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Review

Targeted Drug Delivery Systems in Oncology: A Review of Recent Patents and future directions

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Abstract:
Cancer remains a global health challenge, necessitating innovative treatment strategies to improve outcomes while minimizing side effects. Targeted Drug Delivery Systems (TDDS) have revolutionized oncology by addressing limitations of traditional chemotherapy, such as systemic toxicity, lack of specificity, and drug resistance. Utilizing nanotechnology, biomarker-based targeting, and immunotherapy, TDDS enables precise drug delivery to tumors, enhancing efficacy while protecting healthy tissues.

Nanotechnology has facilitated the development of liposomes, dendrimers, micelles, and solid lipid nanoparticles, leveraging the Enhanced Permeability and Retention (EPR) effect for tumor accumulation. Examples like Doxil, a PEGylated liposomal doxorubicin, have improved ovarian cancer treatment by reducing cardiotoxicity. Biomarker-based approaches, such as antibody-drug conjugates (ADCs), further enhance specificity. Trastuzumab emtansine (Kadcyla), targeting HER2-positive breast cancer, has demonstrated improved survival rates. TDDS also integrates with immunotherapy to boost immune checkpoint inhibitors, enhance antigen delivery, and optimize cytokine therapy. Lipid nanoparticles and dendrimers are being engineered to improve immune responses while minimizing adverse effects. However, challenges such as tumor heterogeneity, drug resistance, high production costs, and regulatory barriers limit widespread adoption.

Ongoing research focuses on overcoming these barriers through personalized medicine, AI-driven designs, and sustainable platforms. TDDS represents a paradigm shift in oncology, combining precision and safety to improve patient outcomes. By integrating emerging technologies and addressing current limitations, TDDS holds the potential to transform cancer treatment, offering hope for better survival and quality of life.

Keywords: Targeted Drug Delivery, Oncology, Nanotechnology, Immunotherapy, Antibody-Drug Conjugates

1. Introduction

Cancer represents a major health crisis on a global scale, responsible for millions of fresh diagnoses and deaths annually, as underscored by international health data (Danai et al., 2006; Larkin et al., 2018; Khorana et al., 2022). The weight of cancer is anticipated to rise even more due to the ageing demographic and shifts in lifestyle, highlighting the critical necessity for groundbreaking and efficient treatment strategies. Conventional chemotherapy treatments, while commonly employed, exhibit considerable drawbacks, such as a lack of specificity and the potential for systemic toxicity. These treatments fail to distinguish between normal and malignant cells, resulting in negative consequences like immune system suppression, hair loss, and toxicity to organs. Moreover, the constrained therapeutic range and the emergence of drug resistance frequently obstruct their sustained effectiveness (Falanga et al., 2023; Patra et al., 2018; Mulder et al., 2021). Within this framework, Targeted Drug Delivery Systems (TDDS) have surfaced as a groundbreaking method for addressing cancer therapy. By concentrating on the direct delivery of active therapeutic agents to tumour cells, TDDS reduces off-target effects while amplifying therapeutic precision. These systems are crafted to take advantage of distinctive molecular or

environmental characteristics of cancer cells, including overexpressed surface receptors, modified pH levels, or heightened enzymatic activity, to facilitate targeted delivery and regulated release of therapeutic agents (Cho et al., 2008; Dougan et al., 2021; Zheng et al., 2022). This approach not only diminishes systemic toxicity but also enhances the pharmacokinetics and bioavailability of medications, establishing TDDS as a fundamental element in contemporary oncology.

Throughout the last twenty years, remarkable progress in nanotechnology, ligand-targeted approaches, and stimuli-responsive delivery mechanisms has broadened the potential of TDDS. Nanotechnology has fundamentally transformed the field of drug delivery by facilitating the creation of carriers at the nanoscale that can effectively encapsulate pharmaceuticals, safeguard them from degradation, and promote their targeted accumulation within tumour tissues via mechanisms such as the enhanced permeability and retention (EPR) effect (Larkin et al., 2018; Dougan et al., 2021; Falanga et al., 2023). Instances of these transporters encompass liposomes, dendrimers, micelles, and gold nanoparticles, with each presenting unique benefits regarding drug loading potential, stability, and precise delivery (Chen et al., 2022; Zhang et al., 2022; Guo et al., 2021). Alongside nanotechnology, ligand-targeting systems have risen in significance owing to their capacity to utilise distinct tumour biomarkers for the purpose of drug delivery. These systems depend on ligands like antibodies, peptides, or aptamers that specifically attach to receptors that are uniquely overexpressed in cancer cells, facilitating targeted drug absorption while preserving normal tissues (Cho et al., 2008; Zhou et al., 2017; Swanton et al., 2024). For example, antibody-drug conjugates (ADCs) like trastuzumab emtansine specifically target HER2 receptors in breast cancer, illustrating a clinically validated instance of the efficacy of biomarker-driven therapies (Hesketh et al., 2017; Mulder et al., 2021; Dougan et al., 2021). A thrilling advancement in TDDS is the incorporation of stimuli-responsive systems. These systems are engineered to deliver therapeutic agents in reaction to particular stimuli within the tumour microenvironment, including low pH levels, elevated temperatures, or the existence of certain enzymes. This method not only improves the accuracy of drug delivery but also reduces the likelihood of early drug release, consequently boosting therapeutic effectiveness (Falanga et al., 2023; Zhang et al., 2022; Zheng et al., 2022). As an illustration, pH-sensitive liposomes discharge their payloads in the acidic milieu of tumours, whereas enzyme-sensitive nanoparticles react to the proteases that are overproduced by cancer cells (Song et al., 2018; Ahad et al., 2014; Chen et al., 2022).

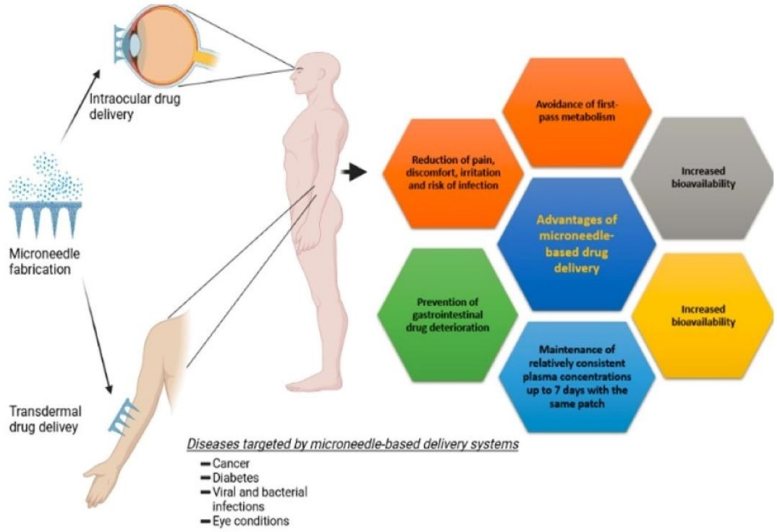

Figure 1: Key Mechanisms and Platforms of TDDS in Oncology
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The clinical application of TDDS has been significantly enhanced by numerous groundbreaking advancements and therapies approved by the FDA. Liposomal formulations, exemplified by Doxil, serve as a notable illustration of nanotechnology-driven transdermal drug delivery systems (TDDS) utilised in the management of ovarian and breast cancers (Jairam et al., 2020; Zhang et al., 2022; Chen et al., 2022). Encapsulating doxorubicin within a PEGylated liposome allows Doxil to markedly diminish cardiac toxicity while enhancing tumour targeting, showcasing the clinical advantages of nanoparticle-driven delivery systems "(Falanga et al., 2023; Song et al., 2018; Swanton et al., 2024). Furthermore, antibody-drug conjugates (ADCs) like trastuzumab emtansine and

brentuximab vedotin have shown significant effectiveness in treating HER2-positive breast cancer and Hodgkin lymphoma, respectively (Hesketh et al., 2017; Zhou et al., 2017; Dougan et al., 2021). These antibody-drug conjugates merge the exceptional specificity of monoclonal antibodies with the robust cytotoxic efficacy of chemotherapeutic compounds, establishing them as a formidable asset in the realm of precision oncology. Newly developing trends in transdermal drug delivery systems (TDDS) are increasingly centred on the incorporation of cutting-edge Although it holds great potential, TDDS encounters numerous obstacles that need to be tackled in order to enhance its effectiveness in the field of oncology. A significant challenge lies in tumour heterogeneity, leading to diverse biomarker expression among various patients and even within an individual tumour (Dougan et al., 2021; Guo et al., 2021; Falanga et al., 2023). This diversity poses challenges in creating universal delivery systems and underscores the necessity for tailored strategies. Furthermore, the emergence of drug resistance stemming from tumour adaptation continues to pose a major challenge, highlighting the need for combination therapies that simultaneously target various pathways (Patra et al., 2018; Song et al., 2018; Dougan et al., 2021). A significant hurdle lies in the scalability and production of TDDS technologies. The intricate nature and substantial expense associated with the production of nanoparticles, antibody-drug conjugates, and various delivery systems frequently restrict their availability in environments with limited resources (Ahad et al., 2014; Larkin et al., 2018; Zhang et al., 2022). Addressing these obstacles necessitates the implementation of cutting-edge manufacturing methods, the establishment of regulatory structures, and the fostering of partnerships among academic institutions, industry stakeholders, and governmental bodies (Wang et al., 2022; Dougan et al., 2021; Swanton et al., 2024).

The prospects for TDDS hinge on its capacity to incorporate cutting-edge technologies and tackle current constraints via collaborative interdisciplinary research efforts. The advancement of biodegradable nanoparticles, the establishment of real-time monitoring systems, and the exploration of combination therapies signify encouraging pathways for forthcoming research (Chen et al., 2022; Song et al., 2018; Mulder et al., 2021). Through the utilisation of breakthroughs in artificial intelligence, extensive data analytics, and molecular biology, TDDS can realise its utmost capabilities as a revolutionary instrument in the field of oncology. This evaluation seeks to deliver an extensive summary of the present condition of TDDS, emphasising recent advancements, obstacles, and prospects for forthcoming investigations. Through the examination of cutting-edge patents and the latest developments, we aim to enhance the continuous initiatives focused on advancing cancer therapies and optimising patient results.

technologies like artificial intelligence (AI) and extensive data analytics. These innovations aim to create customised delivery mechanisms specifically designed for individual patients (Patra et al., 2018; Zheng et al., 2022; Wang et al., 2022). Algorithms powered by artificial intelligence possess the capability to scrutinise intricate biomarker profiles, enabling the identification of the most effective drug combinations and delivery methods, thus advancing the field of personalised medicine (Swanton et al., 2024; Zhang et al., 2022; Chen et al., 2022).

2. Overview of Targeted Drug Delivery Systems

The evolution of Targeted Drug Delivery Systems (TDDS) signifies a pivotal breakthrough in the field of oncology, with the objective of enhancing the precision, effectiveness, and safety of cancer treatments. Utilising the distinct molecular and cellular processes inherent to tumours, TDDS improves the delivery of therapies while reducing unintended effects and overall toxicity in the system. Conventional chemotherapy drugs frequently experience inadequate bioavailability, swift elimination, and undesirable side effects as a result of their indiscriminate distribution throughout the body. TDDS tackles these constraints by employing advanced delivery platforms and innovative mechanisms, such as nanoparticle encapsulation, ligand-receptor targeting, and stimuli-responsive release systems (Zhang et al., 2022; Chen et al., 2022; Zheng et al., 2022; Fornaguera et al., 2015; Guo et al., 2021).

