REVIEW PAPER

Targeted Nanocarrier-Based Drug Delivery in Breast, Lung, and Pancreatic Cancers: A Systematic Review of Clinical and Translational Studies (2018–2025).

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ABSTRACT

Objectives: To evaluate the clinical and translational landscape of targeted nanocarriers in breast, lung, and pancreatic cancers (2018–2025), focusing on improving pharmacokinetics (PK) and addressing physiological barriers.

Materials and Methods: We conducted this systematic review by following PRISMA 2020 guidelines.

We limited our search to human clinical trials (Phase 1–3) and high-impact translational data published between January 2018 and December 2025.

Results: Significant variation in pharmacological success was dependent on type of malignancy. We saw-

1.High success rate in breast cancer with median progression-free survival of 9.7 months for Sacituzumab govitecan in metastatic triple-negative breast cancer due to highly leaky vasculature and a strong Enhanced Permeability and Retention (EPR) effect.

2. Moderate success for lung cancer which requires inhalable nanocarriers with aerodynamic diameters of 1-5 micrometres to enter heterogeneous vasculature.

3. "Low success" for pancreatic cancer as it remains a challenge due to the dense desmoplastic stroma. But the 2024 FDA approval of NALIRIFOX was a major breakthrough due to the stroma-penetrating effect of this combination delivery. [8-10, 14]

But we identified an "EPR Paradox" where approximately only 0.7% of administered doses reached the tumour in humans despite preclinical success.

Conclusion: Targeted nanomedicine is now moving towards "active", stimuli-responsive drug delivery and thus bridging the gap from research to practical application by using AI-driven design and by customising treatment plan. [10, 11, 16-18]

Keywords: Nanocarriers, Pharmacokinetics, EPR Effect, Breast Cancer, Pancreatic Ductal Adenocarcinoma, NALIRIFOX.

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INTRODUCTION

The therapeutic management of breast, lung, and pancreatic cancers has reached a critical juncture where conventional systemic chemotherapy often fails to balance efficacy with systemic safety. Despite decades of refinement, standard cytotoxic agents remain hindered by narrow therapeutic windows, poor aqueous solubility, and the rapid development of multidrug resistance [1, 2]. The development of targeted nanocarriers between 2018 and 2025 has marked a significant shift in pharmacological strategies, steering oncological treatment toward a site-specific drug delivery approach. This strategy takes advantage of the distinct pathophysiological features of the tumor microenvironment (TME) to improve therapeutic precision and efficacy.

The clinical success of these nanotherapies depends not only on the chemical design of the nanomedicines but also on the

intrinsic pharmacological properties of the **active drug**—such as ionization state and molecular weight—as well as host-specific biological factors..

Recent evidence suggests that patient demographics, specifically age and ethnicity, play a determinative role in nanomedicine outcomes [5]. Age-related changes in hepatic clearance and vascular permeability can significantly alter the half-life of liposomal formulations, while genetic polymorphisms across different ethnic groups affect the metabolic activation of nano-encapsulated prodrugs [6, 7].

This period has seen increasing clinical evaluation and adoption of liposomal formulations and antibody–drug conjugates (ADCs) designed to overcome biological barriers such as the desmoplastic stroma [8]. This review systematically synthesizes these advances and critically examines the remaining challenges in patient stratification and regulatory standardization that must be addressed for nanomedicine to become a cornerstone of personalized cancer care.

METHODOLOGY

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework

1. PRISMA Flow Diagram of Study Selection

Phase	Description	Number of Records
Identification	Records identified from PubMed, Scopus, ClinicalTrials.gov (2018–2025).	3528
Screening	Records screened via title and abstract evaluation.	2583
Eligibility	Reports assessed for full-text eligibility (Phase 1–3 trials).	171
Included	Final studies included in the systematic review.	**26**

2. Inclusion and Exclusion Criteria

- **Inclusion:** Human clinical trials (Phase 1–3);
- randomized controlled trials (RCTs);
- high-impact translational data with human relevance (2018–2025) for breast, lung, or pancreatic malignancies.
- **Exclusion:** Purely animal studies; reviews without original data synthesis; non-English publications.

3. Pathophysiological Rationale and Comparison of Success

The efficacy and success of targeted nanocarriers is governed by the unique tumour microenvironment (TME). Conventional chemotherapy often lacks specificity, leading to myelosuppression, neurotoxicity and many side effects, sometimes even affecting patients compliance.

Figure 1: Comparative Pharmacological Outcomes and Physiological Barriers- specifies it.

Breast cancer exhibits high success due to leaky vasculature and a strong EPR effect.

Lung cancer shows moderate success, often requiring localized delivery.

Pancreatic cancer remains a "low success" challenge due to the dense desmoplastic stroma that traps nanoparticles outside the tumor tissue. [1, 8, 14, 21-25]

Molecular Pharmacology and Pharmacokinetic Optimization

Nanocarriers change drug effects by shielding active drug agents from systemic clearance and protecting them from enzymatic degradation in circulation.

