastasis, and resistance to chemotherapy makes the disease a major challenge in terms of treatment [1]. Paclitaxel is the first-line chemotherapeutic agent, and it has been applied over time in treatment of other solid tumours, including breast cancer. Older formulations of paclitaxel including Taxol are, however, restricted by low solubility in water, the use of liquid toxic solvents like Cremophor EL and dose-limiting hypersensitivity responses. This is not only a loss to the patient safety but also places a limitation to the optimal delivery of drugs to malignancies that lead to suboptimal therapeutic effects [2]. In order to contain such limitations, nanotechnology has presented a paradigm shift in contemporary oncological practices. Nanomedicine uses nanoscale carriers over the 10200 nm range to encapsulate or conjugate therapeutic molecules in order to deliver them in a controlled and targeted manner. Using the Enhanced permeability and retention (EPR) effect, the nanocarriers will preferentially deliver drugs to tumour tissues instead of the systemic circulation thereby maximizing local drug action and reducing systemic toxicity [3]. In addition to passive targeting nanocarriers can be surface functionalized allowing active targeting via interactions with ligand receptors leading to improved cellular uptake and retention of drugs intracellularly. These innovations have transformed cancer drug delivery in which they have facilitated the safety and effectiveness of the available chemotherapeutics formulations [4].

Abraxane (nab-paclitaxel) is one of the formulations based on nanomedicine that has received approval of the U.S. Food and Drug Administration (FDA). Abraxane is a paclitaxel albumin-binding nanoparticle that

has a mean particle size of about 130 nm. It does not require the use of Cremophor EL unlike the traditional solvent-based formulations, thus dramatically lowering hypersensitivity and allergic reactions. The natural biological transportation and uptake rely on the albumin-based design. Namely, albumin combines with gp60 receptor of endothelial cells, promoting transcytosis across the vascular endothelium into tumour tissue. Also, the formulation has affinity to SPARC (Secreted Protein Acidic and Rich in Cysteine), a protein also commonly overexpressed in tumour stroma, further selective accumulation in the tumour microenvironment is observed [5].

The development of Abraxane is not a mere redefinition of a pharmaceutical, it embodies the clinically relevant definition of nanotechnology to precision oncology. The drug Abraxane has a prolonged systemic circulation, higher tumour penetration and greater bioavailability of paclitaxel as shown by its pharmacokinetic profile. In addition, a high response rate, positive tolerability, and prolonged progression-free survival have always been observed in clinical trials, as opposed to standard regimens in paclitaxel. They are especially of great importance in aggressive or treatment-resistant forms of breast cancer [6]. Even with these developments, there is drug resistance who have proved a strong obstacle towards long-term control of cancer. The persistence of refractory disease is caused by such mechanisms as efflux transporter overexpression, modulation of tubulin binding, metabolic adjustment under hypoxia conditions, and the survival of cancer stem cells. Abraxane, though, has demonstrated positive possibilities in overcoming some of the mechanisms of resistance. Its delivery as nanoparticles avoids efflux via P-glycoprotein and improves intracellular drug retention, in addition to remodelling the tumour microenvironment to ensure improved drug penetration. Also, recent research indicates that Abraxane could have immunomodulatory effects, which facilitate immunogenic cell death and enhance antitumor immune responses [7]. Considering these advantages in multidimensional therapy, it is important to carefully analyse and assess the use of Abraxane as a drug delivery system and resistance-controlling agent in breast cancer. Its associated mechanisms are vital to the understanding of how to maximize the existing treatment protocols and suggest the future generation of nanotherapeutic designs [8].

The present review is intended to give a general account of how targeted nanomedicine has developed in the field of oncology and specifically, on Abraxane as an example system. It discusses the architecture, kinetics and clinical practice of Abraxane, explains its new mechanisms in being able to overcome multidrug resistance, and provides summation of preclinical and clinical outcomes that inform about its efficacy [9]. Lastly, it is then followed by a discussion on the combination strategies, future point of view and the overall implication of nanomedicine in promoting precision cancer treatment. In this analysis, the paper highlights the fact that nanotechnology has still continued to transform the landscape of therapeutics with the hope that more potent and individualized approach to treatment of the resistant breast cancer can be achieved [10].

2. Nanomedicine in Oncology

2.1 Concept and Evolution of Targeted Nanomedicine

Nanomedicine is a meeting point of nanotechnology and pharmacology to improve the diagnostics, treatment, and monitoring of diseases on a nanoscale. To address these shortcomings of the conventional chemotherapy in oncology, nanomedicine provides an effective solution of overcoming the following limitations: poor solubility, unselectively and systemic toxicity of traditional therapeutic drugs, through the use of nanoscale assemblies that facilitate the targeted drug delivery. It was discovered in the 1970s that liposomes would make good drug carriers, then polymeric micelles, dendrimers, and nanoparticle systems, which progressed through the 1990s and early 2000s to form the basis of Nanomedicine [11].

In 1986, Matsumura and Maeda proposed their EPR effect that describes the ability of the nanoparticles to passively target tumour tissues due to the presence of leaky vasculature and impaired lymphatic drainage. This property has the ability to localize additional therapeutic agents into the tumour site as compared to increasing the exposure of the systemic exposure. Along with passive targeting, advanced nanomedicine has increased to active targeting, with nanoparticles made functional by attaching to tumour-associated receptors using ligands, antibodies, or peptides [12]. The clinical translation of this technology has led to a number of nanomedicine formulations being approved by FDA to treat cancer in the last twenty years. There are examples of Doxil (liposomal doxorubicin) in ovarian, DaunoXome (liposomal daunorubicin) in Kaposi sarcoma, Onivyde in pancreatic cancer, and Abraxane in breast, lung, and pancreatic cancers. The formulations represent the appropriateness of nanoscale delivery systems to enhance therapeutic index, off-target toxicity and longer circulation time relative to their traditional counterparts [13].

