Readers Insight
Publisher of open access books and journals

PJMLS OPEN ACCESS

Print ISSN: 2707-4471. Online ISSN: 2707-448X

Review Article
DOI: 10.31580/pjmls.v8i4.3437
Vol. 8 No. 4, 2025: pp. 925-940
www.readersinsight.net/pjmls

Pak-Euro Journal of Medical and Life Sciences
Copyright © All rights are reserved by Corresponding Author

Revised: December 03 , 2025
Accepted: December 22, 2025
Submission: August 31, 2025
Published Online: December 31, 2025

LIGAND-TARGETED NANOPARTICLES IN PRECISION ONCOLOGY: RECENT ADVANCES AND TRANSLATIONAL CHALLENGES

Amber Nawab[1], Irum Afzal[2]*, Zubia Begum[3], Mahnoor Jamil[1], Syeda Shazma Kanwal[4], Muhammad Waqar[5], Mehwish Nisar[6], Adam Ali[7]

[1]**Department of Pharmaceutics**, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan
[2]**Department of Pharmacy Practice**, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[3]**Department of Pharmacology**, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan
[4]**Department of Pharmacognosy**, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan
[5]**Faculty of Pharmacy**, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan
[6]**Department of Pharmaceutics**, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[7]**Plant Operations,** Mission Pharmaceuticals, Karachi, Pakistan

***Correspondence Author:** Irum Afzal. E. mail: irum.afzal@hamdard.edu.pk

Abstract

This review evaluates poor pharmacokinetics and drug resistance represent two major problems with standard chemotherapies for cancer, a key health concern worldwide. The aim of precision oncology is tumor biology-based treatment; however, it often fails owing to problems with drug delivery and side effects. Ligand-targeted nanomedicine is one such approach that has the potential to enhance the efficacy and safety of anticancer therapies. Focus is given to the targeting mechanisms and FDA-approved choices of ligand-functionalized nanocarriers, inclusive of liposomes and dendrimers. Tumor heterogeneity and manufacturing problems are also discussed, together with future developments of advanced design and personalised nanomedicine. Finally, ligand-targeted nanomedicine is presented as one of the revolutionary approaches in precision oncology, aimed at the development of patient-specific treatments with safety and increased efficiency.

Keywords: *Ligand-targeted nanoparticles, Precision oncology, Targeted drug delivery, Translational challenges, Tumor microenvironment*

INTRODUCTION

Life expectancy is affected by cancer, which is still the second most frequent cause of death globally, even with the progress made. Because of various risk factors, GLOBOCAN estimated 19.3 million new cases and 9.7 million deaths in 2022 (1). In 2050, there are expected to be 35 million cases. Lung, breast, colorectal, prostate, and stomach cancers are the most frequent (2). The major cancers, such as breast, lung, and colorectal cancers, are affected by late diagnoses and inadequate healthcare facilities, and more than 70% of cancer-related deaths in low- and middle-income countries such as Pakistan are associated with inadequate access to modern care and early detection (3, 4).

SCALE AND TRENDS OF THE GLOBAL CANCER BURDEN

Cancer is a significant global health crisis, resulting in 10 million deaths and 19-20 million new cases every year (5, 6), with estimates of 28-35 million cases in the 2040-2050 period mainly because of the aging population (7, 8). The main causes of cancer-related deaths are lung, breast, colorectal, liver, and stomach cancers. The economic burden is substantial, estimated at US$25.2 trillion between 2020 and 2050, equivalent to 0.55% of the global GDP, with lung cancer alone accounting for $167 billion of welfare costs in 2021 (9, 10). Middle-income countries are expected to experience an increasing incidence of hematologic malignancies, while low- and middle-income countries have reported substantial but unrecognized economic burden (11, 12). In the U.S., there are over 600,000 cancer deaths and 1.9 million new cases every year(13), and Europe alone accounts for more than 25% of the global burden (14, 15). If the trend continues, there could be 35 million cancer patients by 2050, mainly in developing countries with underdeveloped healthcare infrastructure (16-19).

ECONOMIC IMPACT OF CANCER ON HEALTHCARE SYSTEMS

In the global setting, cancer is a burden to the economy through medical expenses, non-medical expenses, and lost economic production. A macroeconomic analysis estimates that a total cost of 29 major types of cancer to the global economy is projected to cost US$25.2 to US$35 trillion for the period 2020 to 2050, or about 0.55% of GDP per annum (20). More than 50-80% of cancer patients and their families can incur catastrophic health expenses in LMICs, often leading to depletion of assets, borrowing, and poverty. The Economic Burden's Components shown in Table I. Healthcare systems are often severely impacted financially by cancer, especially in places where out-of-pocket costs are the most common (21, 22).

Table I. The economic burden's components

Type of cost	What it contains	Scale and evidence	References
Direct medical	Hospital care, surgery, drugs, radiation and chemotherapy, testing, and follow-up	The principal driver of the rise in cancer costs for Canada, South Korea, and Iran is the accelerating cost of hospital and systemic therapies, which could reach $35,000 per year in Iran	(23-25)
Direct non-medical	Housing, food, transportation, and carers' time and travel	Significant percentage of patient costs in studies on LMIC lung cancer in Nepal and India 11121420. Due to travel, patients in rural areas face additional financial challenges	(26, 27)
Indirect/productivity	Early death, reduced income, and quitting the workforce	The global economic cost of cancer is rising substantially, with indirect costs estimated to be in the trillions of dollars, and particular losses of productivity due to gastric cancer in Spain estimated to be in the billions of euros	(26, 28, 29)

METHODOLOGY

The systematic review was performed by employing the PRISMA-guided narrative review technique. An extensive search was performed for peer-reviewed scientific articles published during the period from January 2015 through January 2025 from the PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar electronic databases. "Precision oncology," "nanomedicine," "ligand-targeted nanoparticles," "active targeting," "pharmacokinetics," and "chemotherapy toxicity" were some search terms that have been employed by combining the Boolean logic.

Relevance was determined for titles and abstracts after removing the duplicate records. After that, the full-text articles were assessed for relevance based on certain inclusion and exclusion criteria. Articles on preclinical, translational, and clinical research involving nanoparticle systems functionalized with a ligand for use in cancer therapy were considered for selection. A qualitative narrative synthesis was carried conducted rather than a quantitative meta-analysis due to heterogeneity in nanocarrier platforms, targeting ligands, and outcome measures. The detailed selection and screening process, including database searches, removal of duplicate and ineligible records, assessment of eligibility, and final inclusion of studies in the systematic review, is illustrated in Fig. 1.

CRITERIA FOR INCLUSION AND EXCLUSION

Peer-reviewed original research articles, review articles, and clinical studies related to ligand-targeted nanocarriers for cancer therapy, which showed the enhancement of pharmacokinetics, tumor targeting ability, or reduced toxicity, were the types of literature considered for inclusion. Non-cancer literature, ligand-free nanocarriers, conference proceedings, editorials, unreviewed literature, and literature published before 2015 were the sources considered for exclusion.

EXAMINE THE SELECTION AND SCREENING PROCEDURE

PRISMA guidelines were followed in selecting the study for the review. Every study entry that was obtained from the databases had to be imported, and duplicate articles had to be removed. The procedure also included independently evaluating the abstracts and titles to ensure they were relevant to the review's objective in order to avoid duplication. The full-text articles that were selected for evaluation used the inclusion and exclusion criteria, and the authors reached a consensus on any conflicts that might have arisen, particularly with regard to the selection of papers for assessment.