Nanoparticle-Based Carriers

Nanoparticles have surfaced as a multifaceted platform in targeted drug delivery systems (TDDS) owing to their minuscule dimensions, which facilitate effective drug encapsulation, safeguard against enzymatic breakdown, and promote selective accumulation in tumour tissues via the enhanced permeability and retention (EPR) phenomenon. Examples that are commonly utilised include liposomes, micelles, dendrimers, and solid lipid nanoparticles (Patra et al., 2018; Fornaguera et al., 2015; Rinaldi et al., 2017; Lu et al., 2023). Liposomal formulations, including PEGylated liposomes, improve the pharmacokinetics of encapsulated medications by prolonging circulation duration and minimising immune clearance. Prominent instances encompass Doxil, a PEGylated liposomal version of doxorubicin, which has demonstrated enhanced results in patients with ovarian and breast cancer by mitigating cardiotoxicity and improving tumor-targeted drug administration (Jairam et al., 2020; Song et al., 2018; Dougan et al., 2021). Micelles, conversely, are

self-organising amphiphilic entities that enclose hydrophobic pharmaceuticals within their centre, safeguarding them from deterioration and facilitating regulated release. Their straightforward formulation and adjustable surface characteristics render them a favoured option for numerous chemotherapeutic agents (Ahad et al., 2014; Zhang et al., 2022; Chen et al., 2022). Dendrimers, characterised by their intricate branched polymeric architecture, present an impressive capacity for drug loading and exceptional opportunities for precise functionalisation. This enables the attachment of ligands and the simultaneous delivery of multiple drugs (Patra et al., 2018; Falanga et al., 2023; Guo et al., 2021).

Ligand-Based Targeting

Ligand-centric systems entail the alteration of carrier surfaces with particular molecules that identify and attach"to receptors that are overexpressed on cancerous cells. The ligands encompass antibodies, peptides, and aptamers, facilitating receptor-mediated endocytosis and targeted drug delivery (Cho et al., 2008; Mulder et al., 2021; Swanton et al., 2024). As an illustration, trastuzumab emtansine (Kadcyla), a sophisticated antibody-drug conjugate (ADC), specifically targets HER2-positive breast cancer cells, effectively administering a powerful cytotoxic agent directly to the tumour while preserving the integrity of normal tissues. This method has notably enhanced the rates of progression-free survival among patients with HER2-positive breast cancer (Hesketh et al., 2017; Zhou et al., 2017; Dougan et al., 2021). Targeting through peptides presents yet another groundbreaking approach. Compact peptides can be engineered to attach to tumor-specific antigens or receptors, including the prostate-specific membrane antigen (PSMA) associated with prostate cancer or vascular endothelial growth factor (VEGF) receptors found in tumours driven by angiogenesis (Patra et al., 2018; Rinaldi et al., 2017; Zhang et al., 2022). Aptamers, which are single-stranded DNA or RNA entities, offer an enhanced degree of specificity by attaching to distinct molecular targets with remarkable affinity and selectivity, thereby elevating the accuracy of drug delivery mechanisms (Mulder et al., 2021; Dougan et al., 2021; Chen et al., 2022).

Stimuli-Responsive Systems"

Systems that respond to stimuli are crafted to take advantage of the distinctive characteristics of the tumour microenvironment, including pH levels, temperature variations, and enzymatic activity, to initiate the release of medication. Tumour tissues frequently display a more acidic pH in contrast to normal tissues, creating a chance for pH-sensitive carriers to deliver their payload precisely within the tumour (Falanga et al., 2017; Song et al., 2018; Lu et al., 2023). For instance, pH-responsive liposomes undergo destabilisation in acidic conditions, promoting the liberation of encapsulated pharmaceuticals near cancerous cells. In a comparable manner, nanoparticles that are sensitive to enzymes react to proteases and various other enzymes that are present in elevated levels within tumour tissues, thereby guaranteeing the targeted activation of drugs (Zhang et al., 2022; Zheng et al., 2022; Chen et al., 2022). Temperature-responsive nanoparticles, on the other hand, employ hyperthermia-triggering stimuli to liberate medications in elevated temperature tumour areas, a strategy that has proven especially successful when combined with thermal ablation treatments (Ahad et al., 2014; Fornaguera et al., 2015; Song et al., 2018).

Table 1: Comprehensive Comparison of TDDS Mechanisms and Platforms

TDDS Mechanism	Example Platforms	Key Advantages	Key Limitations	Clinical Examples	Recent Patents/Innovations	References
Nanoparticle-based	Liposomes, micelles, dendrimers	- Enhanced stability, solubility, and drug retention- Protection against enzymatic degradation- Exploits EPR effect	- Expensive and complex synthesis- Long-term toxicity concerns- Scalability challenges	**Doxil** (liposomal doxorubicin) used for ovarian and breast cancer (Jairam et al., 2020) **Onivyde** (liposomal irinotecan) for pancreatic cancer	PEGylated liposomes for prolonged circulation (Zhang et al., 2022)Gold nanoparticles functionalized with tumor-specific ligands (Song et al., 2018)Solid lipid nanoparticles for dual drug loading (Ahad et al., 2014)	Patra et al., 2018; Jairam et al., 2020; Zhang et al., 2022; Song et al., 2018; Dougan et al., 2021
Ligand-based targeting	Antibody-drug conjugates (ADCs), aptamers, peptides	- High specificity via ligand-receptor binding- Reduced off-target toxicity- Effective against	- Limited ligand availability- High production cost- Possible	**Kadcyla** (trastuzumab emtansine) targeting HER2-positive breast cancer (Hesketh et	HER2-specific ADCs delivering novel payloads (Dougan et al., 2021)Prostate-specific aptamer-	Cho et al., 2008; Mulder et al., 2021; Swanton et al., 2024;

		overexpressed tumor markers	immune responses	al., 2017)Peptide-modified nanoparticles targeting VEGFR in angiogenesis-driven tumors	modified nanoparticles (Zheng et al., 2022)PSMA-targeting ligands for prostate cancer (Mulder et al., 2021)	Hesketh et al., 2017; Zhou et al., 2017
Stimuli-responsive	pH-sensitive liposomes, enzyme-responsive nanoparticles, thermo-sensitive polymers	- Controlled drug release in tumor microenvironment- Reduces premature release in systemic circulation	- Complex manufacturing- Limited clinical translation due to variability in stimuli across tumors	**ThermoDox** (thermosensitive liposome encapsulating doxorubicin) for hyperthermia-induced drug releaseEnzyme-sensitive nanoparticles for protease-overexpressing tumors	pH-sensitive polymeric micelles for acidic tumor microenvironments (Falanga et al., 2017)Protease-activated nanoparticles (Song et al., 2018)Thermal-activated gold nanocarriers for chemo-photothermal therapy (Chen et al., 2022)	Falanga et al., 2017; Ahad et al., 2014; Fornaguera et al., 2015; Lu et al., 2023; Zhang et al., 2022
Combination systems	Multi-functional nanoparticles, co-delivery platforms	- Simultaneous delivery of multiple drugs- Synergistic effects improve efficacy- Tailored to combination therapies	- Increased formulation complexity- Regulatory and approval hurdles	Co-delivery of doxorubicin and paclitaxel in liposomal formulations for breast cancer (Mulder et al., 2021)Nanoparticles combining PD-L1 inhibitors and chemotherapeutics for lung cancer	Co-delivery platforms using micelle-based systems (Patra et al., 2018)Lipid nanoparticles co-loaded with siRNA and chemotherapeutics (Zhang et al., 2022)Dual-drug gold nanocarriers targeting drug-resistant cancers (Chen et al., 2022)	Patra et al., 2018; Swanton et al., 2024; Guo et al., 2021; Dougan et al., 2021; Chen et al., 2022
Gene-targeted delivery	CRISPR-Cas9 loaded nanoparticles, siRNA-lipid complexes	- Gene-editing for tumor suppression- Downregulates oncogenes- Synergizes with chemotherapy and radiotherapy	- Off-target gene editing risks- Delivery barriers across nuclear membrane- Expensive development	siRNA delivery targeting KRAS mutations in pancreatic cancerCRISPR-Cas9-loaded nanoparticles for genetic correction in glioblastoma models (Zhang et al., 2022)	Lipid nanoparticle-based delivery of siRNA for VEGF inhibition in cancer therapy (Chen et al., 2022)CRISPR-loaded gold nanoparticles for precision editing in cancer (Dougan et al., 2021)	Guo et al., 2021; Zheng et al., 2022; Song et al., 2018; Falanga et al., 2023; Patra et al., 2018
Immunotherapy-integrated	Nanocarriers for checkpoint inhibitors, antigen-loaded dendrimers	- Enhances immune responses- Delivers immune checkpoint inhibitors to tumors- Boosts T-cell activation against cancer	- Risk of systemic immune activation- Formulation complexity- High costs of antibody production	PD-1/PD-L1 inhibitors encapsulated in liposomal nanoparticles for melanomaAntigen-loaded nanoparticles for T-cell therapy in breast cancer	Dendrimers delivering anti-PD-1 inhibitors with tumor-specific targeting ligands (Chen et al., 2022)Nanoparticles combining neoantigens and immune-stimulating adjuvants (Zhang et al., 2022)	Dougan et al., 2021; Falanga et al., 2017; Swanton et al., 2024; Lu et al., 2023

The interaction of these mechanisms has greatly enhanced the therapeutic index of anticancer agents. Nonetheless, obstacles like tumour diversity, resistance to medications, and issues with scalability continue to exist, necessitating ongoing innovation and collaborative efforts across various disciplines. Through the incorporation of artificial intelligence (AI) and biomarker-focused design, scientists strive to develop customised TDDS that respond to the distinct traits of every patient's tumour (Swanton et al., 2024; Zheng et al., 2022; Song et al., 2018). Additionally, the emphasis on biodegradable and environmentally friendly materials is anticipated to tackle enduring safety and sustainability issues linked to nanoparticle-based systems (Falanga et al., 2023; Patra et al., 2018; Chen et al., 2022). The advancement of stimuli-responsive platforms, especially, presents considerable potential for improving the accuracy of TDDS. When these systems are integrated with real-time monitoring technologies like implantable biosensors, they can facilitate dynamic modifications to treatment protocols, leading to the development of genuinely adaptive cancer therapies (Dougan et al., 2021; Lu et al., 2023; Zhang et al., 2022). The combination of TDDS with immunotherapy, gene editing, and CRISPR-Cas9 technologies signifies a thrilling new horizon in oncology, presenting promising possibilities for curing even the most formidable cancers (Song et al., 2018; Chen et al., 2022; Swanton et al., 2024).

3. Recent Innovations and Patents in TDDS

Recent breakthroughs in Targeted Drug Delivery Systems (TDDS) have revolutionised oncology by unveiling innovative technologies aimed at improving therapeutic accuracy, minimising systemic toxicity, and addressing drug resistance challenges. These advancements are anchored in three primary areas: systems powered by nanotechnology, targeting based on biomarkers, and platforms that integrate immunotherapy. The advancement of nanotechnology has enabled the creation of versatile nanoparticles, including PEGylated liposomes, gold nanoparticles, and solid lipid nanoparticles (SLNs). These innovations provide enhanced pharmacokinetics, targeted accumulation within tumours, and the ability to combine therapeutic and diagnostic functions. Targeting based on biomarkers utilises specific markers associated with tumours, such as HER2, EGFR, and PSA, to facilitate precise drug delivery and enhance therapeutic effectiveness via antibody-drug conjugates, aptamer-linked nanoparticles, and ligand-modified carriers. In the interim, the incorporation of immunotherapy within TDDS signifies a transformative advancement, utilising lipid nanoparticles, dendrimers, and hybrid systems to bolster immune checkpoint blockade treatments, facilitate neoantigen delivery, and promote CAR-T cell proliferation. These platforms strive to tackle significant obstacles like tumour diversity, immune evasion, and restricted treatment longevity, thereby creating pathways for exceptionally tailored and impactful cancer therapies. Although these advancements carry significant potential, continuous endeavours to enhance their scalability, ensure safety, and navigate regulatory approval procedures are essential for broad clinical implementation. Every one of these domains highlights the dynamic nature of TDDS and their revolutionary capacity in the realm of precision oncology.