2.2 Mechanisms of Action of Nanocarrier Systems

Nanocarriers operate in a variety of mechanisms that determine biodistribution, cellular uptake and therapeutic response. Both their mechanisms can be grouped in broad strokes as passive targeting, active targeting and stimulus responsive release systems . Passive targeting is based on the EPR effect in which nanoparticles are used to take advantage of the abnormal tumour vasculature of accumulating in cancer tissues. Examples of carriers based on this principle are liposomes, polymeric nanoparticles and solid lipid nanoparticles. Critical parameters to determine the distribution and clearance of the particle in vivo are its size (usually 50-200 nm), surface charge, and hydrophilicity [14]. There is specificity with active targeting where the ligands which bind to receptors on the over-expressed receptor of the tumour cells attach to the nanoparticle surface. As an example, folate, transferrin and epidermal growth factor (EGF) ligands have been effective in targeting breast and ovarian cancer. The albumin component in Abraxane is endothelial cell-mediated by the gp60 receptor to initiate caveolae-mediated transcytosis and preferential retention in tumour stroma by the SPARC receptor [15].

The other important modulation is the tumour microenvironment modulation. Nanocarriers have the capability to modify the local conditions including pH, oxygenation and enzyme activity that enhance the availability and performance of drugs. An example is pH-sensitive nanoparticles release their drug cargo in the acid tumours and therefore induce more cytotoxicity on tremor cells than healthy tissues. Moreover, combination therapies (chemotherapy, immunotherapy, and imaging) have been achieved through the integration of nanomedicine with stimuli-responsive and multifunctional designs (including magnetic or photothermal nanoparticles) [16].

This Figure 1 Shows the Nanocarrier releases that can be controlled in order to release drugs are also crucial in ensuring that therapeutic concentration is sustained in the tumour. The carrier rate of drug release is determined by the physicochemical characteristics of the carrier such as the composition of the polymer and the coating of the polymer surfaces to maintain long-term exposure and reduce the side effects experienced by the systemic system. Schematic representation of passive and active tumour-targeting nanomedicine. Passive targeting occurs through the EPR effect, enabling nanocarriers to accumulate within tumour tissue. Active targeting involves ligand–receptor interactions, where surface-modified nanomedicines bind specifically to overexpressed tumour receptors to enhance cellular uptake [17].

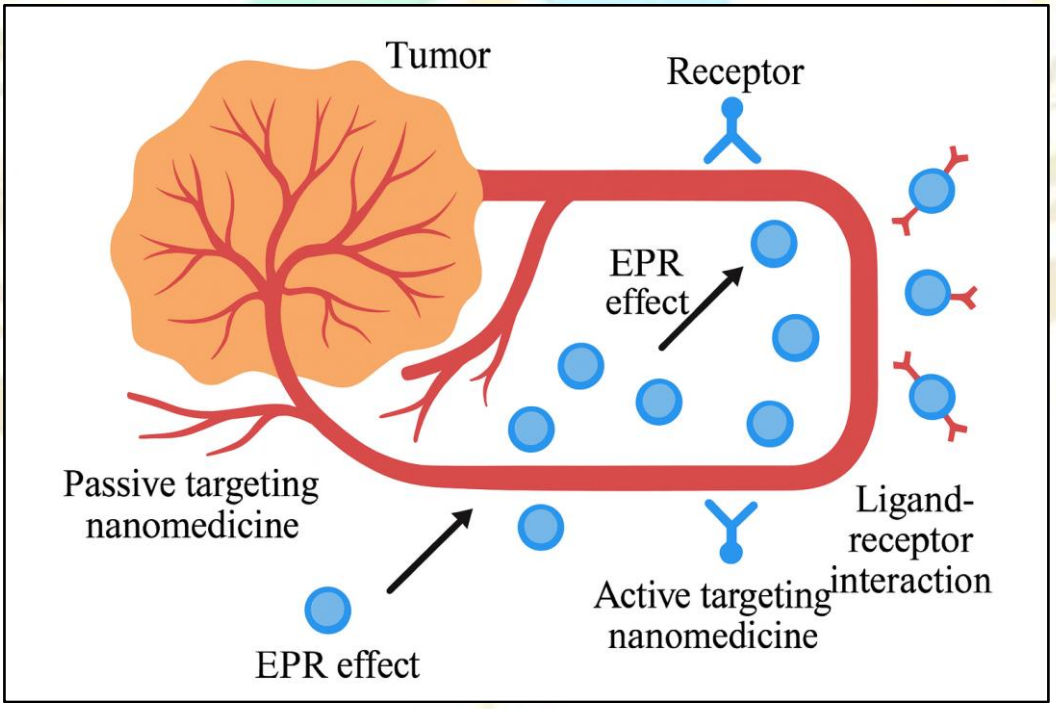


Figure 1: Mechanisms of Passive and Active Tumour Targeting in Nanomedicine

This figure illustrates how nanomedicine utilizes both passive targeting via the EPR effect and active targeting through specific ligand–receptor interactions to improve drug delivery within tumour tissues.

3. Abraxane: A Paradigm in Nanomedicine

3.1 Composition and Physicochemical Characteristics

Abraxane (nab-paclitaxel) is a breakthrough formulation in the field of nanomedicine aimed at surmounting the setbacks of conventional systems of paclitaxel delivery. It is a paclitaxel formulation in the form of albumin-bound nanoparticle with mean particle size of about 130 nanometres that has been developed in order to eliminate toxic solvents like Cremophor EL and ethanol needed in traditional preparations of paclitaxel (Taxol). The solvent-free structure of Abraxane removes hypersensitivity reactions, which means that it could administer safely without premedication using corticosteroids or antihistamines [18]. Both nanoparticles are paclitaxel molecules which are non-covalently conjugated with human serum albumin by hydrophobic interactions. Albumin is a natural plasma protein, which is biocompatible and improves cellular transport, solubility, and stability. Paclitaxel and albumin complex reproduce endogenous albumin transport pathways, where the interaction with gp60 (albondin) on endothelial cells occurs resulting in receptor-mediated transcytosis. This process helps in the delivery of nanoparticles across the vascular endothelium to the tumour interstitium [19]. When into the tumour environment, Abraxane selectively concentrates in areas of high SPARC protein hyperexpression's that have been found in cancers such as breast, pancreatic and other cancers. This Heregulin Affinity and SPARC induce retention of the nanoparticles by the tumour stroma causing a longer indexed cytotoxic effect and a greater concentration of the drug into the cancer cell [19]. Abraxane nanoparticles have a neutral surface charge, small size distribution, and high plasma stability physiochemically. All the mentioned characteristics help to achieve a longer time to circulation, better tumour targeting, and less systemic toxicity in contrast to solvent-based paclitaxel [20].