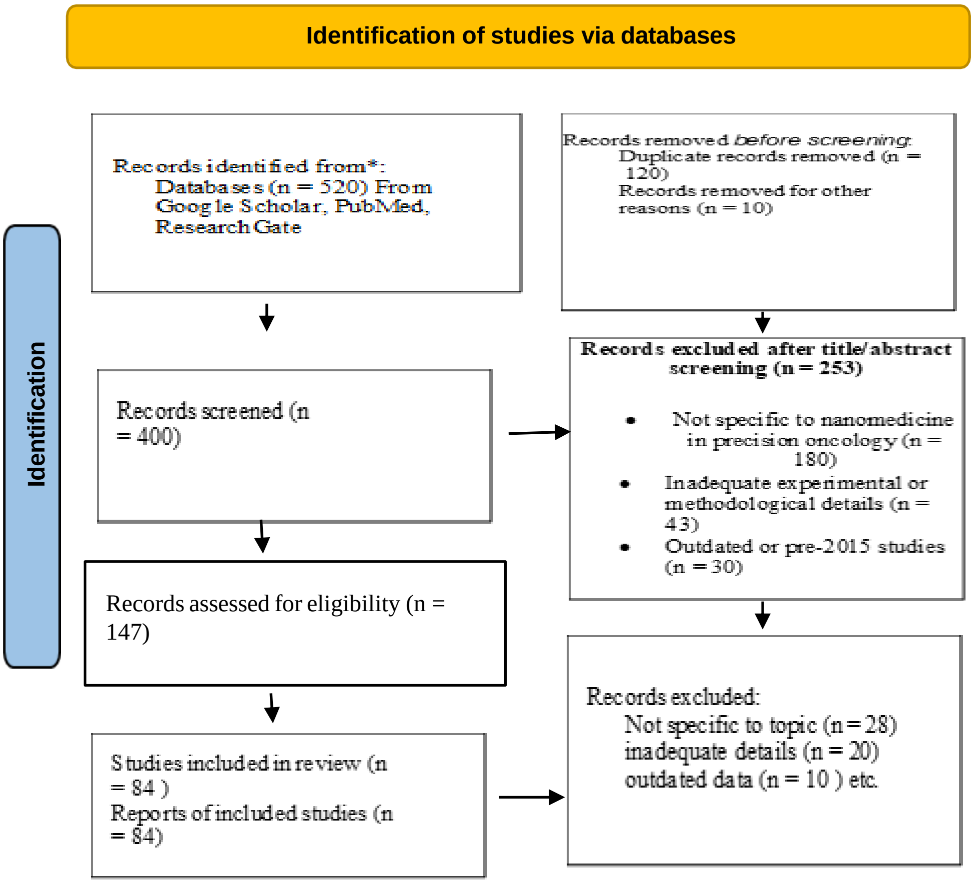

Fig. 1. Steps involved in choosing a study, such as database searches, eliminating duplicate and ineligible records, determining eligibility, and adding the studies to the systematic review

SYSTEM-LEVEL CONSEQUENCES

FOCUS ON SUSTAINABILITY AND HEALTH BUDGETS

Around 1.1% of the GDP in the EU, 1.8% in the USA, and 0.1–0.8% in the Middle East and Africa can be ascribed to cancer care, making an additional burden on the already stretched health budget, challenging the budgetary allotments for cancer car (25, 26, 29). Even for the top economies, the sustainability concerns come into play with the pricing of drugs and technology costs (30, 31).

ACCESS WITH CARE AND FINANCIAL TOXICITY

Global pooled prevalence of catastrophic health expenditures in cancer patients is 56%. Nine. Based on country studies, prevalence of CHE is between 80-97% in India, and more so above 80% in Nepal, which often translates into selling some assets, borrowing, or being poor (32, 33). Out-of-pocket payments, lost productivity, and deferred or foregone services, including in universal health coverage countries (Canada, Europe, and Slovenia), settings (34-36), this affects outcomes and undermines investments in cancer control (37, 38).

VULNERABLE GROUPS AND INEQUALITY

Financial toxicity and access problems are often expected in cases of lower income, poor insurance coverage, rural location, lower educational attainment, and younger age (34, 36). Cancer capacity is further weakened and the gap of equity is widened by sanctions and underfunding (23, 37).

LIMITATIONS OF CONVENTIONAL CANCER THERAPIES

Traditional chemotherapy and radiation have challenges such as myelosuppression and organ toxicity, especially in rapidly proliferating normal cells (39, 40). Resistance mechanisms such as TME-induced hypoxia, DNA repair, and cancer stem cells make it difficult to treat solid tumors (40-42). additionally, the tumor microenvironment prevents drug and immune cell access because of the abnormal vasculature and high interstitial fluid pressure (43, 44). Current research emphasizes these problems, implying the need for accurate tumor-targeting approaches, such as nanoparticle-mediated delivery and ligand-targeted vectors, to improve treatment efficacy and minimize adverse effects and resistance (45-47). The following table II lists FDA-approved nanomedicines that employ specific molecular ligands, such as antibodies or carbohydrates, for "active targeting" with a guarantee of high precision delivery and reduced systemic toxicity.

Table II. FDA-approved targeted nanomedicines

Approved nanomedicine	Targeting strategy /l	Clinical indication	References
Patisiran (Onpattro)	GalNAc-conjugated Lipid NP	Hereditary Transthyretin-mediated Amyloidosis	(48-50)
Givosiran (Givlaari)	GalNAc-conjugated siRNA	Acute Hepatic Porphyria	(51-53)
Brentuximab vedotin	Anti-CD30 Monoclonal Antibody	Hodgkin Lymphoma / ALCL	(45, 46, 54)
Trastuzumab emtansine	Anti-HER2 Antibody-Drug Conjugate	HER2-positive Breast Cancer	(55)

EMERGENCE OF PRECISION CANCER MEDICINE

Precision cancer medicine is based on oncogenic pathways and utilizes genomics and molecular diagnostics to provide personalized therapy based on genetic changes (56, 57). However, challenges such as immunological adverse effects and drug delivery are still present. Immunotherapy is currently the primary focus, which has led to improved outcomes (58, 59), but challenges related to tumor heterogeneity and targeting therapies require further research. Next-generation sequencing and multi-omics analysis improve diagnosis and therapy (60, 61), but only 5-10% of patients benefit from combination therapies. Precision cancer medicine includes targeted therapies and tumor-agnostic therapies, highlighting the importance of the tumor microenvironment and biomarkers (62-64).

ROLE OF NANOTECHNOLOGY IN ADVANCING PRECISION ONCOLOGY

Nanotechnology is an important area in precision oncology, as it helps improve cancer therapies through effective drug delivery (65, 66). Nanoparticle-based drug delivery systems help improve the solubility, stability, and circulation of drugs, enabling targeted delivery to cancer cells through active ligand targeting or passive targeting (EPR effect) (67, 68). This results in improved drug uptake through endocytosis, decreased cytotoxicity, and simultaneous delivery of therapeutic agents (69, 70). Moreover, they enable the combination of diagnostics and therapeutics and can be integrated with artificial intelligence (71). Marking a paradigm shift towards personalized cancer therapy, which focuses on maximizing therapeutic benefits with minimal toxicity to normal cells (72-74).

DESIGN, CHALLENGES, AND CLINICAL PRACTICE IN PRECISION NANOMEDICINE

Addressing the Limitations of Conventional: The lack of specificity, manifested by non-specific toxicity profiles and pharmacokinetics (PK), represents the fundamental limitation of conventional chemotherapy (75). With the introduction of tumor-selective drug delivery systems (DDS) capable of overcoming the existing limitation by addressing the issue of multidrug resistance (MDR) and off-target toxicity, nanomedicine represents the existing revolution within precision oncology (75, 76).

THE EMERGENCE OF LIGAND-TARGETED NANOPLATFORM VARIOUS

There have been advancements in the engineering of many nanoparticle (NP) platforms in the following ways:Liposomal and polymeric micelles are some examples of organic systems (77). Iron oxide nanoparticles, silica, and gold are some examples of inorganic frameworks. Bio-Inspired Systems: Biomimetic platforms coated with Site-Specific Release and these preparations are functionalized with specific targeting moieties such as the following for higher tumor accumulation and longer circulation time for high affinity receptor binding, employ the use of peptides and antibodies. Aptamers: For the proper identification of molecules (75). They allow controlled and specific delivery of medication, securing the target dosage directly into the cancerous tissue without harming healthy cells (53).