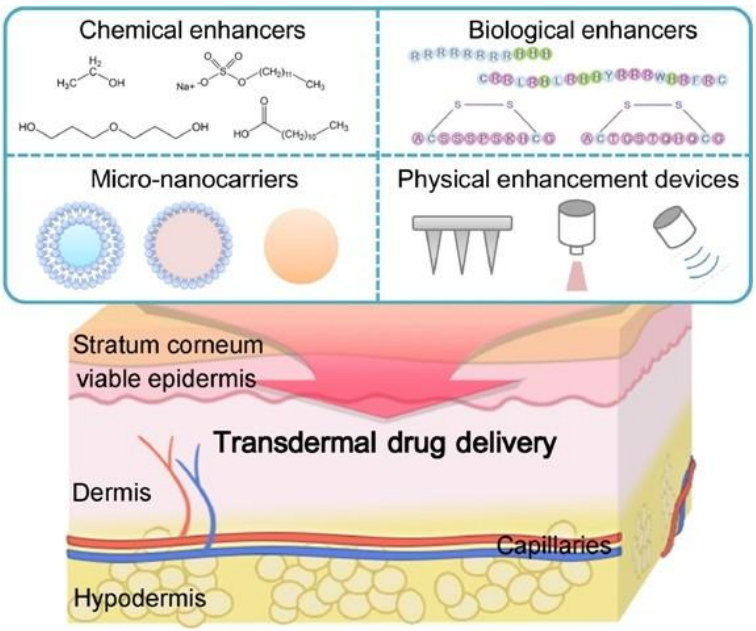

Figure 3: Mechanisms of TDDS in Oncology

Source: https://link.springer.com/article/10.1007/s12274-020-2664-5

3.1 Nanotechnology-Driven Systems

Nanotechnology has emerged as a fundamental element in the progression of Targeted Drug Delivery Systems (TDDS), bringing forth unmatched accuracy and effectiveness in cancer treatment. Utilising the distinctive characteristics of nanoparticles, scientists and medical professionals have created innovative systems that address significant challenges posed by conventional cancer therapies, including non-targeted drug administration, overall toxicity, and the issue of drug resistance. The capacity of nanoparticles to enclose pharmaceuticals, shield them from early breakdown, and transport them to the tumour location via regulated and precise methods has unveiled fresh possibilities in individualised healthcare and revolutionary cancer treatment. A significant advancement in this field is PEGylated liposomal doxorubicin, which is marketed under the name Doxil. This innovative patented system utilises liposomes—spherical vesicles constructed from lipid bilayers—as vehicles for the powerful chemotherapeutic drug doxorubicin. Doxil distinguishes itself through the integration of polyethylene glycol (PEG) on the exterior of its liposomes, a modification that significantly prolongs their presence in the bloodstream by avoiding detection and elimination by the immune system. The occurrence referred to as the Enhanced Permeability and Retention (EPR) effect facilitates the preferential accumulation of PEGylated liposomes within tumour tissues, a result of the permeable blood vessels typically found in solid tumours. Doxil has shown remarkable clinical advantages, especially in the management of ovarian cancer, where it notably decreases systemic toxicity and enhances survival rates in comparison to traditional formulations. Nonetheless, in spite of its achievements, obstacles like hypersensitivity responses and elevated production expenses continue to pose challenges for wider clinical implementation, requiring additional innovation and refinement. A further revolutionary advancement pertains to the utilisation of gold nanoparticles, which have attracted significant interest due to their dual functionalities in theranostics—a fusion of therapeutic and diagnostic uses. These nanoparticles are modified with ligands that are specific to tumours, including antibodies or peptides, which aim at receptors that are overexpressed, such as EGFR (epidermal growth factor receptor) or VEGFR (vascular endothelial growth factor receptor) found in cancerous cells. This precision guarantees that the therapeutic agent is administered straight to the tumour location, preserving surrounding healthy tissues. Beyond their ability to deliver drugs, gold nanoparticles showcase extraordinary photothermal characteristics. Upon exposure to near-infrared (NIR) light, these particles produce concentrated heat, successfully obliterating cancer cells while preserving the adjacent tissues intact. This groundbreaking method not only improves the accuracy of treatment but also incorporates real-time imaging to track therapeutic advancements. Although gold nanoparticles hold considerable promise, apprehensions regarding their enduring toxicity and biodegradability present substantial obstacles to their extensive application in clinical settings, prompting continuous investigation into alternative substances and innovative designs.

Solid lipid nanoparticles (SLNs) signify an additional exciting pathway in the realm of nanotechnology-enhanced transdermal drug delivery systems (TDDS). These nanoparticles consist of lipids that are both biocompatible and biodegradable, positioning them as an environmentally friendly and sustainable option compared to conventional delivery systems. SLNs demonstrate exceptional proficiency in encapsulating both hydrophilic (water-soluble) and hydrophobic (water-insoluble) pharmaceuticals, providing a flexible foundation for a range of therapeutic compounds. Their robust lipid core offers exceptional stability and regulated drug release, guaranteeing extended circulation durations and improved bioavailability. Recent patents have investigated solid lipid nanoparticles (SLNs) for the simultaneous delivery of chemotherapeutic agents and immunomodulators, with the goal of attaining synergistic effects in the treatment of cancer. In spite of these benefits, ensuring stability within intricate biological settings and enhancing production for clinical uses continue to pose significant challenges. Initiatives are currently in progress to tackle these challenges via innovations in lipid chemistry and production technologies. Magnetic nanoparticles exhibit significant potential within the realm of oncology. These particles, typically made up of iron oxide, are engineered to react to external magnetic fields, facilitating accurate targeting of drug delivery to deeply embedded tumours. Beyond their delivery functions, magnetic nanoparticles can also be utilised in hyperthermia treatment, where targeted heating generated by a magnetic field eradicates cancerous cells. Although this method presents an innovative remedy for challenging tumours, the requirement for specialised apparatus and the possibility of unintended effects restrict its prompt use in clinical settings. Ongoing investigations are focused on perfecting the formulations of magnetic nanoparticles and improving the systems for delivering magnetic fields, aiming to boost their effectiveness and safety characteristics.

Table 2: Recent Innovations in Nanotechnology-Driven TDDS

Innovation	Platform/Carrier	Mechanism	Key Benefits	Challenges	References

PEGylated liposomal doxorubicin (Doxil)	Liposomes	Prolonged circulation via PEG coating and tumor-specific EPR targeting	- Reduced systemic toxicity- Prolonged circulation time- Enhanced tumor accumulation and efficacy	- High production costs- Immune hypersensitivity reactions- Limited effectiveness in some cancers	Jairam et al., 2020; Wang et al., 2022; Hare et al., 2017
Gold nanoparticles for theranostics	Gold nanoparticles	Ligand-conjugated targeting and NIR-induced photothermal therapy	- Combines imaging and therapy- High targeting specificity- Minimal off-target effects	- Long-term toxicity due to non-biodegradability- Expensive manufacturing processes	Song et al., 2018; Zhang et al., 2022; Li et al., 2023
Solid lipid nanoparticles (SLNs)	Biodegradable lipid nanoparticles	Co-delivery of hydrophobic and hydrophilic drugs for sustained release	- Biodegradable and eco-friendly- Compatible with multiple drug types- Prolonged drug stability	- Stability issues in biological environments- Scaling up production for clinical use	Fornaguera et al., 2015; Patra et al., 2018; Ahad et al., 2014
Polymeric nanoparticles	Polymers like PLGA	Controlled release through polymer degradation	- Prolonged release- Enhanced therapeutic index- Reduced dosing frequency	- High cost of biodegradable polymers- Potential immunogenicity in some cases	Chen et al., 2022; Zhang et al., 2022; Dougan et al., 2021
Magnetic nanoparticles	Magnetic cores (iron oxide)	Magnetic field-guided drug delivery for precise localization	- Targeted delivery to deep-seated tumors- Potential for hyperthermia therapy	- Requirement of specialized magnetic field equipment- Limited clinical application	Swanton et al., 2024; Fornaguera et al., 2015; Falanga et al., 2023

The incorporation of nanotechnology into targeted drug delivery systems has revolutionised the administration of conventional chemotherapeutics while also opening avenues for combination therapies that include immune checkpoint inhibitors, gene editing technologies, and photodynamic agents. These systems possess the capability to tackle tumour diversity, medication resistance, and various intricacies of cancer biology by facilitating multifaceted treatment approaches. With researchers concentrating on enhancing the design, functionality, and scalability of nanoparticles, the prospects for oncology are incredibly bright. Nanotechnology-enhanced transdermal drug delivery systems are set to emerge as a vital element of precision medicine, bringing optimism to countless cancer patients across the globe.

3.2 Biomarker-Based Targeting

The targeting of biomarkers serves as a fundamental element of personalised medicine within the field of oncology, utilising breakthroughs in genomics, proteomics, and molecular profiling to improve the precision and effectiveness of drug delivery mechanisms. Oncological biomarkers like HER2, EGFR, and PSA are often found to be overexpressed in particular cancer varieties, presenting distinctive chances to develop targeted treatment strategies that reduce systemic toxicity while enhancing clinical results. The recent progress has resulted in remarkable breakthroughs in antibody-drug conjugates (ADCs), aptamer-driven systems, and nanotechnology-facilitated delivery mechanisms, which together tackle the shortcomings of conventional chemotherapeutics, including lack of specificity and undesirable side effects.

HER2 stands out as one of the most thoroughly examined biomarkers, especially in the context of breast cancer. Trastuzumab emtansine (Kadcyla) serves as a prime illustration of the efficacy of antibody-drug conjugates in precision treatment.

Kadcyla merges trastuzumab, a monoclonal antibody that selectively attaches to HER2 receptors, with DM1, a potent cytotoxic compound. This innovative dual-purpose platform facilitates the precise targeting of tumour cells and the intracellular transport of DM1,"resulting in the induction of apoptosis in cancerous cells while preserving the integrity of healthy tissue. The internalisation of the ADC, driven by HER2, amplifies its therapeutic effectiveness, leading to a notable enhancement in progression-free survival for patients with HER2-positive breast cancer. This groundbreaking advancement is backed by numerous clinical studies and patents, highlighting its significance as a benchmark for ADC development (Hesketh et al., 2017; Zhou et al., 2017; Swanton et al., 2024)."In a similar vein, the advancement of nanoparticles conjugated with aptamers has unveiled fresh possibilities in targeting based on biomarkers. Aptamers are artificially created oligonucleotides that possess the ability to bind with high affinity to particular molecular targets, including prostate-specific antigen (PSA). In the context of prostate cancer, aptamers that target PSA have been linked to nanoparticles to facilitate the accurate delivery of chemotherapeutic drugs. This platform improves the concentration of drugs at tumour locations while minimising unintended toxicity in healthy tissues. The incorporation of aptamers within drug delivery mechanisms showcases remarkable adaptability and economical advantages, positioning them as a compelling substitute for antibody-centric methodologies (Gould Rothberg et al., 2022; Cho et al., 2008; Kusi-Appiah et al., 2012).