3.2 Pharmacokinetic and Pharmacodynamic Advantages

The Abraxane pharmacodynamics and pharmacokinetic are significantly improved compared to the normal paclitaxel. Abraxane has a nonlinear pharmacokinetic profile meaning that greater exposure in the systemic and within tumours at high doses with a nonproportional increase in toxicity [21].

Abraxane does not use Cremophor EL micelles to entrap paclitaxel and restrict bioavailability as Taxol does. It has been established that the maximum plasma concentration and area under the curve of paclitaxel are much greater when patients receive the Abraxane thus resulting in increased drug exposure to the locations of the tumour. The half-life of the elimination is extended, as well, and it helps to enhance the therapeutic efficacy [22]. Regarding the pharmacodynamic perspective, the Abraxane preserves the microtubule-stabilizing effect of paclitaxel but is more cytotoxically effective since it is more effective in cellular absorption and retention. Also, it minimizes hypersensitivity, myelosuppression and neurotoxicity usually related to solvent formulations of paclitaxel [23].

The role of defining the formation of endothelial caveolae has been identified as a result of preclinical and clinical studies that show that albumin-mediated delivery results in the basement membrane positioning of drugs in tumour tissue. The processes occur in this active form of transport and would circumvent the constraints of passive diffusion as experienced in the classical formulations. Also, SPARC binding of albumin means that the drug accumulates selectively in malignant tissues and not healthy ones because of the natural biocompatibility of albumin being combined with SPARC binding [24].

The Table 1 Shows A comprehensive comparison between conventional paclitaxel (Taxol) and Abraxane (albumin-bound paclitaxel), highlighting the key differences in their formulation, delivery mechanisms, pharmacokinetics, toxicity profile, and clinical benefits. Conventional paclitaxel relies on Cremophor EL as a solvent, which contributes to hypersensitivity reactions, limited tumour penetration, and the need for premedication [25]. Abraxane is a solvent-free, albumin-bound nanocarrier system that enhances drug solubility, enables active tumour targeting through gp60 and SPARC pathways, increases intratumoral drug concentration, and reduces toxicity. The table also summarizes their comparative impact on clinical outcomes, with Abraxane demonstrating improved objective response rates, better progression-free survival, and superior tolerability, especially in resistant tumours [26].

Table 1: Comparative Overview of Conventional Paclitaxel (Taxol) and Abraxane (Nab-Paclitaxel) in Formulation, Pharmacology, Safety, and Clinical Performanc

S.no.	Parameter	Conventional Paclitaxel (Taxol)	Abraxane (Nab-paclitaxel)	References
1.	Formulation	Paclitaxel dissolved in Cremophor EL + ethanol	Albumin-bound paclitaxel nanoparticles (~130 nm)	[27]
2.	Solubility	Poor solubility; requires toxic solvent	Excellent solubility; solvent-free formulation	[28]

3.	Delivery Mechanism	Passive diffusion; limited tumour penetration	Active transport via gp60-mediated transcytosis + SPARC-mediated accumulation	[29]
4.	Pharmacokinetics	Linear PK; lower intratumorally concentration	Nonlinear PK; 30–40% higher tumour concentration	[30]
5.	Plasma Protein Binding	High but not optimizable	Albumin-bound → enhanced stability & extended circulation	[31]
6.	Dosing Requirements	Requires steroid + antihistamine premedication	No premedication needed due to absence of Cremophor EL	[32]
7.	Hypersensitivity Reactions	High (due to Cremophor EL)	Minimal	[33]
8.	Myelosuppression	More pronounced neutropenia	Reduced myelosuppression (dose-dependent)	[34]
9.	Neurotoxicity	Higher incidence	Lower incidence at equivalent effective dose	[35]
10.	Clinical Advantages	Established therapy; lower cost	Higher ORR, better PFS, improved tolerability, effective in resistant tumours	[36]

4. Mechanisms of Drug Resistance in Breast Cancer

4.1 Common Resistance Mechanisms

The issue of resistance to drugs is one of the most critical problems in the management of breast cancer despite the significant advances in systemic therapies. The mechanisms of intrinsic and acquired resistance decrease the effectiveness of the chemotherapeutic agents, which result in failure of treatment, recurrence, and metastasis. The above-mentioned mechanisms can be categorized into cellular transport changes, molecular target changes, and tumour microenvironmental changes [37]. One of the primary causes of MDR belongs to the overexpression of efflux transporters (mainly P-glycoprotein (P-gap; encoded by ABCB1), multidrug resistance-associated protein 1 (MRP1; ABCC1), and breast cancer resistance protein (BCRP; ABCG2). These anticancer drugs are actively pumped out of cells by these ATP-binding cassettes (ABC) transporters and, hence, their intracellular concentrations become lower than therapeutic. Paclitaxel is a substrate of P-gap and is very frequently used to treat breast cancer, and is known to cause rapid glycosylphosphatidylinositol (P-gap)-mediated efflux and decreased cytotoxicity of resistant tumours [38].