INTEGRATING THE PRINCIPLES OF PRECISION MEDICINE

A pathway-guided and TME-informed nanomedicine design combines genetic knowledge and molecular profiling to maximize therapeutic ratios, minimize chemotherapy toxicity (74), and improve outcomes by designing NPs that selectively target particular TME factors, like hypoxia and acidity (75). Major hurdles include overcoming drug resistance, especially involving P-Glycoprotein and ABC transporters, and evading immune system-mediated clearance to extend circulation half-lives in the face of highly aggressive TME factors (78). Although progress has been made, for example, with albumin-bound paclitaxel, translational hurdles remain in terms of scalability, biosafety, long-term toxicity, cost of production, and regulatory approval for combination nanotherapies. Immune reactions where the body attacks the nanoparticles, toxicity from the nanoparticles that could harm healthy organs in the body, and the challenges of manufacturing "smart" nanoparticles are some of the challenges that could prevent the application of innovations in the lab to patients (79, 80).

PROSPECTS OF THE FUTURE: COOPERATION BETWEEN VARIOUS

There is an urgent need to have a paradigm shift in the methods of conducting scientific studies to translate promising model studies into personalized therapies for cancer (73). This review argues that the future for the given field would depend on the following: The Design Principles: Identifying Guidelines Concerning NP Design and Its Association with Patient Benefits. Promoting a "bench-to-bedside" setting where regulatory scientists, immunologists, oncologists, and nanotechnologists work together is known as interdisciplinary collaboration (81, 82).

MECHANISMS FOR TARGETING: PASSIVE VS. ACTIVE

Both passive and active targeting techniques have been employed for ligand-targeted delivery in the case of nanoparticles (83).

This process of harnessing the EPR effect makes it possible for the passive targeting of nanoparticles between 10 nm and 200 nm in size to extravasate the leaky tumor vasculature and accumulate in the tumor due to incomplete lymphatic drainage. Compared to freely administered drugs, passive targeting enhances tumor localization (66). On the other hand, active targeting involves the conjugation of targeting ligands. This is done on the surface of the nanoparticles. The ligands promote receptor-mediated endocytosis as well as the intracellular delivery of the drug by binding to the tumor-specific receptors. Passive vs active targeting mechanism illustration in cancer nanomedicine as shown in Fig. 2. It is vital to note that this process boosts the selectivity of cells after the accumulation of the nanoparticles in the tumor environment, as opposed to the passive process (84).

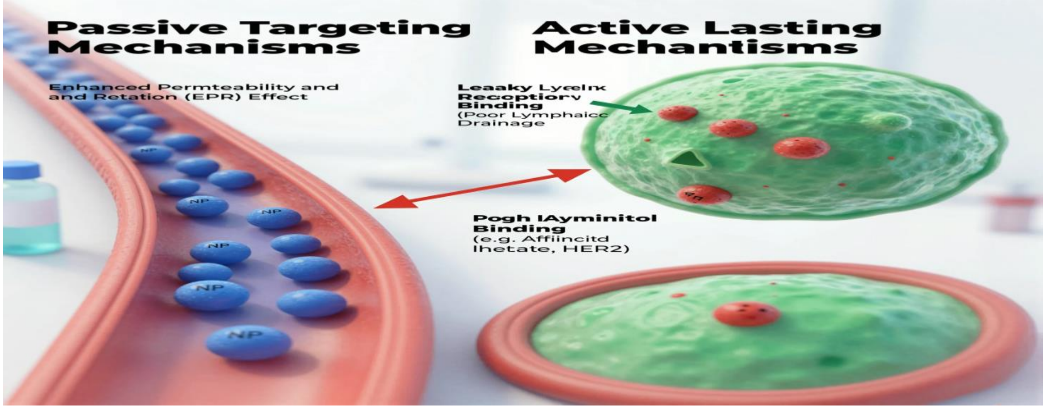

Fig. 2. Passive vs active targeting mechanism illustration in cancer nanomedicine: EPR effect for nanoparticles accumulation in a tumor vasculature with increased permeability, together with active targeting by ligand-receptor interaction (e.g., anti-HER2 antibodies) resulting in receptor-mediated endocytosis *[Adapted from Danhier 2016 (85)]*

TYPES OF LIGANDS INTENDED IN NANOPARTICLE SYSTEMS

Many ligands, each offering a unique advantage related to specificity, stability, or clinical relevance, have also been investigated as promising molecules to functionalize nanoparticles in cancer treatment.

Antibody fragments, also referred to as monoclonal antibodies and their fragments (Fab, scFv) are able to show high specificity and binding affinity for tumor-associated antigens such as HER2, EGFR, PSMA, and CD44. In the case of lung, breast, and prostate cancers, antibody-conjugated nanoparticles were able to demonstrate enhanced tumor-targeting efficacy and therapeutic outcomes (86). Nevertheless, their enormous size, immunogenicity, and cost of production might restrict their widespread clinical use (87).

Peptides: The advantages of peptide ligands such as RGD peptides binding to integrin αvβ3 include small size, least immunogenicity, and easy production. RGD-modified nanoparticles have demonstrated enhanced tumor penetration and internalisation especially in angiogenic tumors (88, 89).

Aptamers are short single-stranded DNA or RNA molecules and have high target selectivity. However, they are also more stable, less immunogenic, and their chemical modification is easier compared to antibodies. Aptamer-functionalized nanoparticles demonstrated encouraging results in models of breast, ovarian, and prostate cancer (90, 91).

Due to their high receptor expression in tumor cells and favourable safety profiles, small molecules like folic acid, transferrin, and hyaluronic acid are some of the commonly used ligands. the process of the ligand-targeted nanoparticles, with surface-bound ligands, binding onto the overexpressed receptors on the surface of the cancer cell and the subsequent receptor-mediated endocytosis as shown in Fig.3. For example, nanoparticles targeted by folate receptors have shown enhanced absorption in lung, breast, and ovarian malignancies with minimal damage to normal tissues (92-94).

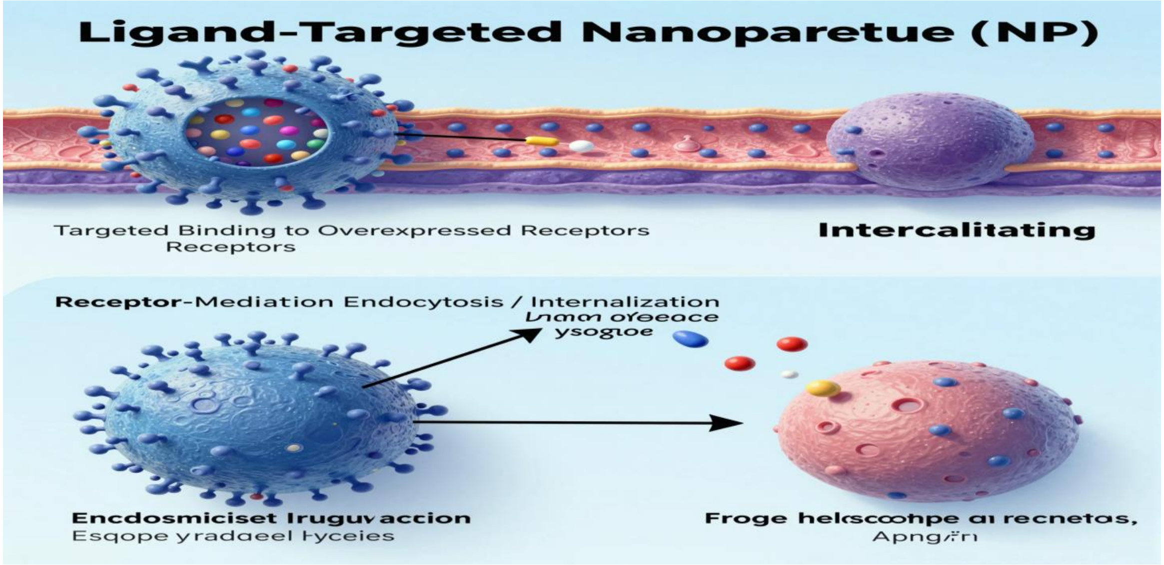

Fig. 3. Details of the blood vessels, the tumor cells, and the nanoparticles is explained as follows: the process of the ligand-targeted nanoparticles, with surface-bound ligands, binding onto the overexpressed receptors on the surface of the cancer cell and the subsequent receptor-mediated endocytosis *[Adapted from Shi et al,2017 (95)]*

IMPROVING PHARMACOKINETICS AND SELECTIVITY THROUGH LIGAND-TARGETED NANOPARTICLES

Ligand-targeted nanoparticles improve tumor accumulation and decrease off-target uptake by coating the surface of carriers with antibodies, peptides, or small molecules that target the binding of receptors preferentially overexpressed on tumor cells or tumor vasculature (96). Ligand-targeted NPs facilitate receptor-mediated endocytosis, extend circulation lifetimes, enhance tumor accumulation, and minimize systemic toxicity by leveraging a combination of passive targeting based on the enhanced permeability and retention (EPR) effect and active targeting by functionalization with antibodies, peptides, aptamers, and small molecules on their surface (97, 98).