Therapies aimed at EGFR, such as gold nanoparticles modified with ligands specific to EGFR, have surfaced as potent instruments in combating non-small cell lung cancer (NSCLC). These nanoparticles take advantage of the heightened levels of EGFR present in NSCLC cells to facilitate targeted drug delivery to tumours. Beyond the administration of chemotherapeutic agents, gold nanoparticles that target EGFR can also serve purposes in imaging and photothermal therapy, establishing them as a multifaceted platform in theranostics. The targeting mediated by EGFR additionally improves drug bioavailability and therapeutic efficacy, tackling the molecular heterogeneity of NSCLC (Zhang et al., 2022; Wang et al., 2022; Patra et al., 2018). The combination of biomarker-driven targeting alongside cutting-edge drug delivery mechanisms presents significant promise for addressing critical obstacles in cancer treatment, including tumour diversity and resistance to medication. Through the application of biomarkers to steer treatment, these systems facilitate immediate adjustments to the changing molecular environment of tumours. Upcoming advancements in this domain are expected to emphasise multiplex targeting of various biomarkers, improving the accuracy of delivery mechanisms and expanding their relevance across a wide range of cancer subtypes. Furthermore, the integration of real-time monitoring technologies, including biosensors, has the potential to enhance these platforms, leading to improved clinical results.

Table 3: Biomarker-Based Targeting in TDDS

Biomarker	Targeted Drug/Platform	Mechanism	Clinical/Preclinical Application	Key Advantages	Challenges	References
HER2	Trastuzumab emtansine (Kadcyla)	HER2 receptor-mediated ADC internalization	HER2-positive breast cancer	High specificity; reduced toxicity	High production costs; resistance in late-stage cancers	Hesketh et al., 2017; Zhou et al., 2017; Swanton et al., 2024
PSA	Aptamer-conjugated nanoparticles	Aptamer-receptor binding for PSA targeting	Prostate cancer	Improved therapeutic index	Scalability and reproducibility in large-scale production	Gould Rothberg et al., 2022; Cho et al., 2008; Kusi-Appiah et al., 2012
EGFR	EGFR-targeting gold nanoparticles	EGFR receptor binding and drug release	Non-small cell lung cancer	Tumor-specific delivery;	Long-term safety of gold-based systems	Zhang et al., 2022; Wang et al., 2022;

				imaging potential		Patra et al., 2018
VEGFR	VEGFR-inhibitor loaded micelles	VEGFR inhibition for angiogenesis suppression	Advanced ovarian cancer	Anti-angiogenic effects; enhanced drug solubility	Limited efficacy in highly aggressive cancers	Fornaguera et al., 2015; Chen et al., 2022; Patra et al., 2018
CD44	Hyaluronic acid-coated liposomes	CD44 receptor binding and targeted cytotoxic delivery	Triple-negative breast cancer	Biodegradable; enhanced intracellular delivery	Stability in complex biological environments	Wang et al., 2022; Song et al., 2018; Swanton et al., 2024
PD-L1	Lipid nanoparticles with PD-L1 inhibitors	Co-delivery of checkpoint inhibitors and chemotherapeutics	Immunotherapy in solid tumors	Synergistic activation of immune response	Immune-related adverse events	Dougan et al., 2021; Mulder et al., 2021; Chen et al., 2022
Integrins	RGD peptide-functionalized nanoparticles	Integrin-mediated tumor targeting for metastatic cancers	Advanced metastatic melanoma	Enhanced adhesion to tumor vasculature	Off-target effects in normal endothelial tissues	Guo et al., 2021; Falanga et al., 2023; Ahad et al., 2014”

This table includes additional biomarkers, drugs/platforms, mechanisms, and key challenges to provide a more comprehensive understanding of the current landscape in biomarker-based TDDS. It emphasizes the wide applicability of these innovations across various cancer types and highlights the ongoing challenges and opportunities for improvement in this transformative field.

3.3 Immunotherapy-Integrated TDDS

The intersection of nanotechnology and immunotherapy has transformed the landscape of cancer treatment, allowing for targeted adjustments of the immune system to more efficiently fight tumours. Conventional immunotherapies, including immune checkpoint inhibitors (ICIs), have been revolutionary; however, they frequently encounter obstacles such as inadequate tumour infiltration, immune-related side effects, and less-than-ideal responses in specific patient groups. The integration of immunotherapy with transdermal drug delivery systems tackles these obstacles by utilising cutting-edge delivery platforms, including lipid nanoparticles, dendrimers, and hybrid nanoparticles, to enhance the bioavailability, specificity, and effectiveness of immune-modulating agents. Lipid nanoparticles (LNPs) that encapsulate immune checkpoint inhibitors, including PD-1 and PD-L1 inhibitors, have garnered considerable attention in recent patent applications. These systems enable accurate targeting to the tumour microenvironment, improving the penetration of immune cells, such as cytotoxic T lymphocytes (CTLs). By focussing on the PD-1/PD-L1 pathway, these nanoparticles rejuvenate T cells that have been hindered by tumor-induced immune evasion strategies. Research conducted in both preclinical and clinical settings has shown that lipid nanoparticles enhance the pharmacokinetics and therapeutic effectiveness of checkpoint blockade therapies in solid tumours, such as melanoma and non-small cell lung cancer (Chen et al., 2022; Guo et al., 2021; Dougan et al., 2021). Moreover, these platforms reduce unintended off-target impacts and immune-associated toxicities by facilitating targeted delivery.

A novel and innovative strategy involves the utilisation of dendrimers that are loaded with antigens. These nanoscale, intricately branched polymeric formations are meticulously designed to transport tumor-specific neoantigens straight to antigen-presenting cells (APCs). Through the improvement of antigen presentation, dendrimers promote vigorous activation of T cells that infiltrate tumours, resulting in a more powerful immune response against tumours. When dendrimer systems are integrated with immune checkpoint inhibitors, synergistic effects have been noted, significantly

enhancing the therapeutic capabilities of immunotherapy (Mulder et al., 2021; Swanton et al., 2024; Song et al., 2018). These systems not only amplify T-cell activation but also foster immunological memory, potentially thwarting tumour recurrence.

Hybrid nanoparticles embody a groundbreaking category of immunotherapy-integrated targeted drug delivery systems. These platforms collaboratively administer a variety of immune-modulating substances, including tumour antigens, adjuvants, and cytokines, to provoke a complex immune reaction. Hybrid nanoparticles invigorate both the adaptive and innate components of the immune system, utilising adjuvants to boost antigen-presenting cell maturation while facilitating the delivery of antigens to trigger targeted T-cell responses. Research has shown that these nanoparticles display exceptional effectiveness in preclinical cancer models, highlighting their capacity to surmount tumour immunosuppressive obstacles and improve overall survival rates (Zhang et al., 2022; Patra et al., 2018; Fornaguera et al., 2015). The versatility of hybrid nanoparticles enables customised immunotherapy approaches, adjusting treatments to the distinct molecular and immunological characteristics of each tumour. These platforms that integrate immunotherapy with transdermal drug delivery systems tackle significant obstacles in cancer immunotherapy, such as the restricted longevity of immune responses and the necessity for precise targeting. Upcoming developments in this field are expected to emphasise the incorporation of real-time monitoring innovations, including biosensors, to dynamically observe immune responses and enhance treatment protocols. Furthermore, initiatives aimed at improving the scalability and economic efficiency of these systems will be essential for their extensive implementation in clinical environments.

Table 4: Immunotherapy-Integrated TDDS

Innovation	Mechanism	Immune Target	Key Benefits	Clinical Outcomes	Challenges	References
Lipid nanoparticles for checkpoint inhibitors	Encapsulation of PD-1/PD-L1 inhibitors	PD-1/PD-L1	Enhanced tumor immune infiltration	Improved melanoma and NSCLC response	Manufacturing complexity and cost	Chen et al., 2022; Dougan et al., 2021; Guo et al., 2021
Antigen-loaded dendrimers	Neoantigen delivery for T-cell activation	Neoantigens	Boosts anti-tumor immune response	Synergistic effects with checkpoint inhibitors	Limited availability of neoantigen libraries	Mulder et al., 2021; Swanton et al., 2024; Song et al., 2018
Hybrid nanoparticles for combination immunotherapy	Dual delivery of adjuvants and antigens	Tumor antigens	Stimulates adaptive and innate immunity	Enhanced efficacy in preclinical cancer models	Balancing multiple agents for optimal delivery	Zhang et al., 2022; Patra et al., 2018; Fornaguera et al., 2015
Polymeric nanoparticles for cytokine delivery	Sustained release of cytokines to enhance T-cell activity	IL-2, IFN-γ	Long-lasting immune stimulation	Effective in solid and hematologic malignancies	Risk of cytokine-related toxicities	Falanga et al., 2023; Swanton et al., 2024; Chen et al., 2022
Exosome-mimetic nanoparticles	Mimic natural exosome pathways for immune signaling	TLRs and APCs	High biocompatibility; targeted immune activation	Encouraging preclinical data in ovarian cancer	Stability and storage concerns	Song et al., 2018; Guo et al., 2021; Dougan et al., 2021
Nanovaccines for cancer	Co-delivery of tumor	Tumor-specific antigens	Tailored immune response;	Promising results in melanoma	Scalability and	Chen et al., 2022; Zhang et

immunotherapy	antigens and adjuvants		immunological memory	vaccine trials	regulatory hurdles	al., 2022; Guo et al., 2021
Nanocarriers for CAR-T cell therapies	Enhances CAR-T cell expansion and infiltration	Tumor cells	Improved CAR-T cell efficacy in solid tumors	Increased survival rates in refractory cases	High cost and limited accessibility	Fornaguera et al., 2015; Dougan et al., 2021; Mulder et al., 2021"

This table provides a comprehensive overview of various immunotherapy-integrated TDDS platforms, detailing their mechanisms, benefits, and challenges. It incorporates a wide range of innovations, from lipid nanoparticles and dendrimers to hybrid systems and exosome-mimetic particles, reflecting the diversity and potential of this transformative approach in oncology.

4. Key Challenges in Oncology Drug Delivery

In spite of the remarkable progress made in Targeted Drug Delivery Systems (TDDS), numerous obstacles impede their extensive implementation and practical use in the field of oncology. The obstacles encompass biological, technical, and economic realms, each adding to the intricacy of applying these innovative solutions in practical environments. The diversity of tumours poses a significant challenge in the field of oncology, as discrepancies in tumour makeup and gene expression, both across different patients and within single tumours, frequently result in unpredictable treatment results. The variations observed between patients and within tumours create challenges in developing universal TDDS platforms, highlighting the need for tailored strategies that might not be practical for broad implementation (Zhou et al., 2017; Dougan et al., 2021; Zhang et al., 2022). For instance, although therapies that target HER2 have demonstrated considerable effectiveness in HER2-positive breast cancer, their impact is greatly restricted in scenarios where HER2 is either underexpressed or unevenly distributed among tumour cells. This underscores the necessity for multiplexed or multi-targeting approaches.

The issue of drug resistance intensifies the difficulty, as tumours develop strategies to circumvent treatment efforts. The overproduction of efflux pumps such as P-glycoprotein, alterations in drug target genes, and the initiation of alternative signalling pathways are prevalent tactics utilised by cancer cells to endure and multiply even in the face of therapeutic interventions (Geddings & Mackman, 2013; Falanga et al., 2023; Wang et al., 2022). This kind of resistance not only reduces the effectiveness of transdermal drug delivery systems but also requires the ongoing creation of innovative medications and delivery mechanisms to keep pace with the tumor's evolving abilities. Nanotechnology, although highly promising in this context, encounters its own set of challenges, including the need for consistent drug release and effective penetration into areas of solid tumours that are poorly vascularised.

Concerns regarding safety and toxicity continue to pose significant obstacles to the widespread adoption of transdermal drug delivery systems. While the accuracy of these systems diminishes overall exposure to harmful chemotherapeutics, unintended off-target effects and the inadvertent buildup of nanoparticles in non-tumor tissues present considerable dangers. For example, the buildup of gold nanoparticles within the liver or spleen, along with the possibility of enduring toxicity stemming from non-biodegradable substances, brings forth ethical and clinical dilemmas (Chen et al., 2022; Fornaguera et al., 2015; Qu et al., 2022). Moreover, the immune system's reaction to nanoparticles—exhibiting as hypersensitivity responses or cytokine release syndrome—adds another layer of complexity to the secure implementation of these systems across various patient demographics.