The other significant action is the change of molecular target of the drug. Paclitaxel binds to 2 -tubulin in order to stabilize tubules and prevent cell division. The β-tubulin gene mutations or post-translation modifications cause changes in microtubules dynamics, reduce affinity with paclitaxel, and generate resistance. Also, the presence of triplet 2III-tubulin has been associated with taxane resistance and poor clinical prognosis of triple-negative and metastatic breast cancer [39]. The factors of microenvironment of the tumour also become central in the regulation of resistance. Hypoxic tumour milieu stimulates hypoxia-inducible factors (HIF- 1 alpha and HIF-2 alpha) that enhanced angiogenesis, glycolytic metabolism and surviving-related genes. These transformations decrease drug perfusion and facilitate a listless phenotype less reacting to body therapy forces. Additionally, the thick and connective tissue (ECM) surrounding the cells and elevated pressure of the interstitial fluids also pose physical challenges which hinder drug absorption further reducing treatment effects [40].

There is an increase in the repair ability of DNA and anti-apoptotic signalling, which also leads to chemotherapy resistance. Repair enzymes stimulated in response to tumour cells include PARP and BRCA1/2 and ERCC1 which stimulate efficient repair of DNA damage caused by drugs. At the same time, the stimulation of pro-survival signals such as PI3K/Akt/mTOR, NF- B, and Bcl-2 family-proteins facilitate the resistance to apoptosis allowing the cells to survive during the chemotherapeutic stressor [41].

4.2 Role of Tumour Heterogeneity and Cancer Stem Cells

Tumour heterogeneity affecting both intertumoral and intratumorally (within an individual tumour mass) is a core cause of treatment resistance. Breast cancer is a set of several molecular subtypes, all of which have different genetic, epigenetic, and metabolic profiles (luminal A/B, HER2-enriched, triple-negative). In one

tumour, different populations of cells have co-existed with varying rates of proliferation, expression of receptors and drug sensitivity [42].

Cancer stem cells (CSCs) are one of these subpopulations that have proven to be the key factors of recurrence and multidrug resistance. CSCs have a minute group of tumour cells that possess self-renewal, differentiation, and tumorigenic capabilities. CD44+/CD24-/low and ALDH1+ CSCs phenotypes in breast cancer are quiescent and possess high DNA repair ability. These properties allow them to avoid cytotoxicity of chemotherapy which is mostly restricted to fast-dividing cells. Besides, CSCs have high-level of the efflux transporters like P-gap and BCRP, which fortifies their resistance profile. The effect of cSCs on the tumour microenvironment is also dynamic as it maintains resistance [43]. They release cytokines and growth factors that stimulate angiogenesis, EMT (epithelial-mesenchymal transition) and immune evasion: IL-6, TGF- 2, VEGF among others. EMT itself increases invasion and drug tolerance by down regulating the epithelial markers (E-cadherin) and up regulating mesenchymal markers (vimentin, N-cadherin). This phenotypic plasticity enables the cancer cells to be resistant to chemotherapeutic stress and to restore once more the heterogeneous populations despite seemingly shrink studies [44].

Targeting of CSCs is still a challenging issue. Traditional agents do not eliminate the CSC populations, whereas selective inhibitors (PI3K or Notch pathway blockers) have poor clinical activity because of adaptive feedback loops. Newer methods of drug delivery such as nanoparticle-based drug carriers are currently being explored and work with cytotoxic agents or siRNA in particular types of niches of CSCs allowing avoidance of resistance systems that are founded on tumour hierarchies and heterogeneity [45].

5. Novel Mechanisms of Abraxane in Overcoming Drug Resistance

To overcome multidrug resistance reversal (MDR) in breast cancer, it is necessary to develop strategies to avoid efflux pumps, improve tissue invasion, and also to control the tumour microenvironment. Abraxane (paclitaxel albumin bound) has been shown to be able to circumvent these shortfalls in both pharmacological and biological ways. Abraxane, unlike solvent-based paclitaxel, makes use of the natural pathways used in the body to carry paclitaxel to the resistant areas of the body, escalating intracellular retention, and enhancing treatment efficacy [46].

5.1 Bypassing P-glycoprotein–Mediated Efflux

The ATP-binding cassette transporters, especially the P-glycoprotein (P-gap), act as one of the uniform resistance mechanisms against the use of drug therapy by actively egesting drugs out of the cancer cells and minimizing intracellular drug levels. As a known P-gap substrate, conventional paclitaxel is easily effluxes resulting in the attainment of cytotoxicity and subtherapeutic cytoplasmic concentrations [47].

Abraxane also overcomes this constraint by using a receptor-mediated endocytosis pathway. Abraxane is an albumin that is conjugated with the endothelial gp60 receptor (albondin), and this leads to transcytosis through caveolae across the endothelial cell barrier. This is done without using conventional diffusion pathway that is prone to efflux activity. On internalization, albumin-bound paclitaxel bypasses lysosomal degradation and directly releases the drug into the cytoplasm to ensure high levels of intracellular paclitaxel levels are maintained. Abraxane is observed to induce 3-5 times more accumulation of paclitaxel within the cell lines of tumours that have been over-expressed with the P-gap than the solvent-based paclitaxel [48]. In addition to avoiding the efflux, albumin may also indirectly inhibit the P-gap activity. It regulates the level of oxidative stress and intracellular ATP which play an essential role in the working of P-gap and, hence, decreases its efficacy in pumping drugs. A combination of these mechanisms makes Abraxane a better formulation that can circumvent the transporter-mediated resistance on the cellular level [49].

5.2 Enhanced Tumour Penetration and Accumulation

Passive tumour targeting is based on the EPR effect of most nanomedicines, with Abraxane being no exception. Nonetheless, active tumour targeting (SPARC-binding and gp60-binding) is also adopted by Abraxane which led to increased tumour accumulation [50]. The overexpression of SPARC in the stroma of breast and pancreatic tumours is common and contributes to the extracellular matrix remodelling and angiogenesis. This suggestive specificity facilitates the consumption of Abraxane nanoparticles by the high affinity between albumin and SPARC in the SPARC tumours enriched tissues. It leads to greater concentration of paclitaxel at the local level, prolonged exposure and decrease in off-target toxicity [51]. As of preclinical experiments, Abraxane was shown to raise concentrations of intratumor paclitaxel up to 33 times high than Taxol resulting in better tumour regression in resistant xenograft models. In addition, it has a small particle size (decahedrism size of about 130 nm), which allows penetration to a deeper point in

tumours through the leaky vasculature and interstitial space to traumatise the binding-site barrier that limits large-molecule therapies [52].