CLINICAL INSTANCES INCLUDE

Clinical vignettes: PSMA-targeted-docetaxel nanoparticle BIND-014 showed greater efficacy for some Refractory cancers; pharmacokinetic profiles were altered by vascular retention, with reduction of PSA levels metastatic castration-resistant prostate cancer (96, 99). In the phase II trial, HER2-specific liposomal doxorubicin (MM-302), proven efficacious in HER2-positive breast cancers, demonstrated better safety profiles, but failed to outdo conventional chemo-regimens in combination with trastuzumab (96, 100). EGFR-targeted nanocells and immunoliposomes.

For targeted delivery based on a receptor in glioblastoma, non-small cell lung cancer, and mesothelioma, a combination of cytotoxics or miRNA mimics with anti-EGFR antibodies should be used (101, 102). If considered cumulatively, it is apparent that this class of compounds demonstrates that ligand targeting can, in some manner, modulate pharmacokinetics (96).

NANOCARRIER-BASED NUCLEIC-ACID PRECISION THERAPY

As naked oligonucleotides undergo rapid degradation and elimination (half-life 5–10 min), nanodelivery is almost exclusively relied on for genomics-guided siRNA, miRNA, antisense, plasmid DNA, and gene-editing constructs (103, 104). Among the polymer and lipid-based nanocarriers: Protect nucleic acids from nucleases to increase plasma half-life and permit tumor growth both at primary and metastatic sites (105, 106).The use of PEG and chemical base changes is required for the purpose of reducing the haematologic toxicities and cytokine release that afflicted the first-generation systems, including CALAA-01 and PNT2258 (106).

On-target mRNA silencing in individual human cancers has been validated in initial clinical trials of siRNA NPs designed against VEGFA/KSP (ALN-VSP), BCL2, PLK1, KRAS, and other targets, but the cumulative clinical results have been somewhat limited, in many cases due to immune-related toxities and the treatment of unpredictable patients who have been pretreated in the clinic (107). To address such challenges, a new generation of nucleic-acid nanomedicines started incorporating more tolerated carriers as well as rational chemical modifications in 2016 (106).

TUMOR MICROENVIRONMENT

Researchers point out that since factors such as vascular permeability, interstitial pressure, stromal density, and immunological content of the microenvironment highly influence the passage or transfer of NP, precision should also extend beyond genes.

Important strategies include: Anti-angiogenic therapy and vessel normalization may improve perfusion and NP size-dependent delivery in the range of 10-20 nm particles (108). When combined with nanomedicine, stroma modulation (e.g., losartan, PEG-hyaluronidase, and hedgehog inhibitors) can decrease the pressures of the arteries and increase the penetration of ~100-nm liposomes such as Doxil, Dense stroma, Angiogenesis, and Immune checkpoints envelope the core of hypoxia found in a cross-sectional scientific representation of the tumor microenvironment as seen in Fig. 4. with initial clinical evidence of improved survival in pancreatic cancer (109). The proposed 2020s strategy of trying to marry nanomedicines with stromal, vascular, and immunologic "priming" protocols is expected in this view that is metrological and mindful of the tumor microenvironment (109, 110).

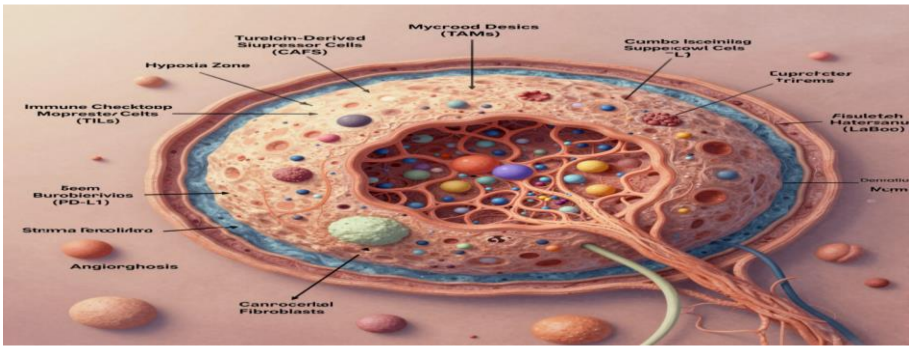

Fig. 4. Tumor-associated fibroblasts (CAFs), Tumor-associated macrophages (TAMs), Tumor-infiltrating lymphocytes (TILs), PD-L1 expression, Dense stroma, Angiogenesis, and Immune checkpoints envelope the core of hypoxia found in a cross sectional scientific representation of the tumor microenvironment *[Adapted From Hanahan & Weinberg 2017 (111)]*

NANOPLATFORMS FOR THERANOSTIC AND IMAGING

'Theranostic' nanomedicines are proven most effectively by the use of ultrasmall, ligand-targeted silica C-dots that are marked with PET/Optical reporters, which are efficacious in high-contrast lesion delineation, delineating the margin of resection, and visualizing their biodistribution in real time, while having low off-target persistence and rapid renal excretion (112, 113). They are in line with precision oncology because they relate to the diagnosis, selection, and therapy of the patient as well.

Findings in Translation Studies Applied for the Future (2016-2025) Personalization for each patient is required to make NP decisions due to differences in the EPR effect, expression level of receptors, microenvironment, and previous treatments that often lead to inconsistent outcomes of similar nanocarriers (83, 114). Since 2016, the focus of industry as well as the academic community has been on emphasizing.

To reduce batch variability and increase the correlation between characteristics and clinical performance, the characterisation and manufacturing of NP should be standardized. The Fig. 5. shows that the nanoplatform can be described as a multifunctional theranostic nanoparticle for cancer applications. It further depicts cellular uptake, tumor targeting arrows, and diagnostic signal emission (115). Similar to the folate-receptor imaging paradigm, biomarkers are used to select patients likely to benefit from specific ligand-targeted NPs (67, 116).

Combination techniques combine nanocarriers with immune checkpoint inhibition and radiation to take advantage of complimentary processes (116).

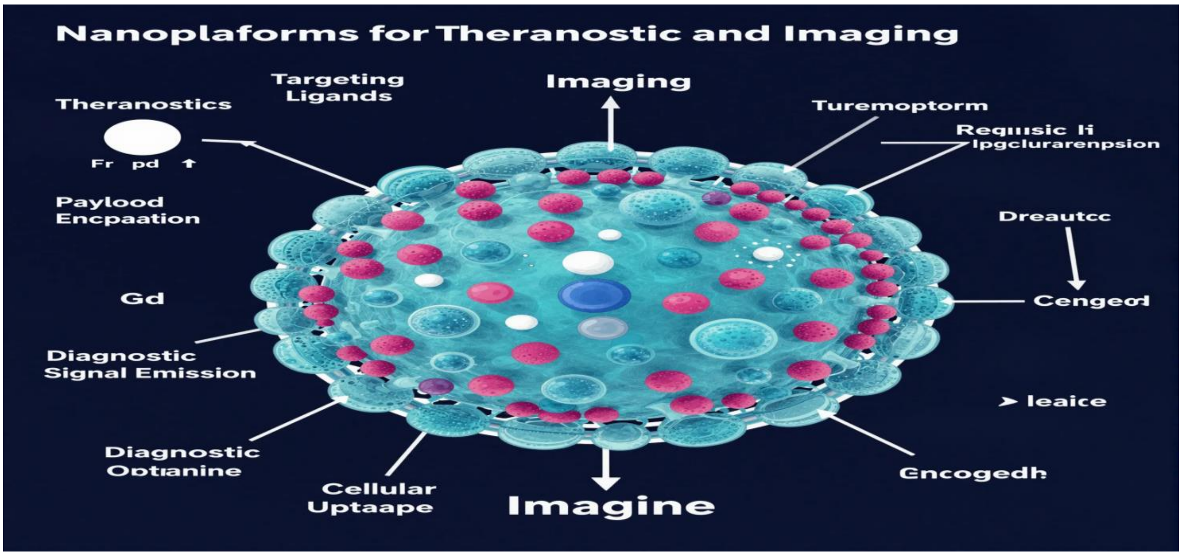

Fig. 5. Science illustration of spherical-shaped nanoplatforms in blue color, with targeting ligand on the surface, encapsulated drug payload inside the core, integrated Gd enhancing contrast agents, and fluorescent dyes for imaging. This nanoplatform can be described as a multifunctional theranostic nanoparticle for cancer applications. It further depicts cellular uptake, tumor targeting arrows, and diagnostic signal emission. Clearly labelled on a dark-colored diagram *[Adapted from Chen et al., 2016 (117)].*

CURRENT ADVANTAGES

These drugs function like GPS-guided missiles, traveling straight for cancer cells and avoiding most healthy cells. Compared to conventional chemotherapy, patients frequently have fewer adverse effects since the medications are targeted. They can aid in the treatment of tumors that have developed resistance to conventional medications.