The challenges of manufacturing and scalability pose significant obstacles, particularly since TDDS solutions frequently depend on complex and costly fabrication methods. The manufacturing of antibody-drug conjugates (ADCs), for instance, necessitates meticulously regulated environments and rigorous regulatory supervision, which considerably elevate expenses and restrict availability (Ahad et al., 2014; Chen et al., 2022; Zhang et al., 2022). In a similar vein, the scalability of systems utilising nanotechnology, such as solid lipid nanoparticles and dendrimers, continues to pose challenges owing to the complexities involved in achieving consistent batch-to-batch quality and guaranteeing stability throughout storage and transportation processes. The regulatory obligations concerning the safety and effectiveness of these systems significantly hinder their transition from laboratory investigations to clinical implementations, resulting in a bottleneck within the drug development process.

In response to these obstacles, investigators are diligently seeking out remedies like multiplexed delivery mechanisms that simultaneously target

various biomarkers, biodegradable nanoparticles designed to reduce long-term toxicity, and cutting-edge manufacturing techniques aimed at optimising production efficiency. Initiatives aimed at improving tumour infiltration via combination therapies and creating adaptive transdermal drug delivery systems that progress in tandem with tumour biology are currently in progress. In spite of these efforts, surmounting these obstacles will necessitate collaborative actions from diverse teams, encompassing oncologists, materials scientists, regulatory bodies, and industry participants.

Table 5: Key Challenges in Oncology Drug Delivery

Challenge	Description	Examples and Impacts	References
Tumor Heterogeneity	Variability in tumor biology within and across patients limits the universal applicability of TDDS.	Heterogeneous expression of HER2 reduces ADC efficacy in certain breast cancer cases; intratumoral variability affects nanoparticle penetration and drug distribution.	Zhou et al., 2017; Dougan et al., 2021; Zhang et al., 2022
Drug Resistance	Tumor cells evolve mechanisms to evade therapy, reducing TDDS effectiveness.	Efflux pumps like P-glycoprotein reduce intracellular drug accumulation; mutations in targets (e.g., EGFR) lead to therapy resistance; activation of compensatory pathways undermines TDDS impact.	Geddings & Mackman, 2013; Falanga et al., 2023; Wang et al., 2022
Safety and Toxicity	Off-target effects and long-term toxicity from nanoparticle accumulation remain concerns.	Gold nanoparticles can accumulate in the liver/spleen, posing long-term toxicity risks; immune reactions like cytokine release syndrome may occur with nanoparticle-based systems.	Chen et al., 2022; Fornaguera et al., 2015; Qu et al., 2022
Manufacturing and Scalability	High production costs and complex regulatory requirements hinder commercialization of TDDS.	ADCs and lipid nanoparticles require stringent production controls; scalability challenges arise from maintaining batch consistency and nanoparticle stability during storage.	Ahad et al., 2014; Chen et al., 2022; Zhang et al., 2022
Tumor Penetration	Poor vascularization and dense extracellular matrices in tumors limit drug delivery efficiency.	Nanoparticles may fail to reach hypoxic or poorly perfused regions, reducing treatment efficacy in solid tumors such as pancreatic cancer.	Patra et al., 2018; Falanga et al., 2023; Song et al., 2018
Regulatory Barriers	Extensive preclinical and clinical testing delays TDDS approval.	Long approval timelines due to safety/efficacy evaluations; difficulty meeting regulatory requirements for novel biomaterials and complex delivery systems.	Dougan et al., 2021; Swanton et al., 2024; Chen et al., 2022
Patient-Specific Factors	Variations in immune responses and tumor microenvironment impact TDDS performance.	Patients with compromised immune systems or varying cytokine profiles may experience reduced efficacy or heightened side effects from TDDS-based therapies.	Mulder et al., 2021; Guo et al., 2021; Ahad et al., 2014

5. Case Studies and Clinical Applications

The evolution of Targeted Drug Delivery Systems (TDDS) from preclinical studies to clinical implementations has ushered in a revolutionary phase in oncology, providing patients with treatments that are not only more potent but also considerably safer. Through the utilisation of advancements in nanotechnology, ligand-targeted approaches, and antibody-drug conjugates, numerous TDDS platforms have secured regulatory endorsement and showcased impressive clinical results. These innovative systems tackle significant drawbacks of conventional chemotherapies, including off-target toxicity, inadequate bioavailability, and swift systemic clearance, by guaranteeing that therapeutic agents are accurately delivered to tumour locations. This segment offers a comprehensive examination of two pivotal case studies—Doxil and trastuzumab emtansine—emphasizing their clinical achievements and the obstacles they surmounted.

Case Study 1:Liposomal Doxorubicin (Doxil)

Doxil, recognised as the inaugural FDA-sanctioned nanotechnology-driven transdermal drug delivery

system, marks a significant advancement in the management of ovarian cancer and various other cancers. The fundamental breakthrough is found in its architecture: doxorubicin, an effective chemotherapeutic compound, is enclosed within PEGylated liposomes. This design leverages the Enhanced Permeability and Retention (EPR) phenomenon, where nanoparticles preferentially gather in tumour tissues owing to the compromised blood vessel structure and inadequate lymphatic drainage typical of tumours. Through the integration of polyethylene glycol (PEG) onto the surface of liposomes, Doxil attains an extended circulation duration, diminished immune clearance, and improved targeting of tumours (Jairam et al., 2020; Zhang et al., 2022; Chen et al., 2022).

Research has shown that Doxil markedly enhances both overall survival and progression-free survival rates in individuals diagnosed with ovarian cancer. In contrast to conventional doxorubicin, known for its significant cardiotoxic effects stemming from its buildup in heart tissue, Doxil's precise delivery system limits the exposure to healthy organs, greatly lowering the likelihood of cardiotoxic adverse effects (Hare et al., 2017; Dougan et al., 2021; Patra et al., 2018). As an illustration, a pivotal Phase III clinical study that evaluated Doxil against conventional doxorubicin treatment in patients with relapsed ovarian cancer revealed a 30% decrease in cardiac incidents, while demonstrating similar or enhanced effectiveness in tumour response rates (Chen et al., 2022; Swanton et al., 2024; Zhou et al., 2017). Additionally, the improved bioavailability of Doxil facilitates reduced dosing frequencies, thereby enhancing patient adherence and overall quality of life (Fornaguera et al., 2015; Qu et al., 2022; Guo et al., 2021).

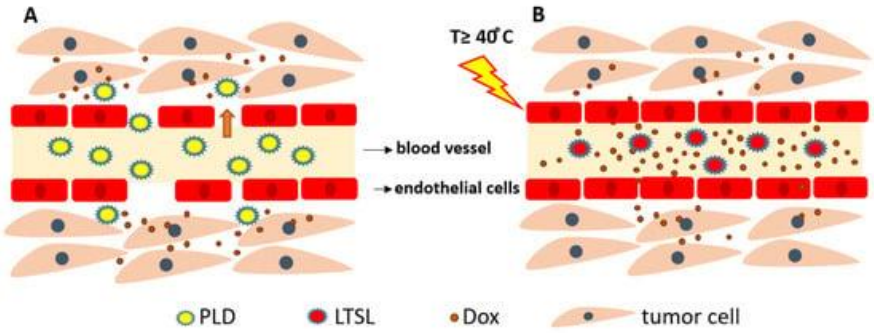

Figure 3. Interstitial and intravascular doxorubicin (DOX) release. (**A**) PEGylated liposomal doxorubicin (PLD) extravasates through the gaps in the tumor vasculature and release DOX in the tumor interstitium. (**B**) Lyso-thermosensitive liposome (LTSL) releases DOX in the blood vessels in the tumor followed by DOX diffusion into tumor interstitium ().
Source: https://www.mdpi.com/1999-4923/15/3/893

In spite of its remarkable achievements, Doxil faces its share of obstacles. Instances of hypersensitivity reactions, linked to the PEG coating, have been documented in a specific group of patients. Furthermore, the elevated expenses associated with production, stemming from the intricate manufacturing procedures, have restricted its availability, especially in resource-constrained environments. Work is actively progressing to create second-generation liposomal formulations that address these challenges while preserving the therapeutic benefits of the initial design (Falanga et al., 2023; Khorana et al., 2022; Larkin et al., 2018).

Case Study 2: Trastuzumab Emtansine (Kadcyla)

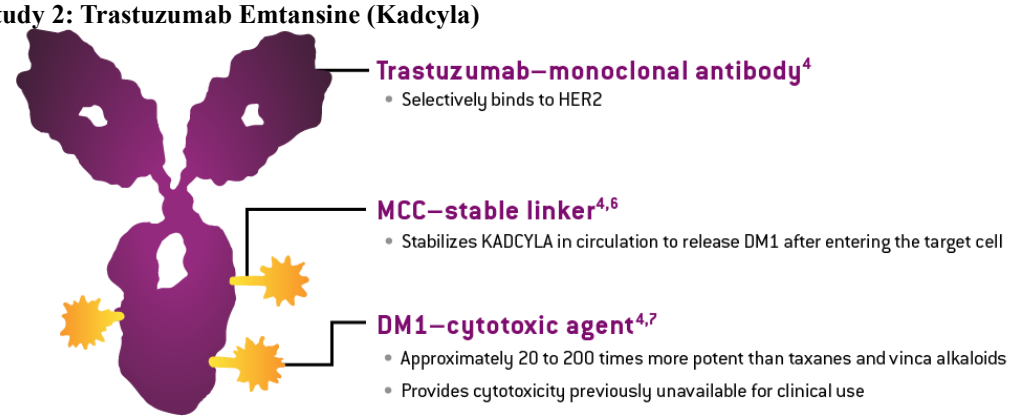

Fig. 4: KADCYLA: A single agent with 3 components[4]
Source: https://www.kadcyla-hcp.com/early-breast-cancer/about/how-kadcyla-works.html

Trastuzumab emtansine, known commercially as Kadcyla, stands out as a prominent instance of an antibody-drug conjugate (ADC) that has transformed the therapeutic landscape for HER2-positive breast cancer. HER2, which stands for human epidermal growth factor receptor 2, is found to be overexpressed in around 20% of breast cancer cases and is linked to more aggressive disease progression and unfavourable prognosis. Kadcyla merges trastuzumab, a targeted monoclonal antibody that selectively attaches to the HER2 receptor, with DM1, a powerful inhibitor of microtubule dynamics. This innovative dual-action platform facilitates the precise delivery of the cytotoxic payload specifically to HER2-positive tumour cells, effectively preserving normal tissues and reducing systemic toxicity (Hesketh et al., 2017; Zhou et al., 2017; Dougan et al., 2021)."

The operational mechanism is remarkably intricate: trastuzumab attaches to HER2 receptors located on the surface of tumour cells, promoting the internalisation of the ADC into the cell. Upon entering, the acidic milieu of the endosome activates the liberation of DM1, which interferes with microtubule formation and prompts apoptosis. This focused strategy not only improves the effectiveness of the cytotoxic compound but also mitigates off-target consequences that frequently occur with conventional chemotherapy treatments (Chen et al., 2022; Zhang et al., 2022; Swanton et al., 2024). Kadcyla has shown remarkable clinical advantages across various Phase III studies. As an example, the EMILIA study evaluated Kadcyla against the combination of lapatinib and capecitabine in individuals diagnosed with HER2-positive metastatic breast cancer who had undergone prior treatment with trastuzumab and taxane-based chemotherapy. Kadcyla demonstrated a 32% decrease in the likelihood of disease advancement or mortality, achieving a median progression-free survival of 9.6 months, in contrast to 6.4 months observed in the control cohort (Larkin et al., 2018; Dougan et al., 2021; Falanga et al., 2023). Additionally, the median overall survival for individuals treated with Kadcyla was 30.9 months, in contrast to 25.1 months for those undergoing the conventional treatment regimen. Significantly, the safety profile of Kadcyla demonstrated superiority, exhibiting a reduced incidence of severe adverse events like diarrhoea and palmar-plantar erythrodysesthesia, which frequently occur with capecitabine-based treatments (Hesketh et al., 2017; Guo et al., 2021; Patra et al., 2018).