5.3 Modulation of the Tumour Microenvironment

The tumour microenvironment TME is a complicated system of stromal cells, fibroblasts, immune infiltrates and extracellular matrix organelles that aid in drug resistance. Breast cancer has a thick stroma that surrounds the cancers and raises the pressure of interstitial fluid restricting drug diffusion and perfusion [53]. It has been demonstrated that Abraxane regulates the TME by signalling and physically remodelling tumour stroma via albumin. Due to the interaction between albumin and gp60 receptor, endothelial caveolin-1 is phosphorylated, and the vascular permeability is increased, and IGP is lowered. This increases the delivery of therapeutic agents not only of Abraxane itself but also of the drug that is going to be co-administered [54]. In addition, Abraxane has also shown stromal depletion activity in desmoplastic tumours. Preclinical research in pancreatic and breast cancer models showed that wording in Abraxane leads to the reduction of fibroblast activation protein positive stromal fibroblasts and collagen density that allow diffusion of drugs easier. These are corroborated by clinical imaging evidence of improved perfusion and oxygenator of the tumour tissues after the Abraxane therapy [55].

The other important mechanism is that of synergistic antiangiogenic activity. Abraxane suppresses vascular endothelial growth factor indirectly without triggering that process and promoting vascular normalization which indirectly benefits the better of perfusion and drug delivery. In association with antiangiogenic DNA bevacizumab, Abraxane enhances therapeutic activity by maximizing vascular one-dimension and decreased hypoxic niches [56].

5.4 Immunomodulatory Effects of Abraxane

There have been some emerging indications that immunogenic modulation brought about by chemotherapy is a driver of overall therapeutic success of nanomedicines. It has been described that Abraxane augments the antitumor immunity in a number of complementary processes [57].

To begin with, research on Abraxane causes immunogenic cell death, which enhances the release of damage-associated molecular patterns including the exposure of calreticulin, ATP, and HMGB1 on dying tumour cells. Such signals attract the dendritic cells and stimulate the process of antigen presentation to T cells, thus triggering the development of adaptive immunity [58]. Secondly, albumin is also a natural immune modulator on its own. Albumin-bound drugs that are taken up by the antigen-presenting cells can further stimulate cross-presentation of tumour antigens which causes increased activation of cytotoxic T lymphocytes (CD8-3). A review of the literature in mouse models of breast cancer showed that Abraxane therapy led to a significant increase in the ratio of $CD8^{-}$ Tregs/Tregs in the tumour microenvironment, which is positively correlated with survival [58]. Abraxane is synergistic with anti-PD-1 and anti-CTLA-4 antibodies (immune checkpoint inhibitors). It has been demonstrated, on clinical, that the objective response rates are greater in metastatic triple-negative breast cancer (mTNBC) with combination regimens than monotherapy. This increased immunogenicity can probably be attributed to the fact that, through the effect of Abraxane, immunologically cold tumours are transformed into immunologically hot tumours that have a massive influx of T-cells and release cytokines [59].

In passive targeting, nanoparticles accumulate within the tumour microenvironment through the EPR effect, which arises from leaky tumour vasculature and poor lymphatic drainage. This allows nanosized particles to preferentially enter and remain within tumour tissue without the need for surface modifications [60].

This Figure 2 is Show about Active targeting involves functionalizing nanoparticles with specific ligands that recognize and bind to overexpressed receptors on the tumour cell surface. This ligand–receptor interaction promotes selective uptake of the nanocarrier, improving intracellular drug delivery and therapeutic efficiency. Together, these mechanisms form the basis of advanced targeted nanomedicine strategies aimed at enhancing cancer treatment specificity while minimizing systemic toxicity [61].