REQUIREMENTS FOR FUTURE RESEARCH

We need to create nanoparticles according to the genetic information of a specific patient. Research is required to produce nanoparticles that will "unlock" and release the drug only when they detect a particular signal from the tumor. AI is employed before the commencement of human trials to predict how these drugs will work in the human body. Developing "two-in-one" nanoparticles that can treat a tumor and image it on a scan.

DISCUSSION

The growing significance of ligand-targeted nanomedicine in improving precision oncology is thoroughly highlighted in this review. Rapid systemic clearance, poor tumor selectivity, dose-limiting toxicity, and multidrug resistance are common drawbacks of conventional chemotherapeutic and even molecularly targeted treatments. By increasing drug accumulation at tumor locations while reducing off-target exposure, ligand-functionalized nanoparticle systems have emerged as a successful method to address these issues.

Active targeting using ligands such as antibodies, peptides, aptamers, folic acid, and transferrin enables receptor-mediated endocytosis, which significantly improves intracellular drug delivery and enhance therapeutic efficacy. Such targeting methods, in addition, improve pharmacokinetics-it prolongs the circulation duration, enhances bioavailability, and allows for controlled drug release. Furthermore, it was shown that ligand-targeted nanoparticles can bypass efflux transporters to surmount multidrug resistance and allow for better treatment outcome even in resistant tumor models. The amalgamation of diagnostic imaging capabilities with therapeutic interventions by the inclusion of targeting ligands in the nanocarriers has led to beneficial therapeutic outcomes in addition to potential combination therapy or theranostic capabilities. Nevertheless, the list of challenges for their translational potential in mainstream medical practices still includes many factors despite such promising advances. They include tumor-specific variations of specific receptors, biological reproducibility for mass production of these nanocarriers, long-term biological compatibility, immunogenic reactions of the carriers, and complex regulatory processes.

CONCLUSION

Through the optimization of therapeutic efficacy and the simultaneous attenuation of systemic toxicity, ligand-targeted nanomedicines provide a precise alternative to conventional drugs, which is a major shift in the field of oncology. While the results are highly encouraging in the preclinical setting, there is a need for joint optimization efforts in nanoparticle design, comprehensive safety evaluation, and harmonized regulatory guidelines to translate these platforms into mainstream clinical practice. Ultimately, the key frontier for improved therapeutic outcomes for individual patients remains the integration of genetic screening with nanomedicine.

Future Directions:

Ligand-targeted nanomedicines offer promising approaches for targeted oncology, but there are several obstacles that currently limit their translation from the laboratory to the clinic. The first challenge is the presence of biological barriers and heterogeneity, where differences among individuals make nanoparticle targeting difficult. There is a need to develop personalized approaches that integrate genetic analysis with nanoparticle design. Moreover, the complexity of drug release is a problem, where current carriers tend to leak drugs prematurely; new carriers that are sensitive to specific stimuli are required to provide localized drug delivery. Multidrug resistance (MDR) in cancer is also a complication in treatment, where there is a need to conduct research on dual-targeted and multifunctional nanoparticles. Moreover, there are translational and regulatory barriers due to difficulties in scaling up nanoparticle production; AI and machine learning can help in predicting the behavior of formulations to facilitate the process of clinical trials. Finally, the convergence of theranostics—particles that can provide simultaneous diagnosis and treatment—is a future approach that will allow for real-time visualization of drug efficacy and safety.

Funding:

The conducted study was not funded from any platform or organization.

Acknowledgment:

Through this study we wish to acknowledge our organization, Hamdard University, Karachi, which has always motivated and supported in the whole journey of this research.

Conflict of interest:

There are no conflicts of interest for the authors.

Authors' contribution:

AM & IA Conceived the idea & designed the structure of the review; ZB Analyzed recent literature; MJ, SS & SMW Data compilation, referencing, and critical revision of the draft; MN & AA Literature review, language editing.

Declaration of generative AI and AI-assisted technologies in the writing process:

While the article was being prepared, the authors used Chat GPT to make it easier to read. The authors accepted full responsibility for the publication's content after using this tool or service, reviewed it, and made any necessary revisions.

References:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal AJCacjfc. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2024;74(3):229-63.
2. Islami F, Baeker Bispo J, Lee H, Wiese D, Yabroff KR, Bandi P, Sloan K, Patel AV, Daniels EC, Kamal AHJCACJfC. American Cancer Society's report on the status of cancer disparities in the United States, 2023. 2024;74(2):136-66.
3. Awan UA, Bashir S, Hassan U, Khan SN, Awan FM, Jabbar A, Khan S, Guo XJIA, Cancer. HPV–driven breast carcinogenesis: associations with tumor severity, Ki67 expression and metastasis. 2025;20(1):55.
4. Huq MS, Acharya SC, Sharma S, Poudyal S, Sapkota S, Shrestha S, Gautam M, Silwal SR, Haque MM, Uddin AKJTLO. Cancer care and outreach in South Asian Association for Regional Cooperation (SAARC) countries: from epidemiology and the National Cancer Control Programme to screening, diagnosis, and treatment. 2024;25(12):e639-e49.
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel R, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024;74:229-63.
6. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021;71:209-49.
7. Chen S, Cao Z, Prettner K, Kuhn M, Yang J, Jiao L, Wang Z, Li W, Geldsetzer P, Bärnighausen T, Bloom D, Wang C. Estimates and Projections of the Global Economic Cost of 29 Cancers in 204 Countries and Territories From 2020 to 2050. JAMA Oncology. 2023;9:465-72.
8. Fitzmaurice C, Allen C, Barber R, Barregard L, Bhutta Z, Brenner H, Dicker D, Chimed-Orchir O, Dandona R, Dandona L, Fleming T, Forouzanfar M, Hancock J, Hay R, Hunter-Merrill R, Huynh C, Hosgood H, Johnson C, Jonas J, Khubchandani J, Kumar G, Kutz M, Lan Q, Larson H, Liang X, Lim S, Lopez A, MacIntyre M, Marczak L, Marquez N, Mokdad A, Pinho C, Pourmalek F, Salomon J, Sanabria J, Sandar L, Sartorius B, Schwartz S, Shackelford K, Shibuya K, Stanaway J, Steiner C, Sun J, Takahashi K, Vollset S, Vos T, Wagner J, Wang H, Westerman R, Zeeb H, Zoeckler L, Abd-Allah F, Ahmed M, Alabed S, Alam N, Aldhahri S, Alem G, Alemayohu MA, Ali R, Al-Raddadi R, Amare A, Amoako Y, Artaman A, Asayesh H, Atnafu N, Awasthi A, Saleem H, Barać A, Bedi N, Benseñor I, Berhane A, Bernabé E, Betsu B, Binagwaho A, Boneya D, Campos-Nonato I, Castañeda-Orjuela C, Catalá-López F, Chiang P, Chibueze C, Chitheer A, Choi J, Cowie B, Damtew S, Neves JD, Dey S, Dharmaratne S, Dhillon P, Ding E, Driscoll T, Ekwueme D, Endries A, Farvid M, Farzadfar F, Fernandes J, Fischer F, G/hiwot TT, Gebru A, Gopalani S, Hailu A, Horino M, Horita N, Husseini A, Huybrechts I, Inoue M, Islami F, Jakovljevic M, James S, Javanbakht M, Jee S, Kasaeian A, Kedir MS, Khader Y, Khang Y, Kim D, Leigh J, Linn S, Lunevicius R, Razek HMAE, Malekzadeh R, Malta D, Marcenes W, Markos D, Melaku Y, Meles K, Mendoza W, Mengiste DT, Meretoja T, Miller T, Mohammad K, Mohammadi A, Mohammed S, Moradi-Lakeh M, Nagel G, Nand D, Nguyen QL, Nolte S, Ogbo F, Oladimeji K, Oren E, Pa M, Park EK, Pereira D, Plass D, Qorbani M, Radfar A, Rafay A, Rahman M, Rana S, Søreide K, Satpathy M, Sawhney M, Sepanlou S, Shaikh M, She J, Shiue I, Shore H, Shrime M, So S, Soneji S, Stathopoulou V, Stroumpoulis K, Sufiyan M, Sykes B, Tabarés-Seisdedos R, Tadese F, Tedla B, Tessema G, Thakur J, Tran B, Ukwaja K, Uzochukwu B, Vlassov V, Weiderpass E, Terefe MW, Yebyo H, Yimam H, Yonemoto N,