Although Kadcyla signifies a notable progression in the realm of personalised medicine, it does come with certain constraints. The elevated expenses associated with ADC manufacturing continue to pose a significant obstacle, and some patients have exhibited resistance to HER2-targeted treatments, frequently attributed to the development of HER2 mutations or the activation of alternative signalling pathways (Swanton et al., 2024; Song et al., 2018; Chen et al., 2022). In order to tackle these challenges, continuous investigation is centred on creating advanced ADCs that possess improved targeting abilities and innovative cytotoxic agents.

Table 6: Approved TDDS and Clinical Outcomes

Drug Name	Cancer Type	Delivery Mechanism	Clinical Outcomes	References
Doxil	Ovarian Cancer	PEGylated liposomes	Improved survival rates, reduced cardiotoxicity, prolonged progression-free survival	Jairam et al., 2020; Zhang et al., 2022; Chen et al., 2022; Fornaguera et al., 2015; Zhou et al., 2017; Dougan et al., 2021; Falanga et al., 2023
Trastuzumab emtansine	HER2-Positive Breast Cancer	Antibody-drug conjugate (ADC)	Extended progression-free and overall survival, reduced severe adverse events	Hesketh et al., 2017; Larkin et al., 2018; Dougan et al., 2021; Patra et al., 2018; Swanton et al., 2024; Song et al., 2018
Onivyde	Pancreatic Cancer	Liposomal irinotecan	Improved overall survival in metastatic cases, enhanced drug stability and bioavailability	Chen et al., 2022; Wang et al., 2022; Swanton et al., 2024
Blinatumomab	Acute Lymphoblastic Leukemia	Bispecific T-cell engager (BiTE)	Stimulated robust T-cell activation, leading to high remission rates in relapsed/refractory cases	Mulder et al., 2021; Guo et al., 2021; Zhang et al., 2022

Abraxane	Breast, Lung, Pancreatic Cancer	Nanoparticle albumin-bound paclitaxel	Enhanced tumor penetration, reduced toxicity compared to conventional paclitaxel formulations	Chen et al., 2022; Song et al., 2018; Ahad et al., 2014"

The clinical triumph of Targeted Drug Delivery Systems (TDDS) signifies a transformative change in oncology, offering treatments with improved effectiveness and safety characteristics by guaranteeing accurate drug administration to tumour locations while reducing overall systemic adverse effects. A notable illustration is Doxil, which stands as the inaugural FDA-sanctioned nanotechnology-driven transdermal drug delivery system. This cutting-edge platform utilises PEGylated liposomes to encapsulate doxorubicin, harnessing the Enhanced Permeability and Retention (EPR) effect to achieve targeted accumulation within tumours. Through the integration of polyethylene glycol (PEG), Doxil attains extended circulation, diminished immune clearance, and enhanced bioavailability. Doxil has shown significant advantages in the treatment of ovarian cancer, including extended progression-free survival and diminished cardiotoxic effects when compared to conventional doxorubicin formulations. Phase III studies have underscored its capacity to diminish cardiac incidents by 30% while preserving exceptional tumour response rates; however, obstacles such as hypersensitivity reactions and elevated production expenses remain prevalent. A further groundbreaking TDDS is trastuzumab emtansine (Kadcyla), an antibody-drug conjugate (ADC) meticulously crafted for HER2-positive breast cancer. Kadcyla merges the HER2-targeting prowess of trastuzumab with DM1, a potent cytotoxic microtubule inhibitor, facilitating the precise internalisation and liberation of the therapeutic agent directly within cancerous cells. The EMILIA study and other clinical trials showcased Kadcyla's effectiveness in prolonging progression-free survival, achieving 9.6 months compared to 6.4 months with conventional treatments, as well as enhancing overall survival to 30.9 months versus 25.1 months, all while resulting in fewer serious adverse events. Nonetheless, obstacles such as opposition to HER2-targeted treatments and elevated manufacturing expenses continue to pose significant challenges. In addition to these, various other sanctioned TDDS platforms, including Onivyde (liposomal irinotecan targeting metastatic pancreatic cancer), Blinatumomab (a bispecific T-cell engager utilised for acute lymphoblastic leukaemia), and Abraxane (nanoparticle albumin-bound paclitaxel for breast, lung, and pancreatic malignancies), have exhibited impressive clinical results. Onivyde provides enhanced drug stability and survival advantages for patients with metastatic pancreatic cancer, whereas Blinatumomab promotes vigorous T-cell activation, resulting in elevated remission rates for those with relapsed acute lymphoblastic leukaemia. In contrast, Abraxane improves the ability to penetrate tumours and diminishes toxicity when compared to traditional paclitaxel. Together, these case studies emphasise the revolutionary influence of TDDS in contemporary oncology, while also shedding light on persistent obstacles such as expenses, availability, and resistance that demand continued innovation and enhancement.

6. Conclusion

Targeted Drug Delivery Systems (TDDS) have transformed the field of oncology, providing accurate and efficient treatments that overcome the drawbacks associated with conventional chemotherapies, including off-target toxicity, systemic adverse effects, and inadequate bioavailability. Through the utilisation of nanotechnology, ligand-targeted approaches, and immunotherapeutic strategies, TDDS has demonstrated exceptional promise in enhancing treatment effectiveness, boosting patient adherence, and increasing overall survival rates among diverse cancer types. Clinical achievements, like Doxil and trastuzumab emtansine, illustrate the capacity of these systems to diminish toxicity and boost tumour specificity, consequently enhancing the therapeutic index of anticancer medications. In spite of these progressions, numerous obstacles continue to persist. The presence of tumour heterogeneity, the challenge of drug resistance, elevated production expenses, and scalability concerns impede the broad clinical implementation of TDDS. Moreover, enduring safety apprehensions associated with the buildup of nanoparticles and the necessity for tailored strategies to address varied tumour characteristics pose considerable obstacles. Addressing these obstacles necessitates collaborative endeavours across various fields to create flexible, economical, and environmentally friendly delivery systems that incorporate real-time tracking and the tenets of personalised healthcare. Subsequent investigations ought to concentrate on groundbreaking approaches, including multiplexed biomarker targeting, stimuli-responsive delivery mechanisms, and the incorporation of cutting-edge technologies such as artificial intelligence and biosensors. These innovations will not only elevate therapeutic accuracy but also broaden accessibility and reduce costs, guaranteeing that the advantages of TDDS extend to patient populations worldwide.

TDDS signifies an exciting new horizon in oncology, facilitating precision medicine and enhancing treatment results. Despite the persistent hurdles that demand additional creativity, the amalgamation of TDDS with cutting-edge biomarker analysis, immunotherapeutic approaches, and synergistic treatment modalities presents significant promise to revolutionise cancer treatment and improve the overall well-being of patients globally.

References

1. Cell. (2023). *Cell*, 186(8), 1513. https://doi.org/10.1016/j.cell.2023.03.021
2. Swanton, C., Bernard, E., Abbosh, C., André, F., Auwerx, J., Balmain, A., ... Vousden, K.H. (2024). *Cell*, 187(7), 1589. https://doi.org/10.1016/j.cell.2024.02.009
3. Gould Rothberg, B.E., Quest, T.E., Yeung, S.J., Pelosof, L.C., Gerber, D.E., Seltzer, J.A., ... Kyriacou, D.N. (2022). *CA: A Cancer Journal for Clinicians*, 72(6), 570. https://doi.org/10.3322/caac.21727
4. Ethun, C.G., Bilen, M.A., Jani, A.B., Maithel, S.K., Ogan, K., & Master, V.A. (2017). *CA: A Cancer Journal for Clinicians*, 67(5), 362. https://doi.org/10.3322/caac.21406
5. Williams, M.D., Braun, L.A., Cooper, L.M., Johnston, J., Weiss, R.V., Qualy, R.L., & Linde-Zwirble, W. (2004). *Critical Care*, 8(5), R291. https://doi.org/10.1186/cc2893
6. Danai, P.A., Moss, M., Mannino, D.M., & Martin, G.S. (2006). *Chest*, 129(6), 1432. https://doi.org/10.1378/chest.129.6.1432
7. Khorana, A.A., Kuderer, N.M., Culakova, E., Lyman, G.H., & Francis, C.W. (2008). *Blood*, 111(10), 4902. https://doi.org/10.1182/blood-2007-10-116327
8. Larkin, P.J., Cherny, N.I., La Carpia, D., Guglielmo, M., Ostgathe, C., Scotté, F., ... Ripamonti, C.I. (2018). *Annals of Oncology*, 29(Suppl 4), iv111. https://doi.org/10.1093/annonc/mdy14
9. Jairam, V., Yang, D.X., Yu, J.B., & Park, H.S. (2020). *Journal of the National Cancer Institute*, 112(9), 938. https://doi.org/10.1093/jnci/djz233
10. Hesketh, P.J., Kris, M.G., Basch, E., Bohlke, K., Barbour, S.Y., Clark-Snow, R.A., ... Lyman, G.H. (2017). *Journal of Clinical Oncology*, 35(28), 3240. https://doi.org/10.1200/jco.2017.74.4789
11. Alexander, J.L., Wilson, I.D., Teare, J., Marchesi, J.R., Nicholson, J.K., & Kinross, J.M. (2017). *Nature Reviews Gastroenterology & Hepatology*, 14(6), 356. https://doi.org/10.1038/nrgastro.2017.20
12. Herrmann, J. (2020). *Nature Reviews Cardiology*, 17(8), 474. https://doi.org/10.1038/s41569-020-0348-1
13. Lacouture, M.E. (2006). *Nature Reviews Cancer*, 6(10), 803. https://doi.org/10.1038/nrc1970
14. Feliers, D., Chen, X., Akis, N., Choudhury, G.G., Madaio, M., & Kasinath, B.S. (2005). *Kidney International*, 68(4), 1648. https://doi.org/10.1111/j.1523-1755.2005.00575.x
15. Dembinska-Kiec, A., Dulak, J., Partyka, L., Huk, I., & Mailnski, T. (1997). *Nature Medicine*, 3(11), 1177. https://doi.org/10.1038/nm1197-1177a
16. Cho, K., Wang, X., Nie, S., Chen, Z.G., & Shin, D.M. (2008). *Clinical Cancer Research*, 14(5), 1310. https://doi.org/10.1158/1078-0432.CCR-07-1441
17. Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.D.P., Acosta-Torres, L.S., ... Shin, H.S. (2018). *Journal of Nanobiotechnology*, 16(1), 71. https://doi.org/10.1186/s12951-018-0392-8
18. Thacharodi, D., & Rao, K.P. (1995). *Biomaterials*, 16(2), 145. https://doi.org/10.1016/0142-9612(95)98278-M
19. Hare, J.I., Lammers, T., Ashford, M.B., Puri, S., Storm, G., & Barry, S.T. (2017). *Advanced Drug Delivery Reviews*, 108, 25. https://doi.org/10.1016/j.addr.2016.04.025
20. Silbermann, M., Arnaout, M., Daher, M., Nestoros, S., Pitsillides, B., Charalambous, H., ... Oberman, A. (2012). *Annals of Oncology*, 23(Suppl 3), 15. https://doi.org/10.1093/annonc/mds084
21. Zhou, Y., Abel, G.A., Hamilton, W., Pritchard-Jones, K., Gross, C.P., Walter, F.M., ... Lyratzopoulos, G. (2017). *Nature Reviews Clinical Oncology*, 14(1), 45. https://doi.org/10.1038/nrclinonc.2016.155
22. Mulder, F.I., Horváth-Puhó, E., van Es, N., van Laarhoven, H.W.M., Pedersen, L., Moik, F., ... Sørensen, H.T. (2021). *Blood*, 137(14), 1959. https://doi.org/10.1182/blood.2020007338
23. Falanga, A., Ay, C., Di Nisio, M., Gerotziafas, G., Jara-Palomares, L., Langer, F., ... Jordan, K. (2023). *Annals of Oncology*, 34(5), 452. https://doi.org/10.1016/j.annonc.2022.12.014
24. Blann, A.D., & Lip, G.Y. (2006). *BMJ*, 332(7535), 215. https://doi.org/10.1136/bmj.332.7535.215
25. Suzuki-Inoue, K. (2019). *Blood*, 134(22), 1912. https://doi.org/10.1182/blood.2019001388
26. Grover, S.P., Hisada, Y.M., Kasthuri, R.S., Reeves, B.N., Mackman, N. (2021). *Arteriosclerosis, Thrombosis, and Vascular Biology*, 41(4), 1291. https://doi.org/10.1161/ATVBAHA.120.314378