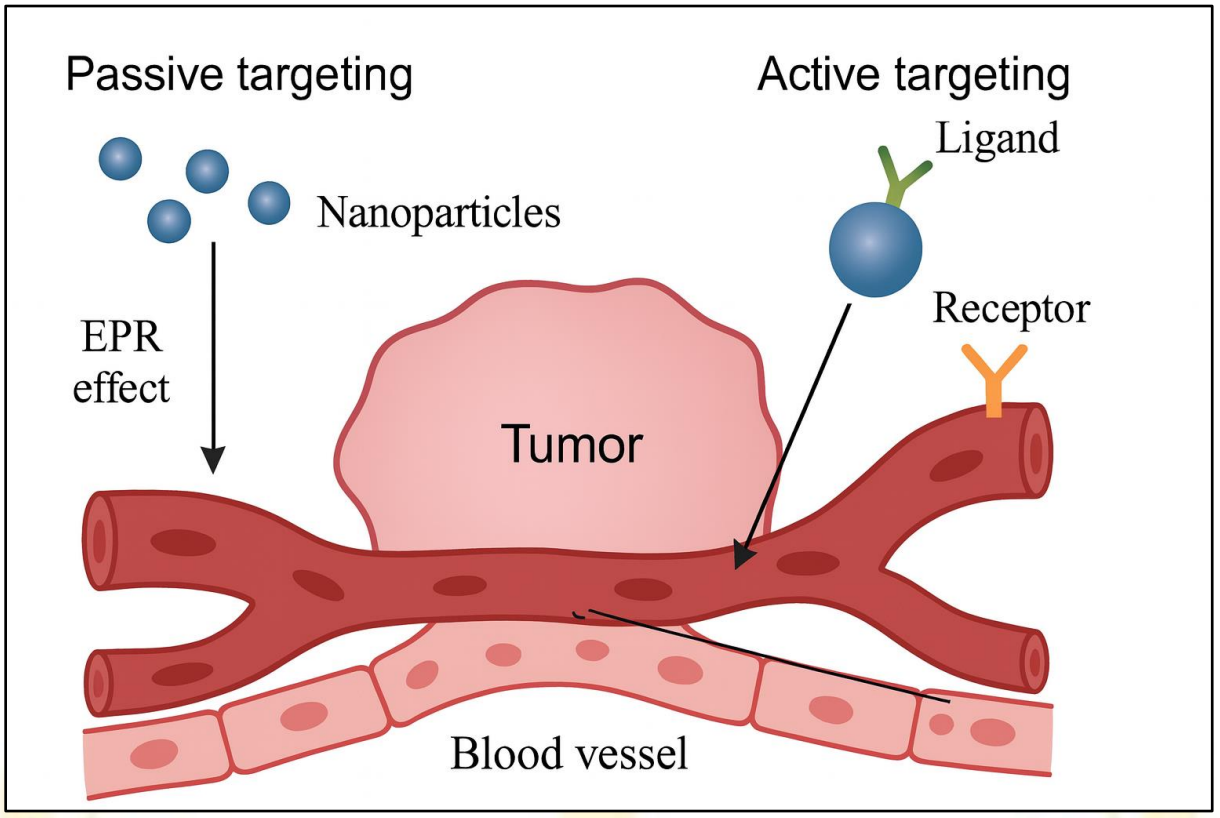


Figure 2: Comparison of Passive and Active Targeting Mechanisms in Tumour-Directed Nanomedicine This figure demonstrates how nanomedicine exploits passive targeting through the EPR effect, allowing nanoparticles to accumulate within tumour tissue, while active targeting utilizes specific ligand–receptor interactions to improve selective uptake by tumour cells.

6. Preclinical and Clinical Evidence

6.1 Key Preclinical Findings

Preclinical trials have been crucial in determining the therapeutic advantages of Abraxane (albumin bound paclitaxel) as compared to traditional solvent-based paclitaxel formulation. These studies have explained its improved pharmacokinetics, cancer penetration, and MDR in several in vitro and in vivo cancer models [62].

In the pioneer pharmacological research, Abraxane was shown to be markedly better accumulated in the tumour than paclitaxel solvates. The enhancement of this delivery was explained by the mediation of endothelial transcytosis with gp60 and retention in tumour stroma with SPARC two typical mediation mechanisms not attained with normal formulations.

Abraxane was able to circumvent efflux-based resistance in P-glycoprotein-overexpressing (MDR) breast cancer cell lines, in which the drug gained access to cells by receptor-mediated endocytosis, instead of passive diffusion. As a result, the intracellular retention of paclitaxel and stabilization of microtubules were significantly increased, which increased apoptotic indices [26]. Abraxane remodels tumour microenvironment by decreasing collagen intensity and fibroblast stimulation. The application of the Abraxane In orthotopic models of breast tumours, Abraxane treatment also resulted in the reduction of stromal stiffness and improved the vascular perfusion, thereby improving the efficacy of later chemotherapy or immunotherapy [63]. Abraxane was found to have a strong synergistic effect with platinum-based agents, antiangiogenic and immune checkpoint inhibitors in combination therapy studies. The preclinical use of anti-PD-1 antibodies combined with Abraxane resulted in enhanced infiltration and surveillance of the tumour by CD8+T-cell and inhibition of regulatory T cells, which confirmed the immunomodulatory effect of Abraxane in the tumour [64].

6.2 Clinical Trials and Outcomes in Breast Cancer

Abraxane has been proven in clinical trials to execute drug resistance successfully through numerous pivotal trials. It has been given the green light with metastatic breast cancer, non-small cell lung cancer and metastatic pancreatic cancer with current research on its uses in early-stage and combinations [65].

CALGB 40502 Trial (Phase III)

The researchers used the trial, Cancer and Leukaemia Group B (CALGB 40502), which involved a comparison of next-arranged metastatic breast cancer between Solvent-based paclitaxel, dumping weekly Abraxane, and still Anaxibepilone. The researchers found that Abraxane had a progression-free survival (PFS) of 7.4 months than paclitaxel standard, which had a 6.5 months duration [66]. The Abraxane recorded better overall response rate of 49 and poorer incidence of hypersensitivity reaction since the drug was solvent-free in design. These results confirmed the safety and effectiveness profile of Abraxane as a second-line treatment of phenomena-resistant breast cancers [67].

MPACT Trial (Phase III)

In metastatic pancreatic cancer Metastatic Pancreatic Adenocarcinoma Clinical Trial compared the use of Abraxane and gemcitabine to gemcitabine only. Although it is not breast cancer specific, the study presents good evidence of the reversal potency of Abraxane in solid tumours. Combination therapy increased median overall survival by 6.7 to 8.5 months and doubled the one-year survival rate (35% vs. 22kg). This increased effectiveness was explained by the possibility of Abraxane to drain stromal obstacles and, therefore, greater access to tumour tissues by gemcitabine [68].

CREAM Study and TNBC Trial

Triple-negative breast cancer is a very aggressive type of disease that is resistant to several types of chemotherapy. The CREAM trial reported patients with advanced TNBC receiving Abraxane reported a mean PFS of 8.1 months and ORR of 48% which is improved compared to solvent-based paclitaxel regimens. Follow-up randomized trials involving the combination of Abraxane and immunotherapy (especially atezolizumab (anti-PD-L1)) in IMpassion130 and KEYNOTE-355 trials brought significant improvements in terms of survival. The IMpassion130 study showed that it had a median PFS of 7.5 months (compared to 5.0 months) with an overall survival of 25 months (compared to 15.5 months) in PD-L1 - positive TNBC patients [69].