Younis M, Yu C, Zaidi Z, Zaki M, Zenebe Z, Murray C, Naghavi M. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncology. 2017;3:524.

9. Liu G, Liu Y, Jing H, Chen T, Wang H, Qiu H, Zhang J, Wu Y. Global, regional, and national economic consequences of tracheal, bronchial, and lung cancer. Lung cancer. 2025;207:108685.
10. Li Z, Chen G, Du G. Global, regional, and national economic burden of hematologic malignancies (1990–2021) with projections to 2050. Frontiers in Public Health. 2025;13.
11. Patterson R, Fischman V, Wasserman I, Siu J, Shrime M, Fagan J, Koch W, Alkire B. Global Burden of Head and Neck Cancer: Economic Consequences, Health, and the Role of Surgery. Otolaryngology–Head and Neck Surgery. 2020;162:296-303.
12. Zheng J, Yao L, Lei K, Huang W, Luo YJZ, Tran PH-X, Guan A, Qiu Y, Adebisi Y, Eliseo DL-P, Zhong C, Wong M, Huang J. Economic burden attributable to high BMI-caused cancers: a global level analysis between 2002 and 2021. BMC Medicine. 2025;23.
13. Lin L, Li Z, Yan L, Liu Y, Yang H, Li H. Global, regional, and national cancer incidence and death for 29 cancer groups in 2019 and trends analysis of the global cancer burden, 1990–2019. Journal of Hematology & Oncology. 2021;14.
14. Siegel RL, Giaquinto AN, Jemal AJCacjfc. Cancer statistics, 2024. 2024;74(1):12-49.
15. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray FJCacjfc. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 2021;71(3):209-49.
16. Bray F, Laversanne M, Weiderpass E, Soerjomataram IJC. The ever-increasing importance of cancer as a leading cause of premature death worldwide. 2021;127(16):3029-30.
17. Giaquinto AN, Sung H, Newman LA, Freedman RA, Smith RA, Star J, Jemal A, Siegel RLJCacjfc. Breast cancer statistics 2024. 2024;74(6):477-95.
18. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, McCullough ML, Patel AV, Ma J, Soerjomataram IJCacjfc. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. 2018;68(1):31-54.
19. Wu Z, Xia F, Lin RJJoh, oncology. Global burden of cancer and associated risk factors in 204 countries and territories, 1980–2021: a systematic analysis for the GBD 2021. 2024;17(1):119.
20. Mao Y, Chu X, Xie F, Fu L, Ding Z, Zhang W, Zhang Q, Tang C, Zhu S, Cao WJFiE. Estimates and projections of the global economic cost of breast cancers from 2021 to 2050. 2025;16:1692619.
21. Prinja S, Dixit J, Gupta N, Dhankhar A, Kataki AC, Roy PS, Mehra N, Kumar L, Singh A, Malhotra PJFiph. Financial toxicity of cancer treatment in India: towards closing the cancer care gap. 2023;11:1065737.
22. Kitaw TA, Tilahun BD, Zemariam AB, Getie A, Bizuayehu MA, Haile RNJBGH. The financial toxicity of cancer: unveiling global burden and risk factors–a systematic review and meta-analysis. 2025;10(2).
23. Irandoust K, Alipour V, Arabloo J, Nahvijou A, Akbari A. Economic burden of five common cancers in Iran: a systematic review of cost-of-illness with a focus on healthcare resource utilization. BMC Health Services Research. 2025;25.
24. Planey A, Spees L, Biddell C, Waters A, Jones E, Hecht H, Rosenstein D, Wheeler S. The intersection of travel burdens and financial hardship in cancer care: a scoping review. JNCI Cancer Spectrum. 2024;8.
25. De Oliveira C, Weir S, Rangrej J, Krahn M, Mittmann N, Hoch J, Chan K, Peacock S. The economic burden of cancer care in Canada: a population-based cost study. CMAJ open. 2018;6 1.
26. Khanal P, Johansson K, Pandey A, Mishra RK, Poudel N, Sharma S, Karmacharya B, Adhikari SR, Aryal K. Financial burden of cancer in Nepal: Factors associated with annual cost and catastrophic health expenditure. PLOS One. 2025;20.
27. Ünal E, Goodchild E, Winkler V, Brenner S, Deckert A, Dambach P, Horstick O, Kaifie A, Louis V. The economic burden of lung cancer in low- and lower-middle-income countries: a systematic review. Archives of Public Health. 2025;83.
28. Darbà J, Ascanio M, Agüera A. Gastric cancer in Spain: evaluating productivity loss and economic impact. Journal of Medical Economics. 2024;27:1331-6.
29. Akhtar MA, Chowdhury I, Taneja B. Healthcare utilisation and economic burden of cancer on Indian households. Scientific Reports. 2025;15.
30. Vancoppenolle J, Franzen N, Azarang L, Juslin T, Krini M, Lubbers T, Mattson J, Mayeur D, Menezes R, Schmitt J, Scotté F, López O, Skaali T, Ubels J, Schlander M, Retèl V, Harten W, Prof.Wim H, Harten V. Financial toxicity and socioeconomic impact of cancer in Europe. ESMO Open. 2025;10.