Table1 -Comparative Pharmacokinetics: Nanoparticulate vs. Solvent-Based

In clinical trials, nab-paclitaxel (Abraxane) achieves a significantly higher "unbound" (pharmacologically active) fraction (0.063 vs 0.024; $P < 0.001$). [10, 28-32]

Synchronization of Payloads: The nal-IRI Paradigm

In pancreatic ductal adenocarcinoma (PDAC), liposomal irinotecan (nal-IRI) shields the drug from breaking down into SN-38 in the plasma. This extends the circulation half-

life by approximately 40-fold relative to free irinotecan helping maintain therapeutic levels of drug for 7.5 days vs 4.4 days.

Clinical Evidence Synthesis (2018–2025)-table2

DISUSSION:

The Need for Translational Reform

The conclusion of clinical and translational data from 2018–2025 reveals a decisive change in oncological nanomedicine:

the transition from "passive accumulation" theories to "active physiological engagement."

While the previous decade focused on the chemistry of the carrier, the current era is defined by the biology of the host and the unique architectural challenges of the TME [9, 10.]

As illustrated in Figure 1 and comparation summary in **Table 3**, clinical success varies significantly across breast, lung, and pancreatic cancers due to intrinsic differences in vascular permeability, stromal density, and immune contexture of the tumour. [1,7,34–36]

These findings collectively dismiss the historical idea of "one-size-fits-all" nanocarrier theory and instead supports a tumour-adaptive delivery model theory.

Bridging the Bench-to-Bedside Gap=

For years, researchers have leaned on the Enhanced Permeability and Retention (EPR) effect as the foundation for nanomedicine design, but the reality in human tumors has been disappointing. Imaging shows that, on average, only about 0.7% of injected nanoparticles actually end up in solid tumors. — a phenomenon often referred to as the "EPR paradox."

This "EPR paradox" has forced this field to rethink its approach.

This review highlights a shift in **contemporary clinical development efforts** toward active and stimulus-responsive targeting approaches that aims to move beyond reliance on passive extravasation. In PDAC, this means moving away from monotherapies to regimens like NALIRIFOX that synchronize the pharmacokinetics of multiple agents to penetrate the desmoplastic stroma. [9, 38-40]

The comparative findings in Table 2 highlight that stromal density is the dominant translational barrier in PDAC, whereas heterogeneity and receptor variability define breast and lung cancer challenges.

This tumor-specific variability explains the improved results with nanoliposomal regimens such as NALIRIFOX. [9,38–40]

Therefore, translational reform must prioritize:

- Pre-treatment TME characterization,
- Biomarker-guided nanoparticle selection,
- Combination strategies integrating stromal modulation.

Overcoming Multidrug Resistance

Targeted nanocarriers provide a unique pharmacological advantage by bypassing ATP-binding cassette (ABC) transporters. [1, 41-43] Stimuli-responsive systems release payloads directly into the cytoplasm or nucleus, overwhelming efflux pumps and ensuring cytotoxic concentrations are achieved even in refractory TNBC and PDAC populations. [7, 44-46]

The comparative data summarized in **Table 2** indicate that tumors with high MDR prevalence derive greater benefit from stimuli-responsive nanocarriers.

Demographic Modifiers: An Underrecognized Determinant of Nano delivery Success

An important translational insight emerging from this review is the limited incorporation of demographic stratification in nanomedicine trials. As summarized in **Table 3**, preliminary human data suggest that age and ethnicity may influence nanoparticle pharmacokinetics and tumor accumulation.

Age-related vascular stiffening, reduced endothelial permeability, and immune senescence in patients ≥65 years may partially explain reduced passive accumulation compared with younger cohorts. Conversely, younger patients (<60 years) may exhibit more robust inflammatory signaling and vascular permeability, potentially enhancing nanoparticle extravasation.

Ethnicity-related variability is even less studied but may involve:

- Differences in metabolic enzyme polymorphisms affecting liposomal clearance,
- Variations in TME fibrosis and immune infiltration patterns,
- Differential prevalence of aggressive TNBC subtypes among African ancestry populations.

Integrated Translational Implications

When Tables 2 and 3 are interpreted collectively, three major conclusions emerge:

The optimal nanotherapeutic deployment requires a three-layer stratification model:

- Tumor-level stratification (stromal density, vascularity)
- Molecular-level stratification (receptor expression, MDR profile)
- Patient-level stratification (age, ethnicity, metabolic variability)

This multi-dimensional framework represents a departure from platform-centric development and moves toward biologically integrated nanomedicine.

Future Horizons: AI and Next-Generation Platforms

The future of nanotechnology (2025–2030) will be defined by the convergence of material science, artificial intelligence, and genetic engineering.

AI-Driven Generative Design

Artificial intelligence is transitioning from simple optimization to "Generative Design" using Variational Autoencoders (VAEs) and Generative Adversarial Networks (GANs). These models learn "latent representations" of nanocarrier features to propose designs with optimized sizes, charges, and release profiles *before* physical synthesis.