Safety and Tolerability

Abraxane has maintained a better safety profile than the traditional paclitaxel. Removal of Cremophor EL minimizes the hypersensitivity reactions, hepatic toxicity and peripheral neuropathy. According to dose escalation studies, it was found that patients could safely take up to 300 mg/m 2 of Abraxane without any premedication needed to take Taxol. Also, pharmacokinetic studies verified the presence of linear systemic clearance and increased tumour bioavailability, which provided support to its use with increased dose intensities with tolerable toxicity [70].

Comparative Efficacy

Randomised trials have been pooled together to provide strong evidence in support of Abraxane. In excess of one thousand and five hundred and sixty patients, Abraxane has been found to have better overall response rates (44-52 rate), time to progression and lower grade 3/4 toxicity than the solvent-based paclitaxel. Its combination possibility with both platinum agents and PARP inhibitors and immunotherapies make it a central component of the contemporary breast cancer treatment plans [71].

6.3 Clinical Relevance and Translational Significance

The collective clinical and preclinical data emphasis Abraxane as a prototype nanomedicine that incorporates the areas of molecular innovation and therapeutic effect. Through albumin-mediated delivery, Abraxane is demonstrating higher tumour selectivity, immune-activation and stromal-remodelling-functionalities which far exceed traditional chemotherapy [72].

It has a strong translational potential in the fact that it can be integrated easily into multimodal regimens such as immunotherapy, targeted therapy and gene-silencing platforms (i.e., siRNA-loaded albumin nanoparticles).

Existing studies are investigating Abraxane-based combinations with PD-L1 inhibitors or microRNA influencers to go a step further to overcome resistance [73].

Abraxane is a good example of how biologically inspired nanocarriers can enhance the pharmacological diffusion barriers, minimise systemic toxicity rates, and enhance the quality of life of patients. Preliminary findings in this direction are one of the critical milestones in personalized nanotherapeutic approaches to cancer [74].

7. Combination Therapies and Future Perspectives

The adaptive and complicated nature of breast cancer requires more than single-agent chemotherapy. Although Abraxane (albumin-bound paclitaxel) has shown impressive activity as a single-agent, its real clinical promise has been as a combination regimen that has the capacity of attacking various hallmarks of tumour progression- angiogenesis, immune evasion as well as DNA repair. Oncology The use of nanotechnology on precision oncology has been supplied with current research and clinical trials that highlight the advantages of Abraxane as an ideal platform on which to employ synergistic multimodal therapies [75].

7.1 Integration with Immunotherapy

Immuno-oncology has reinvented cancer treatment models. Nevertheless, a significant proportion of tumours and even triple-negative breast cancer tumours have been found to be cold immunologically as they possess low T-cell penetration and lack responsiveness to checkpoint blockade. Abraxane has demonstrated the capability to induce immunogenic cell death and tumour vasculature modification to convert immunologically cold tumours to hot [76]. In the historical IMpassion130 study, Abraxane + atezolizumab (anti-PD-L1) showed a notable survival advantage in patients with PD-L1-positive TNBC and the patients placed on chemotherapy alone a 15.5 months median overall survival period as compared to 25.0 months. This synergistic effect is due to two effects of Abraxane; optimizing the release of antigens and intensifying immune-cell entry through vascular normalization of tumours [77]. Subsequent studies like KEYNOTE-355 upheld the advantage of combining Abraxane and pembrolizumab (anti-PD-1), and led to a better progression-free survival (9.7 months vs. 5.6 months) in PD-L1 expressive TNBC. The results firmly establish Abraxane as a kind of immune-priming nanomedicine, which can be used to complement checkpoint blockade therapy [78].

7.2 Synergy with Targeted and Cytotoxic Agents

The solvent free and biocompatible character of Abraxane helps it to be co-purified with various cytotoxic and molecularly targeted agents. Addition to platinum-based drugs including carboplatin increases DNA crosslinking of resistant tumour in the breast and reduces overlapping toxicity. GeparSepto trial demonstrated a superiority in pathologic complete response (pCR) rates using Abraxane + carboplatin over paclitaxel + carboplatin in neoadjuvant TNBC, and this is attributed to a better chemo sensitization [79]. Combination with antiangiogenic therapy like bevacizumab is also promising to be useful. The remodelling processes of the tumour stroma and the decrease in interstitial pressure of Abraxane increase the penetration rates of bevacizumab resulting in improved oxygenation and a decrease in resistance caused by hypoxia [80]. Such combinations of Abraxane PARP-inhibitors (i.e. with Olaparib or talazoparib) are also under investigation in BRCA1/2-mutated and homologous recombination-deficient breast cancers. The mechanism by which this dual approach combats microtubule stability and DNA repair pathways generates some cumulative cytotoxic action and ensures toleration [81].

7.3 Emerging Nanocarrier and Gene-Silencing Strategies

Based on the success of Abraxane, scientists are working on the next generation albumin-based nanocarriers to deliver various agents at the targeted location, such as siRNA, miRNA and immunomodulators. As an example, the Abraxane nanoparticles loaded with siRNA have been engineered to silence either P-gap or anti-apoptotic gene inducing increased sensitivity to paclitaxel of tumours resistant to different drugs [82]. Theragnostic nanoparticles with dual functions that both include imaging probes and drugs will offer real-time drug biodistribution and response monitoring. These types of systems are useful in terms of accuracy in dosing and preventing the appearance of resistance early. Paclitaxel-immunostimulatory CpG oligonucleotides co-loaded into hybrid albumin nanoparticles have been shown to activate T-cells better and eliminate tumours in TNBC preclinical models [83]. Additional improvements in biomimetic nanomedicine such as exosome-inspired or cell membrane-coated nanoparticles also have further potential of immune evasion and tumour homing. These carriers can more effectively imitate endogenous biological membranes, which makes them circulate longer and have a low off-target clearance, the way of the future of Abraxane-derived nanotherapeutics [84].