31. Zafar S. Financial Toxicity of Cancer Care: It's Time to Intervene. Journal of the National Cancer Institute. 2016;108 5.
32. Prinja S, Dixit J, Gupta N, Dhankhar A, Kataki A, Roy P, Mehra N, Kumar L, Singh AK, Malhotra P, Goyal A, Rajsekar K, Krishnamurthy M, Gupta S. Financial toxicity of cancer treatment in India: towards closing the cancer care gap. Frontiers in Public Health. 2023;11.
33. Rubagumya F, Wilson B, Manirakiza A, Mutabazi E, Ndoli D, Rudakemwa E, Chamberlin M, Hopman W, Booth C. Financial Toxicity: Unveiling the Burden of Cancer Care on Patients in Rwanda. The Oncologist. 2023;29.
34. Skubic M, Vöröš K, Bavdaž M, Bonča P, Perhavec A, Redek T, Ratoša I, Logar H. Financial Toxicity Among Cancer Patients in Slovenia. Cancer Medicine. 2025;14.
35. Parikh D, Ragavan M, Dutta R, Edwards JG, Dickerson J, Maitra D, Aggarwal S, Lee F, Patel M. Financial Toxicity of Cancer Care: An Analysis of Financial Burden in Three Distinct Health Care Systems. JCO Oncology Practice. 2021;17.
36. Fitch M, Longo C, Chan R. Cancer patients' perspectives on financial burden in a universal healthcare system: Analysis of qualitative data from participants from 20 provincial cancer centers in Canada. Patient education and counseling. 2020.
37. Muralidharan S, Gore M, Katkuri S. Cancer care and economic burden—A narrative review. Journal of Family Medicine and Primary Care. 2023;12:3042-7.
38. Kitaw TA, Tilahun BD, Zemariam AB, Getie A, Bizuayehu MA, Haile RN. The financial toxicity of cancer: unveiling global burden and risk factors – a systematic review and meta-analysis. BMJ Global Health. 2025;10.
39. Liu Y, Wang X-L, He D-H, Cheng Y-X. Protection against chemotherapy- and radiotherapy-induced side effects: A review based on the mechanisms and therapeutic opportunities of phytochemicals. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2020:153402.
40. Rocha MJF, Ruppen IC, Gesualdo MT, Fernandes MEGC, De Oliveira Barros P, Leandro AC, Hellmann EE, Porcinelli AM, Da Rosa Piccoli L, Gasparotto G, Barreto TC, Zanini CA, Gois GA, Reis LV, Perez HBP. Chemotherapy-Related Toxicities and Clinical Management: An Article Review. Journal of Cancer Research Reviews & Reports. 2025.
41. Lei Z, Tian Q, Teng Q, Wurpel J, Zeng L, Pan Y, Chen ZS. Understanding and targeting resistance mechanisms in cancer. MedComm. 2023;4.
42. Amawi H, Hammad A, Hall F, Hussein N, Rataan A, Mrayyan A, Al-Kofahi T, Hmedat A, Ashby C, Tiwari A. Revisiting strategies to target ABC transporter-mediated drug resistance in CNS cancer. Cancer Biology & Medicine. 2025;22:1158-80.
43. Lyrio RMdC, Rocha BRA, Corrêa ALRM, Mascarenhas MGS, Santos FL, Maia RdH, Segundo LB, de Almeida PAA, Moreira CMO, Sassi RHJFiN. Chemotherapy-induced acute kidney injury: epidemiology, pathophysiology, and therapeutic approaches. 2024;4:1436896.
44. Zhang Y, Ma W, Huang Z, Liu K, Feng Z, Zhang L, Li D, Mo T, Liu QJPiM, Biology. Research and application of omics and artificial intelligence in cancer. 2024;69(21):21TR01.
45. Cecchi D, Jackson N, Beckham W, Chithrani D. Improving the Efficacy of Common Cancer Treatments via Targeted Therapeutics towards the Tumour and Its Microenvironment. Pharmaceutics. 2024;16.
46. Shao X, Zhao X, Wang B, Fan J, Wang J, An H. Tumor microenvironment targeted nano-drug delivery systems for multidrug resistant tumor therapy. Theranostics. 2025;15:1689-714.
47. Yan S, Na J, Liu X, Wu P. Different Targeting Ligands-Mediated Drug Delivery Systems for Tumor Therapy. Pharmaceutics. 2024;16.
48. Wang Y, Zheng W, Yan J, Wang L-Z, Pan D, Xu Y-P, Chen C, Zhou X, Wang X, Yang M. Bioorthogonal liposome-based sequential drug delivery system for enhanced tumor accumulation and targeted therapy. Drug delivery and translational research. 2025.
49. Wang Y, Pang S, Lu Y, Guo X, Li C, Chen M, Ren X. Preliminary study on targeted therapy of breast cancer using tumor cell membrane-coated dual-loaded liposomes based on chemo-photothermal synergistic effects. Drug delivery and translational research. 2025.
50. Chu H, Xu Y, Shan Y, Sun M, Zhao W, Fang X, Shen N, Tang Z. Platelet hitchhiking vascular-disrupting agents for self-amplified tumor-targeting therapy. Journal of Nanobiotechnology. 2025;23.
51. Jiang W, Chen L, Guo X, Cheng C, Luo Y, Wang J, Wang J, Liu Y, Cao Y, Li P, Wang Z, Ran H, Zhou Z, Ren J. Combating multidrug resistance and metastasis of breast cancer by endoplasmic reticulum stress and cell-nucleus penetration enhanced immunochemotherapy. Theranostics. 2022;12:2987-3006.

52. Zhe, Li N, Zhang B, Hui Y, Zhang Y, Lu P, Pi J, Liu Z. Dual drug-loaded nano-platform for targeted cancer therapy: toward clinical therapeutic efficacy of multifunctionality. Journal of Nanobiotechnology. 2020;18.
53. Park S, Lu G, Zheng Y, Davison E, Li Y. Nanoparticle-Based Delivery Strategies for Combating Drug Resistance in Cancer Therapeutics. Cancers. 2025;17.
54. Zhao Y, Tan F, Zhao J, Zhou S, Luo Y, Gong C. Targeting the Enhanced Sensitivity of Radiotherapy in Cancer: Mechanisms, Applications, and Challenges. MedComm. 2025;6.
55. Pousse L, Manchala A, Klein C, Deak C. Advanced cytokine-based immunotherapies: targeted cis-delivery strategies for enhanced anti-tumor efficacy and reduced toxicity. mAbs. 2025;17.
56. Ashley EAJNRG. Towards precision medicine. 2016;17(9):507-22.
57. Collins FS, Varmus HJNEjom. A new initiative on precision medicine. 2015;372(9):793-5.
58. Malone ER, Oliva M, Sabatini PJ, Stockley TL, Siu LLJGm. Molecular profiling for precision cancer therapies. 2020;12(1):8.
59. Postow MA, Sidlow R, Hellmann MDJNEJoM. Immune-related adverse events associated with immune checkpoint blockade. 2018;378(2):158-68.
60. Malone E, Oliva M, Sabatini P, Stockley T, Siu L. Molecular profiling for precision cancer therapies. Genome Medicine. 2020;12.
61. Panda AK, B R, Kumar A, Sairam K, Gudur A, M S. Therapeutic Targets and Treatment Improvement Through Key Oncogenic Pathways in Cancer. Salud, Ciencia y Tecnología. 2025.
62. Wang Y. Advances in cancer immunotherapy and future directions in personalized medicine. Open Life Sciences. 2025;20.
63. Yi M, Li T, Niu M, Zhang H, Wu Y, Wu K, Dai Z-T. Targeting cytokine and chemokine signaling pathways for cancer therapy. Signal Transduction and Targeted Therapy. 2024;9.
64. Garg P, Pareek S, Kulkarni P, Horne D, Salgia R, Singhal S. Next-Generation Immunotherapy: Advancing Clinical Applications in Cancer Treatment. Journal of Clinical Medicine. 2024;13.
65. Shi J, Kantoff PW, Wooster R, Farokhzad OCJNrc. Cancer nanomedicine: progress, challenges and opportunities. 2017;17(1):20-37.
66. Li J, Xie J, Zhu J, Tao J, editors. Multifunctional Nanoparticle Approach for Targeting Melanoma. Journal of Investigative Dermatology Symposium Proceedings; 2018: Elsevier.
67. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WCJNrm. Analysis of nanoparticle delivery to tumours. 2016;1(5):1-12.
68. Vauthier CJJoDT. A journey through the emergence of nanomedicines with poly (alkylcyanoacrylate) based nanoparticles. 2019;27(5-6):502-24.
69. Sharma GJJoEP, Research M. Clinical Translation of Nanomedicine in Oncology: Advances, Challenges, and Future Directions in Hepatic, Renal, Breast, and Brain Malignancies. 2025:53-85.
70. Bhattacharjee S, Brayden DJJEoodd. Addressing the challenges to increase the efficiency of translating nanomedicine formulations to patients. 2021;16(3):235-54.
71. Wang B, Hu S, Teng Y, Chen J, Wang H, Xu Y, Wang K, Xu J, Cheng Y, Gao X. Current advance of nanotechnology in diagnosis and treatment for malignant tumors. Signal Transduction and Targeted Therapy. 2024;9.
72. Tian H, Zhang T, Qin S, Huang Z, Zhou L, Shi J, Nice E, Xie Nn, Huang C, Shen Z. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. Journal of Hematology & Oncology. 2022;15.
73. Gavas S, Quazi S, Karpiński T. Nanoparticles for Cancer Therapy: Current Progress and Challenges. Nanoscale Research Letters. 2021;16.
74. Sabit H, Pawlik T, Radwan F, Abdel-Hakeem M, Abdel-Ghany S, Wadan A-HS, Elzawahri M, El-Hashash A, Arneth B. Precision nanomedicine: navigating the tumor microenvironment for enhanced cancer immunotherapy and targeted drug delivery. Molecular Cancer. 2025;24.
75. Xu M, Han X, Xiong H, Gao Y, Xu B, Zhu G, Li J. Cancer Nanomedicine: Emerging Strategies and Therapeutic Potentials. Molecules. 2023;28.
76. Peng Y, Yu M, Li B, Zhang S, Cheng J, Wu F, Du S, Miao J, Hu B, Olkhovsky I, Li S. Advances in nanocarrier-mediated cancer therapy: Progress in immunotherapy, chemotherapy, and radiotherapy. Chinese Medical Journal. 2025;138:1927-44.
77. Wen F, Wang L, Li X, Zhao J, Xu T, Zhu J, Lijuan, Wang X. Precision Nanomedicine for Cancer: Innovations, Strategies, and Translational Challenges. OncoTargets and Therapy. 2025;18:1125-48.
78. Rachamala HK. Translational Advances in Lipid Nanoparticle Drug Delivery Systems for Cancer Therapy: Current Status and Future Horizons. Pharmaceutics. 2025;17.