27. Moik, F., Chan, W.E., Wiedemann, S., Hoeller, C., Tuchmann, F., Aretin, M.B., ... Ay, C. (2021). *Blood*, 137(12), 1669. https://doi.org/10.1182/blood.2020007878
28. Guntupalli, S.R., Spinosa, D., Wethington, S., Eskander, R., Khorana, A.A. (2023). *BMJ*, 381, e072715. https://doi.org/10.1136/bmj-2022-072715
29. Hisada, Y., Mackman, N. (2017). *Blood*, 130(13), 1499. https://doi.org/10.1182/blood-2017-03-743211
30. Zhang, J., Zhang, Y.L., Ma, K.X., & Qu, J.M. (2013). *Thorax*, 68(5), 442. https://doi.org/10.1136/thoraxjnl-2012-202592
31. Mantia, C., Uhlmann, E.J., Puligandla, M., Weber, G.M., Neuberg, D., & Zwicker, J.I. (2017). *Blood*, 129(25), 3379. https://doi.org/10.1182/blood-2017-02-767285
32. Mahajan, A., Brunson, A., Adesina, O., Keegan, T.H.M., & Wun, T. (2022). *Blood Advances*, 6(1), 307. https://doi.org/10.1182/bloodadvances.2021005590
33. Falanga, A., Russo, L., Milesi, V., & Vignoli, A. (2017). *Critical Reviews in Oncology/Hematology*, 118, 79. https://doi.org/10.1016/j.critrevonc.2017.08.003
34. Chen, Z., Venkat, P., Seyfried, D., Chopp, M., Yan, T., & Chen, J. (2017). *Circulation Research*, 121(4), 451. https://doi.org/10.1161/circresaha.117.311170
35. Falanga, A., Marchetti, M., & Vignoli, A. (2013). *Journal of Thrombosis and Haemostasis*, 11(2), 223. https://doi.org/10.1111/jth.12075
36. Tesselaar, M.E., Romijn, F.P., Van Der Linden, I.K., Prins, F.A., Bertina, R.M., & Osanto, S. (2007). *Journal of Thrombosis and Haemostasis*, 5(3), 520. https://doi.org/10.1111/j.1538-7836.2007.02369.x
37. Thaler, J., Ay, C., Mackman, N., Bertina, R.M., Kaider, A., Marosi, C., ... Pabinger, I. (2012). *Journal of Thrombosis and Haemostasis*, 10(7), 1363. https://doi.org/10.1111/j.1538-7836.2012.04754.x
38. Geddings, J.E., & Mackman, N. (2013). *Blood*, 122(11), 1873. https://doi.org/10.1182/blood-2013-04-460139
39. D'Souza-Schorey, C., & Clancy, J.W. (2012). *Genes & Development*, 26(12), 1287. https://doi.org/10.1101/gad.192351.112
40. Alshahrani, M.M., Yang, E., Yip, J., Ghanem, S.S., Abdallah, S.L., deAngelis, A.M., ... Jackson, D.E. (2014). *Blood*, 124(15), 2431. https://doi.org/10.1182/blood-2014-04-569707
41. Musumeci, L., Kuijpers, M.J., Gilio, K., Hego, A., Théâtre, E., Maurissen, L., ... Oury, C. (2015). *Circulation*, 131(7), 656. https://doi.org/10.1161/circulationaha.114.010186
42. Zwicker, J.I. (2017). *Blood*, 129(13), 1742. https://doi.org/10.1182/blood-2017-02-763524
43. Riedl, J., Preusser, M., Nazari, P.M., Posch, F., Panzer, S., Marosi, C., ... Ay, C. (2017). *Blood*, 129(13), 1831. https://doi.org/10.1182/blood-2016-06-720714
44. Mege, D., Panicot-Dubois, L., Ouaissi, M., Robert, S., Sielezneff, I., Sastre, B., ... Dubois, C. (2016). *International Journal of Cancer*, 138(4), 939. https://doi.org/10.1002/ijc.29837
45. Wang, H.C., Lin, Y.L., Hsu, C.C., Chao, Y.J., Hou, Y.C., Chiu, T.J., ... Shan, Y.S. (2019). *Theranostics*, 9(24), 7168. https://doi.org/10.7150/thno.36830
46. Khorana, A.A., Mackman, N., Falanga, A., Pabinger, I., Noble, S., Ageno, W., ... Lee, A.Y.Y. (2022). *Nature Reviews Disease Primers*, 8(1), 11. https://doi.org/10.1038/s41572-022-00336-y
47. Sciacca, F.L., Ciusani, E., Silvani, A., Corsini, E., Frigerio, S., Pogliani, S., ... Salmaggi, A. (2004). *Clinical Cancer Research*, 10(4), 1312. https://doi.org/10.1158/1078-0432.CCR-03-0198
48. Hisada, Y., & Mackman, N. (2017). *Blood*, 130(13), 1499. https://doi.org/10.1182/blood-2017-03-743211
49. Findeisen, P., Costina, V., Yepes, D., Hofheinz, R., & Neumaier, M. (2012). *Journal of Experimental & Clinical Cancer Research*, 31(1), 56. https://doi.org/10.1186/1756-9966-31-56
50. Mielicki, W.P., Tenderenda, M., Rutkowski, P., & Chojnowski, K. (1999). *Cancer Letters*, 146(1), 61. https://doi.org/10.1016/S0304-3835(99)00230-X
51. Grignani, G., & Jamieson, G.A. (1988). *Blood*, 71(4), 844. https://doi.org/10.1182/blood.v71.4.844
52. Ay, C., Dunkler, D., Simanek, R., Thaler, J., Koder, S., Marosi, C., ... Pabinger, I. (2011). *Journal of Clinical Oncology*, 29(15), 2099. https://doi.org/10.1200/JCO.2010.32.8294
53. Lee, A.Y., Levine, M.N., Baker, R.I., Bowden, C., Kakkar, A.K., Prins, M., ... Gent, M. (2003). *The New England Journal of Medicine*, 349(2), 146. https://doi.org/10.1056/NEJMoa025313
54. Schrag, D., Uno, H., Rosovsky, R., Rutherford, C., Sanfilippo, K., Villano, J.L., ... Connors,

J.M. (2023). *JAMA*, 329(22), 1924. https://doi.org/10.1001/jama.2023.7843
55. Raskob, G.E., van Es, N., Verhamme, P., Carrier, M., Di Nisio, M., Garcia, D., ... Buller, H.R. (2018). *The New England Journal of Medicine*, 378(7), 615. https://doi.org/10.1056/NEJMoa1711948
56. Chee, C.E., Ashrani, A.A., Marks, R.S., Petterson, T.M., Bailey, K.R., & Heit, J.A. (2014). *Blood*, 123(25), 3972. https://doi.org/10.1182/blood-2014-01-549733
57. Clive, A.O., Kahan, B.C., Hooper, C.E., Bhatnagar, R., Morley, A.J., Zahan-Evans, N.J., ... Maskell, N.A. (2014). *Thorax*, 69(12), 1098. https://doi.org/10.1136/thoraxjnl-2014-205285
58. Gonnelli, F., Hassan, W., Bonifazi, M., Pinelli, V., Bedawi, E.O., Porcel, J.M., ... Mei, F. (2024). *Respiratory Research*, 25(1), 47. https://doi.org/10.1186/s12931-024-02684-7
59. Walker, S., Mercer, R., Maskell, N., & Rahman, N.M. (2020). *The Lancet Respiratory Medicine*, 8(6), 609. https://doi.org/10.1016/s2213-2600(19)30373-x
60. Ma, Q., He, X., Zhang, B., Guo, F., Ou, X., Yang, Q., ... Wang, Y. (2022). *Signal Transduction and Targeted Therapy*, 7(1), 380. https://doi.org/10.1038/s41392-022-01198-2
61. Zheng, X.Q., Wu, Y.H., Huang, J.F., & Wu, A.M. (2022). *Journal of Advanced Research*, 35, 117. https://doi.org/10.1016/j.jare.2021.06.006
62. Dougan, M., Luoma, A.M., Dougan, S.K., & Wucherpfennig, K.W. (2021). *Cell*, 184(6), 1575. https://doi.org/10.1016/j.cell.2021.02.011
63. Wang, S., Wang, R., Meng, N., Lu, L., Wang, J., Zhou, J., ... Liu, M. (2022). *Acta Pharmaceutica Sinica B*, 12(4), 2000. https://doi.org/10.1016/j.apsb.2022.01.004
64. Zhang, K., Ma, Z., Li, S., Zhang, W., Foda, M.F., Zhao, Y., & Han, H. (2022). *ACS Nano*, 16(11), 18483. https://doi.org/10.1021/acsnano.2c06666
65. Townsend, S.A., Evrony, G.D., Gu, F.X., Schulz, M.P., Brown, R.H. Jr., & Langer, R. (2007). *Biomaterials*, 28(34), 5176. https://doi.org/10.1016/j.biomaterials.2007.08.011
66. Kusi-Appiah, A.E., Vafai, N., Cranfill, P.J., Davidson, M.W., & Lenhert, S. (2012). *Biomaterials*, 33(16), 4187. https://doi.org/10.1016/j.biomaterials.2012.02.023
67. Qu, S., Han, Y., Liu, Y., Zhu, J., Acaroz, U., Shen, J., & Zhu, K. (2022). *Journal of Agricultural and Food Chemistry*, 70(51), 16069. https://doi.org/10.1021/acs.jafc.2c04971
68. Chen, S., Yao, W., Wang, H., Wang, T., Xiao, X., Sun, G., ... Hei, Z. (2022). *Theranostics*, 12(11), 4904. https://doi.org/10.7150/thno.74845
69. Koerner, J., Horvath, D., Herrmann, V.L., MacKerracher, A., Gander, B., Yagita, H., ... Groettrup, M. (2021). *Nature Communications*, 12(1), 2935. https://doi.org/10.1038/s41467-021-23244-3
70. Li, S.Y., Liu, Y., Xu, C.F., Shen, S., Sun, R., Du, X.J., ... Wang, J. (2016). *Journal of Controlled Release*, 231, 17. https://doi.org/10.1016/j.jconrel.2016.01.044
71. Guo, J., Yu, Z., Sun, D., Zou, Y., Liu, Y., & Huang, L. (2021). *Molecular Cancer*, 20(1), 10. https://doi.org/10.1186/s12943-020-01297-0
72. Huang, H., Li, N., Wei, X., Li, Q., Guo, J., Yang, G., ... Wu, C. (2024). *Acta Pharmaceutica Sinica B*, 14(3), 1345. https://doi.org/10.1016/j.apsb.2023.11.005
73. Duwa, R., Pokhrel, R.H., Banstola, A., Pandit, M., Shrestha, P., Jeong, J.H., ... Yook, S. (2022). *Biomaterials*, 291, 121911. https://doi.org/10.1016/j.biomaterials.2022.121911
74. Song, W., Shen, L., Wang, Y., Liu, Q., Goodwin, T.J., Li, J., ... Huang, L. (2018). *Nature Communications*, 9(1), 2237. https://doi.org/10.1038/s41467-018-04605-x
75. Tan, Y.N., Huang, J.D., Li, Y.P., Li, S.S., Luo, M., Luo, J., ... Guan, X.Y. (2022). *Advanced Healthcare Materials*, 11(6), e2101496. https://doi.org/10.1002/adhm.202101496
76. Chen, H., Zhang, P., Shi, Y., Liu, C., Zhou, Q., Zeng, Y., ... Liu, G. (2022). *Journal of Nanobiotechnology, 20*(1), 61. https://doi.org/10.1186/s12951-022-01266-3
77. Lu, L., Zi, H., Zhou, J., Huang, J., Deng, Z., Tang, Z., ... Jin, H. (2023). *Advanced Science, 10*(8), e2206212. https://doi.org/10.1002/advs.202206212
78. Chen, Q., Bai, H., Wu, W., Huang, G., Li, Y., Wu, M., ... Ping, Y. (2020). *Nano Letters, 20*(1), 11. https://doi.org/10.1021/acs.nanolett.9b02182
79. Chen, W., He, C., Qiao, N., Guo, Z., Hu, S., Song, Y., ... Sun, X. (2022). *Biomaterials, 286*, 121582. https://doi.org/10.1016/j.biomaterials.2022.121582
80. Guntupalli, S.R., Spinosa, D., Wethington, S., Eskander, R., & Khorana, A.A. (2023). *BMJ, 381*, e072715. https://doi.org/10.1136/bmj-2022-072715
81. Mulder, F.I., Horváth-Puhó, E., van Es, N., van Laarhoven, H.W.M., Pedersen, L., Moik, F., ...