7.4 Predictive Biomarkers and Personalized Therapy

One of the future directions will be to determine the biomarkers that are predictive of Abraxane response. High levels of SPARC expression as in the case of high tumour levels of albumin-bound drugs or better clinical outcome is associated with high tumour levels of albumin-bound drugs and improved clinical

outcome. Other biomarkers that could be of interest are gp60 receptor, and tumour stromal density and immune gene signatures that are used to evaluate whether the immune therapy response to Abraxane combinations is possible [85]. A combination of multi-omics profiling and AI-controlled data analytics can be used to further categorize those that are most likely to respond positively to particular nanomedicine combinations to coordinate the highest effectiveness in the most minimal toxicity. Individual tumour and gene-based nanotherapeutics would be supreme in the development of the targeted oncology [86].

8. Challenges and Limitations

Although nanomedicine and Abraxane have made impressive breakthroughs in the medical world, as well as clinical breakthrough, there are still various scientific, economic as well as translational problems that are limiting its uptake. These barriers should be tackled to ensure that the promise of targeted nano therapy in the context of oncology is fulfilled [87].

8.1 Economic and Accessibility Constraints

Nanomedicines are costly to make especially due to their high cost. The involved formation of Abraxane is a complex procedure, consisting of high-purity human serum albumin, nanoparticle stabilization, and sterile filtration, which makes the product highly expensive, relative to generic paclitaxel. Therefore, the availability of the drug Abraxane is frequently limited in low-income countries as well as middle-income economies where the share of this cancer is increasing at the fastest pace. According to the cost-effectiveness analyses, Abraxane is comparatively safer and more effective but its incremental cost per life-year improved is higher than the normal chemotherapy in a large number of healthcare systems. Creating biosimilar or generic nanoparticle preparations and enhancing the manufacturing of such at a large scale would mitigate price and offer greater access to the products worldwide [88].

8.2 Resistance Emergence and Biological Complexity

Even as Abraxane has been able to evade multiple resistance mechanisms, secondary or adaptive resistance can be acquired due to changes in receptor expression, stromal remodelling, or immune evasion mechanisms. This can result in continual exposure leading to SPARC down-regulation or alteration of gp60-mediated transport to limit tumour selectivity with time. In addition, differences in tumour vasculature, ECM density, and immune cell infiltration motivate tumour heterogeneity to drug accumulation, which generates irregular processes in patients. It can only be overcome by active personalization of medication depending on biomarkers, imaging responses and adaptive dosing maps [89].

8.3 Safety, Pharmacokinetics, and Long-Term Evaluation

Although Abraxane does not cause the toxicity associated with solvents, neurotoxicity and myelosuppression are also possible during its use, especially when used as a combination therapy at a higher dose or alone. There is also ongoing investigation on the long-term biodistribution, metabolism and clearance of the nanoparticles-bound drugs. The presence in non-target organs like the liver and spleen would result in subclinical toxicity, and that is why pharmacovigilance and nanotoxicology models have to be extensive [90].

8.4 Regulatory and Translational Barriers

Some nanomedicines such as Abraxane are not necessarily subject to established regulatory pathways due to the complex structure function relationships. Existing approval systems, built mostly to consider small molecules, are not completely prepared to consider such parameters as nanoparticle size, surface charge and stability which play a key role in pharmacodynamics. Having standard characterization procedures and predictive preclinical models is also a priority among international bodies like the FDA and the EMA [91].

9. Conclusion

Abraxane represents a significant advancement in the field of targeted nanomedicine for the treatment of breast cancer, particularly in overcoming multidrug resistance. Through its albumin-bound nanoparticle design, Abraxane enhances tumour-specific drug delivery via gp60-mediated transcytosis and SPARC-based accumulation while bypassing P-glycoprotein–mediated efflux. In addition to improving intracellular paclitaxel retention and tumour penetration, Abraxane favorably remodels the tumour microenvironment and exhibits strong immunomodulatory effects that enhance the efficacy of immunotherapy. Extensive preclinical and clinical evidence demonstrates its superior therapeutic index, improved progression-free survival, and reduced toxicity compared to conventional paclitaxel. Despite challenges related to cost,

resistance evolution, and regulatory complexity, Abraxane stands as a powerful example of how nanomedicine can transform cancer therapy. Future integration with biomarker-driven personalization, gene-silencing approaches, and combination immunotherapies is expected to further refine its clinical impact and strengthen precision oncology strategies.

In summary, this review highlights Abraxane as a clinically successful nanomedicine that effectively overcomes paclitaxel resistance in breast cancer. Its albumin-based nanoparticle design enhances tumour uptake, bypasses efflux mechanisms, and remodels the tumour microenvironment. Abraxane also exhibits strong immunomodulatory properties, improving responses to immune checkpoint inhibitors. Preclinical and clinical trials confirm its superior efficacy and safety compared to conventional paclitaxel. Overall, Abraxane exemplifies the future potential of nanotechnology in personalized cancer therapy.

Abbreviations

AUC – Area Under the Curve
BC – Breast Cancer
CSC – Cancer Stem Cell
CTL – Cytotoxic T Lymphocyte
ECM – Extracellular Matrix
EPR – Enhanced Permeability and Retention
gp60 – Glycoprotein 60 (albondin receptor)
HMGB1 – High-Mobility Group Box 1
HSA – Human Serum Albumin
ICD – Immunogenic Cell Death
IFP – Interstitial Fluid Pressure
IL-6 – Interleukin-6
MBC – Metastatic Breast Cancer
MDR – Multidrug Resistance
NK – Natural Killer (cell)
ORR – Overall Response Rate
OS – Overall Survival
PARP – Poly (ADP-Ribose) Polymerase
PBMC – Peripheral Blood Mononuclear Cells
PFS – Progression-Free Survival
PK – Pharmacokinetics

Author Contribution

F.A. Data Analysis and interpretation, P.C Data collection and Conceptualization, A.S. Visualization, M.T Writing the paper, S.A Study concept or design Z.A. Visualization.

Conflict of Interest

The authors declare no conflict of interest.

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