79. Mousavi-Kiasary S, Senabreh A, Zandi A, Pena R, Cruz F, Adibi A, Hooshmand N. Synergistic Cancer Therapies Enhanced by Nanoparticles: Advancing Nanomedicine Through Multimodal Strategies. Pharmaceutics. 2025;17.
80. Anjum S, Hashim M, Malik S, Khan M, Lorenzo J, Abbasi B, Hano C. Recent Advances in Zinc Oxide Nanoparticles (ZnO NPs) for Cancer Diagnosis, Target Drug Delivery, and Treatment. Cancers. 2021;13.
81. Esmaeilpour D, Ghomi M, Zare EN, Sillanpää M. Nanotechnology-Enhanced siRNA Delivery: Revolutionizing Cancer Therapy. ACS applied bio materials. 2025.
82. Abdullah K, Sharma G, Singh A, Siddiqui J. Nanomedicine in Cancer Therapeutics: Current Perspectives from Bench to Bedside. Molecular Cancer. 2025;24.
83. Maeda H, Khatami MJC, medicine t. Analyses of repeated failures in cancer therapy for solid tumors: poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs. 2018;7(1):11.
84. Marconescu A. Targeting Nanoparticles to Tumor Vasculature 2008.
85. Danhier F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? Journal of Controlled Release. 2016;244:108-21.
86. Basile L, Pignatello R, Passirani CJCdd. Active targeting strategies for anticancer drug nanocarriers. 2012;9(3):255-68.
87. Barenholz YCJJocr. Doxil®—The first FDA-approved nano-drug: Lessons learned. 2012;160(2):117-34.
88. Danhier F, Le Breton A, Préat VJMp. RGD-based strategies to target alpha (v) beta (3) integrin in cancer therapy and diagnosis. 2012;9(11):2961-73.
89. Taheri Z, Mozafari N, Moradian G, Lovison D, Dehshahri A, De Marco RJP. Integrin-Specific Stimuli-Responsive Nanomaterials for Cancer Theranostics. 2024;16(11):1441.
90. Zhou J, Rossi JJNrDd. Aptamers as targeted therapeutics: current potential and challenges. 2017;16(3):181-202.
91. Li Y, Lee J-SJCP. Recent developments in affinity-based selection of aptamers for binding disease-related protein targets. 2019;73(11):2637-53.
92. Guo J, Schlich M, Cryan JF, O'Driscoll CMJJops. Targeted drug delivery via folate receptors for the treatment of brain cancer: can the promise deliver? 2017;106(12):3413-20.
93. Liu J, Liu M, Jiang S, Li S, Deng Y, Chen X, Li J, Wang M, Guo J, Ouyang F. Reducing anaphylaxis reactions and enhancing antiarthritic effects of folate-conjugated sinomenine-loaded human serum albumin nanoparticles in experimental inflammation and arthritis. 2024.
94. Kumar SSD, Abrahamse HJIJoMS. Advancement of nanobiomaterials to deliver natural compounds for tissue engineering applications. 2020;21(18):6752.
95. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nature reviews cancer. 2017;17(1):20-37.
96. Sharma B, Crist R, Adiseshaiah P. Nanotechnology as a Delivery Tool for Precision Cancer Therapies. The AAPS Journal. 2017.
97. Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TFJJoP, Pharmacology. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. 2019;71(8):1185-98.
98. Tian H, Zhang T, Qin S, Huang Z, Zhou L, Shi J, Nice EC, Xie N, Huang C, Shen ZJJoh, oncology. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. 2022;15(1):132.
99. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer RJNrdd. Engineering precision nanoparticles for drug delivery. 2021;20(2):101-24.
100. Anselmo AC, Mitragotri SJB, medicine t. Nanoparticles in the clinic: An update. 2019;4(3):e10143.
101. Ganju V, Marx G, Pattison S, Amaro-Mugridge NB, Zhao J-T, Williams BR, MacDiarmid JA, Brahmbhatt HJCCR. Phase I/IIa trial in advanced pancreatic ductal adenocarcinoma treated with cytotoxic drug-packaged, EGFR-targeted nanocells and glycolipid-packaged nanocells. 2024;30(2):304-14.
102. Rosenthal EL, Warram JM, De Boer E, Chung TK, Korb ML, Brandwein-Gensler M, Strong TV, Schmalbach CE, Morlandt AB, Agarwal GJCCR. Safety and tumor specificity of cetuximab-IRDye800 for surgical navigation in head and neck cancer. 2015;21(16):3658-66.
103. Kulkarni JA, Witzigmann D, Thomson SB, Chen S, Leavitt BR, Cullis PR, Van Der Meel RJNn. The current landscape of nucleic acid therapeutics. 2021;16(6):630-43.
104. Tenchov R, Sasso JM, Zhou QAJBc. PEGylated lipid nanoparticle formulations: immunological safety and efficiency perspective. 2023;34(6):941-60.
105. Pardi N, Hogan MJ, Porter FW, Weissman DJNrDd. mRNA vaccines—a new era in vaccinology. 2018;17(4):261-79.
106. Hou X, Zaks T, Langer R, Dong YJNRM. Lipid nanoparticles for mRNA delivery. 2021;6(12):1078-94.

107. Qiao M, Zeng C, Liu C, Lei Z, Liu B, Xie HJN. The advancement of siRNA-based nanomedicine for tumor therapy. 2024;19(21-22):1841-62.
108. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RKJNrCo. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. 2018;15(5):325-40.
109. Van Cutsem E, Tempero MA, Sigal D, Oh D-Y, Fazio N, Macarulla T, Hitre E, Hammel P, Hendifar AE, Bates SEJJoCO. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. 2020;38(27):3185-94.
110. Murphy JE, Wo JY, Ryan DP, Clark JW, Jiang W, Yeap BY, Drapek LC, Ly L, Baglini CV, Blaszkowsky LSJJo. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. 2019;5(7):1020-7.
111. Hanahan D, Weinberg RA. Biological hallmarks of cancer. Holland-Frei Cancer Medicine. 2017;1:1-10.
112. Sun Z, Li XJJoMCB. A promising mesoporous silica carrier material for the diagnosis and treatment of liver diseases: recent research advances. 2025.
113. Kim J, Chin SO, Kim D, Lee Y-SJHN. Porous silicon nanoparticles for cancer bioimaging and therapy: from early designs to modern theranostic platforms. 2025;1(1):14.
114. Wu JJJopm. The enhanced permeability and retention (EPR) effect: the significance of the concept and methods to enhance its application. 2021;11(8):771.
115. Gawne PJ, Ferreira M, Papaluca M, Grimm J, Decuzzi PJNRM. New opportunities and old challenges in the clinical translation of nanotheranostics. 2023;8(12):783-98.
116. Wang C, Di Z, Xiang Z, Zhao J, Li LJNT. Coordination-driven assembly of proteins and nucleic acids in a single architecture for carrier-free intracellular co-delivery. 2021;38:101140.
117. Chen G, Roy I, Yang C, Prasad PN. Nanochemistry and nanomedicine for nanoparticle-based diagnostics and therapy. Chemical reviews. 2016;116(5):2826-85.