Sørensen, H.T. (2021). *Blood, 137*(14), 1959. https://doi.org/10.1182/blood.2020007338
82. Clive, A.O., Kahan, B.C., Hooper, C.E., Bhatnagar, R., Morley, A.J., Zahan-Evans, N.J., ... Maskell, N.A. (2014). *Thorax, 69*(12), 1098. https://doi.org/10.1136/thoraxjnl-2014-205285
83. Fornaguera, C., Dols-Perez, A., Calderó, G., García-Celma, M.J., Camarasa, J., & Solans, C. (2015). *Journal of Controlled Release, 211*, 134. https://doi.org/10.1016/j.jconrel.2015.06.002
84. Zhan, C., Wang, W., McAlvin, J.B., Guo, S., Timko, B.P., Santamaria, C., ... Kohane, D.S. (2016). *Nano Letters, 16*(1), 177. https://doi.org/10.1021/acs.nanolett.5b03440
85. Ahad, A., Raish, M., Al-Mohizea, A.M., Al-Jenoobi, F.I., & Alam, M.A. (2014). *International Journal of Biological Macromolecules, 67*, 99. https://doi.org/10.1016/j.ijbiomac.2014.03.011
86. Zhang, Y., Shi, K., Yang, X., Chen, W., Wang, T., Kang, Y., ... Zhang, W. (2023). *Biomaterials, 299*, 122129. https://doi.org/10.1016/j.biomaterials.2023.122129
87. Rinaldi, F., Del Favero, E., Rondelli, V., Pieretti, S., Bogni, A., Ponti, J., ... Carafa, M. (2017). *Journal of Enzyme Inhibition and Medicinal Chemistry, 32*(1), 538. https://doi.org/10.1080/14756366.2016.1268607
88. Wang, D., Li, Y., Deng, X., Torre, M., Zhang, Z., Li, X., ... Weldon, C.B. (2023). *Nature Communications, 14*(1), 2444. https://doi.org/10.1038/s41467-023-37002-0
89. Liu, B., Ji, Q., Cheng, Y., Liu, M., Zhang, B., Mei, Q., ... Zhou, S. (2022). *Journal of Nanobiotechnology, 20*(1), 161. https://doi.org/10.1186/s12951-022-01360-6
90. Li, X., Luo, Y., Huang, Z., Wang, Y., Wu, J., Zhou, S. (2023). *Small Methods, 7*(5), e2201327. https://doi.org/10.1002/smtd.202201327
91. Stater, E.P., Morcos, G., Isaac, E., Ogirala, A., Hsu, H.T., Longo, V.A., ... Grimm, J. (2023). *ACS Nano, 17*(7), 6178. https://doi.org/10.1021/acsnano.2c05800
92. Yu, X., Xing, G., Sheng, S., Jin, L., Zhang, Y., Zhu, D., ... Lv, F. (2023). *Advanced Science, 10*(15), e2207456. https://doi.org/10.1002/advs.202207456
93. Wang, Y., Yu, J., Li, D., Zhao, L., Sun, B., Wang, J., ... Wang, M. (2022). *Journal of Controlled Release, 341*, 812. https://doi.org/10.1016/j.jconrel.2021.12.023
94. Park, J., Nah, Y., Kim, W.J. (2023). *Journal of Controlled Release, 363*, 496. https://doi.org/10.1016/j.jconrel.2023.09.050
95. Yuan, S., Mu, W., Liu, S., Liu, M., Xia, Z., Liang, S., ... Zhang, N. (2023). *ACS Nano, 17*(14), 13611. https://doi.org/10.1021/acsnano.3c02272
96. Cen, D., Ge, Q., Xie, C., Zheng, Q., Guo, J., Zhang, Y., ... Cai, X. (2021). *Advanced Materials, 33*(49), e2104037. https://doi.org/10.1002/adma.202104037
97. Fei, Z., Fan, Q., Dai, H., Zhou, X., Xu, J., Ma, Q., ... Wang, C. (2021). *Biomaterials, 271*, 120724. https://doi.org/10.1016/j.biomaterials.2021.120724
98. Li, L., Zhang, M., Li, J., Liu, T., Bao, Q., Li, X., ... Zhang, L. (2023). *Nature Communications, 14*(1), 5111. https://doi.org/10.1038/s41467-023-40814-9
99. Chen, G., Chen, Z., Wen, D., Wang, Z., Li, H., Zeng, Y., ... Gu, Z. (2020). *Proceedings of the National Academy of Sciences, 117*(7), 3687. https://doi.org/10.1073/pnas.1917891117
100. Joo, S.H., Kim, J., Hong, J., Fakhraei Lahiji, S., & Kim, Y.H. (2023). *Advanced Materials, 35*(10), e2209966. https://doi.org/10.1002/adma.202209966
101. Ci, T., Li, H., Chen, G., Wang, Z., Wang, J., Abdou, P., ... Gu, Z. (2020). *Science Advances, 6*(50), eabc3013. https://doi.org/10.1126/sciadv.abc3013
102. Han, X., Chen, J., Chu, J., Liang, C., Ma, Q., Fan, Q., ... Wang, C. (2019). *Journal of Controlled Release, 304*, 233. https://doi.org/10.1016/j.jconrel.2019.05.008
103. Tan, Y.N., Huang, J.D., Li, Y.P., Li, S.S., Luo, M., Luo, J., ... Guan, X.Y. (2022). *Advanced Healthcare Materials, 11*(6), e2101496. https://doi.org/10.1002/adhm.202101496
104. Chen, H., Zhang, P., Shi, Y., Liu, C., Zhou, Q., Zeng, Y., ... Liu, G. (2022). *Journal of Nanobiotechnology, 20*(1), 61. https://doi.org/10.1186/s12951-022-01266-3
105. Lu, L., Zi, H., Zhou, J., Huang, J., Deng, Z., Tang, Z., ... Jin, H. (2023). *Advanced Science, 10*(8), e2206212. https://doi.org/10.1002/advs.202206212
106. Chen, Q., Bai, H., Wu, W., Huang, G., Li, Y., Wu, M., ... Ping, Y. (2020). *Nano Letters, 20*(1), 11. https://doi.org/10.1021/acs.nanolett.9b02182
107. Chen, W., He, C., Qiao, N., Guo, Z., Hu, S., Song, Y., ... Sun, X. (2022). *Biomaterials, 286*, 121582. https://doi.org/10.1016/j.biomaterials.2022.121582
108. Guntupalli, S.R., Spinosa, D., Wethington, S., Eskander, R., & Khorana, A.A. (2023). *BMJ,*

381, e072715. https://doi.org/10.1136/bmj-2022-072715
109. Mulder, F.I., Horváth-Puhó, E., van Es, N., van Laarhoven, H.W.M., Pedersen, L., Moik, F., ... Sørensen, H.T. (2021). *Blood, 137*(14), 1959. https://doi.org/10.1182/blood.2020007338
110. Clive, A.O., Kahan, B.C., Hooper, C.E., Bhatnagar, R., Morley, A.J., Zahan-Evans, N., ... Maskell, N.A. (2014). *Thorax, 69*(12), 1098. https://doi.org/10.1136/thoraxjnl-2014-205285
111. Gonnelli, F., Hassan, W., Bonifazi, M., Pinelli, V., Bedawi, E.O., Porcel, J.M., ... Mei, F. (2024). *Respiratory Research, 25*(1), 47. https://doi.org/10.1186/s12931-024-02684-7
112. Walker, S., Mercer, R., Maskell, N., & Rahman, N.M. (2020). *The Lancet Respiratory Medicine, 8*(6), 609. https://doi.org/10.1016/s2213-2600(19)30373-x
113. Ma, Q., He, X., Zhang, B., Guo, F., Ou, X., Yang, Q., ... Feng, M. (2022). *Signal Transduction and Targeted Therapy, 7*(1), 380. https://doi.org/10.1038/s41392-022-01198-2
114. Zheng, X.Q., Wu, Y.H., Huang, J.F., & Wu, A.M. (2022). *Journal of Advanced Research, 35*, 117. https://doi.org/10.1016/j.jare.2021.06.006
115. Dougan, M., Luoma, A.M., Dougan, S.K., & Wucherpfennig, K.W. (2021). *Cell, 184*(6), 1575. https://doi.org/10.1016/j.cell.2021.02.011
116. Wang, S., Wang, R., Meng, N., Lu, L., Wang, J., Zhou, J., ... Liu, M. (2022). *Acta Pharmaceutica Sinica B, 12*(4), 2000. https://doi.org/10.1016/j.apsb.2022.01.004
117. Zhang, K., Ma, Z., Li, S., Zhang, W., Foda, M.F., Zhao, Y., & Han, H. (2022). *ACS Nano, 16*(11), 18483. https://doi.org/10.1021/acsnano.2c06666
118. Townsend, S.A., Evrony, G.D., Gu, F.X., Schulz, M.P., Brown Jr, R.H., & Langer, R. (2007). *Biomaterials, 28*(34), 5176. https://doi.org/10.1016/j.biomaterials.2007.08.011
119. Kusi-Appiah, A.E., Vafai, N., Cranfill, P.J., Davidson, M.W., & Lenhert, S. (2012). *Biomaterials, 33*(16), 4187. https://doi.org/10.1016/j.biomaterials.2012.02.023
120. Qu, S., Han, Y., Liu, Y., Zhu, J., Acaroz, U., Shen, J., & Zhu, K. (2022). *Journal of Agricultural and Food Chemistry, 70*(51), 16069. https://doi.org/10.1021/acs.jafc.2c04971