Theranostics and Autonomous Systems

The emergence of theranostic platforms (e.g., AGuIX) enables real-time imaging-guided therapy, allowing clinicians to verify tumor accumulation before activating the therapeutic effect [7, 52-54] Looking further ahead, experimental autonomous nanorobots are being designed to perform smart drug release and real-time health monitoring within the tumor niche.

Genetic Payloads and CRISPR Integration

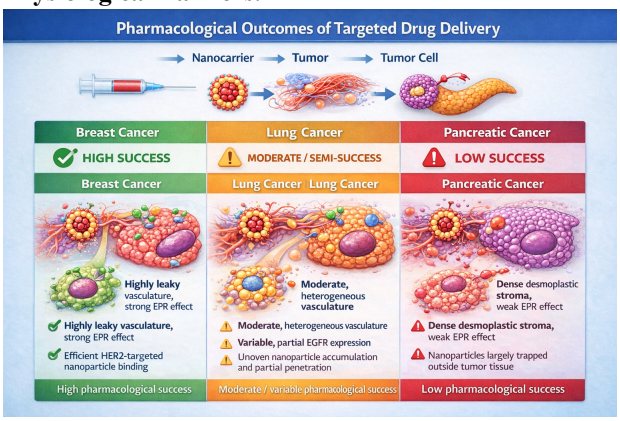
Nanocarriers are now being optimized for the delivery of complex nucleic acids, including mRNA vaccines and CRISPR-Cas9 gene-editing tools. [1, 6, 57-60]

CONCLUSION

Targeted nanocarrier-based drug delivery has successfully transitioned from "proof-of-concept" to a clinical standard of care.

Success in the next decade depends on regulatory standardization (Nano-CQAs), AI-optimized design, and biomarker-driven patient stratification to finally overcome the biological barriers of aggressive malignancies.

Figure 1: Comparative Pharmacological Outcomes and Physiological Barriers.



Tables-

1 Comparative Pharmacokinetics: Nanoparticulate vs. Solvent-Based

PK Parameter	Solvent-Based Paclitaxel	Nab-Paclitaxel (Nanoparticulate)	Pharmacological Benefit
Unbound Fraction	0.024	0.063	2.6-fold increase in active drug availability.
Intratumoral Conc.	Baseline (100%)	133%	Enhanced penetration via GP60/SPARC pathways.
Infusion Time	3 hours	30 minutes	Rapid delivery without steroid premedication.
Vd (Distribution)	Large/ Non-specific	Targeted/Restricted	Reduced cardiotoxicity and neurotoxicity.

Table-2 **Clinical Evidence Synthesis (2018–2025)**

Cancer Type	Target / Mechanism	Drug / Nanocarrier	Outcome / Phase (2018–2025)
Breast (TNBC)	**Trop-2** (Active)	**Sacituzumab Govitecan**	Median PFS 9.7 months vs 6.9 months (Chemo).
Breast	**Passive (EPR)**	**NK105** (Micelles)	Showed non-inferiority to PTX

Cancer Type	Target / Mechanism	Drug / Nanocarrier	Outcome / Phase (2018–2025)
			with reduced neuropathy.
Lung (NSCLC)	**HER2** (Active)	**Trastuzumab Deruxtecan**	Evaluating first-line efficacy in HER2-mutant NSCLC.
Pancreatic	**Multi-drug**	**NALIRIFOX** (Liposomal)	FDA approved (Feb 2024); superior OS to standard chemo.
Lung/Pancreas	**Radiosensitivity**	**AGuIX** (Gd-Nanoparticle)	Acts as MRI contrast and radio-enhancer; Fast Track 2024.

Table-3 Comparative Translational Performance of Nanodelivery (2018–2025)

Parameter	TNBC	NSCLC	PDAC
Vascular Permeability	Moderate–High (heterogeneous)	Moderate	Low
Stromal Density	Moderate	Low–Moderate	Very High (desmoplastic)
EPR Dependence	Partial	Partial	Minimal
Active Targeting Benefit	Significant	Significant	Essential
MDR Prevalence	High	Moderate	Very High
Stimuli-Responsive Advantage	High	Moderate	High
Clinical Translation Success	Moderate	Moderate–High	Limited but improving
Key Translational Barrier	Heterogeneity	Tumor immune evasion	Stromal blockade

Table 4. Demographic Modifiers of Nanomedicine Efficacy

Demographic Factor	Observed Trend	Proposed Mechanistic Explanation	Clinical Evidence Strength
Age < 60 years	Higher tumor accumulation	Greater vascular permeability and inflammatory signaling	Moderate
Age ≥ 65 years	Reduced passive accumulation	Vascular stiffening and immune senescence	Preliminary
Asian populations	Altered PK in liposomal agents	Metabolic enzyme polymorphism variability	Moderate
African ancestry	Potential stromal and immune differences in TNBC	Differential TME composition patterns	Limited
Obesity (cross-ethnic)	Altered nanoparticle distribution	Adipokine signalling and chronic inflammation	Emerging

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