Heritage Journal of Health Sciences and Research
Volume 1, Issue 2, July–December 2026 | Open Access | Peer Reviewed
Gupta V, Reddy M. Heritage J Health Sci Res. 2026;1(2):32-37
Received: 25-10-2026 | Accepted: 01-11-2026 | Published: 06-11-2026
Research Article | Heritage J Health Sci Res

Nanotechnology-Driven Drug Delivery Systems for Targeted Cancer Therapy: Recent Advances and Clinical Challenges

Dr. Vikram Gupta [1*], Dr. Manish Reddy [2]
[1,2] Department of Microbiology, Institute of Health Sciences, Jaipur, India

Abstract

Conventional chemotherapy remains limited by poor tumour selectivity, dose-limiting systemic toxicity and the emergence of multidrug resistance. Nanotechnology offers a way to re-engineer how anticancer agents are packaged, transported and released, so that a larger fraction of the administered dose reaches malignant tissue while healthy organs are spared. This review summarises the principal nanocarrier platforms used in oncology, namely liposomes, polymeric micelles, albumin-bound nanoparticles, inorganic nanoparticles and lipid nanoparticles for nucleic acids. It outlines the passive and active targeting mechanisms that underpin them and the clinical evidence generated by approved products such as Doxil, Abraxane, Onivyde and Vyxeos. Recent advances, including stimuli-responsive carriers, radio-enhancing hafnium oxide nanoparticles and messenger RNA cancer vaccines delivered by lipid nanoparticles, are discussed. Finally, the barriers that continue to slow clinical translation are examined: low tumour delivery efficiency, with a reported median of approximately 0.7 per cent of the injected dose, heterogeneity of the enhanced permeability and retention effect in patients, the protein corona, manufacturing scale-up and regulatory complexity. We argue that patient stratification, rational design and more predictive preclinical models are essential if the next generation of cancer nanomedicines is to deliver on its promise.

Keywords: nanomedicine, targeted drug delivery, liposomes, EPR effect, lipid nanoparticles, cancer therapy, clinical translation

Introduction

Cancer is among the leading causes of death worldwide. The GLOBOCAN estimates published by the International Agency for Research on Cancer indicate close to 20 million new cases and approximately 9.7 million cancer deaths in 2022[8]. Although cytotoxic chemotherapy remains a backbone of treatment for many tumour types, most small-molecule anticancer drugs distribute widely throughout the body after intravenous administration. Only a small proportion of the dose reaches the tumour, while the remainder causes off-target damage to the bone marrow, heart, gastrointestinal tract and peripheral nervous system. These toxicities restrict the dose that can safely be given and therefore narrow the therapeutic window.

Nanotechnology, understood here as the engineering of materials in the 1–100 nm range and extended in drug delivery to roughly 200 nm, provides a set of tools to change the pharmacokinetics and biodistribution of a drug without altering its molecular structure. By encapsulating, adsorbing or conjugating a drug within a nanocarrier it is possible to protect the payload from premature degradation, prolong circulation time, improve the apparent solubility of hydrophobic compounds and concentrate the drug in tumour tissue[6]. Since the approval of pegylated liposomal doxorubicin (Doxil) by the United States Food and Drug Administration in 1995[1], a series of nanoformulations has entered routine oncology practice, as summarised in Figure 1.

This paper reviews the major nanocarrier platforms, the targeting strategies that govern their behaviour in vivo, the clinical evidence accumulated so far, and the scientific, manufacturing and regulatory challenges that continue to limit translation from the laboratory to the clinic.

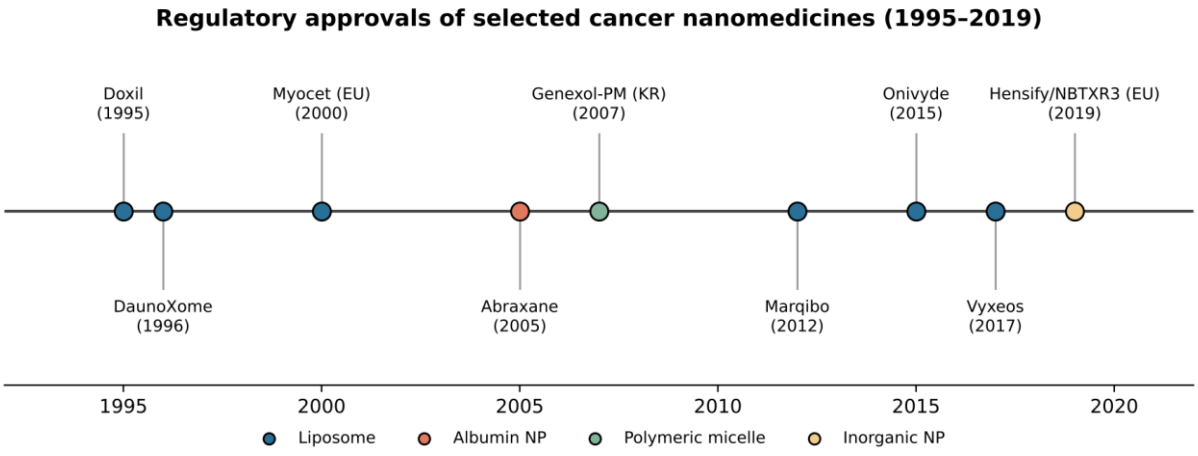


Fig 1: Timeline of regulatory approvals for selected cancer nanomedicines. Unless otherwise indicated (EU, Korea), approvals refer to the United States Food and Drug Administration.

Nanocarrier Platforms in Oncology

A wide range of materials has been investigated as drug carriers. Four classes have achieved regulatory approval in oncology, and lipid nanoparticles have recently emerged as a fifth important class following their validation in messenger RNA vaccines. Figure 2 illustrates the architecture of these platforms and Table 1 lists the principal approved products.

Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core. Hydrophilic drugs are loaded into the core, whereas hydrophobic drugs partition into the bilayer. Surface coating with polyethylene glycol, as in Doxil, reduces recognition by the mononuclear phagocyte system and extends the circulation half-life of doxorubicin from minutes in its free form to approximately two to three days. Liposomes remain the most clinically successful platform and account for Doxil, DaunoXome, Myocet, Marqibo, Onivyde and Vyxeos.

Polymeric Nanoparticles and Micelles

Amphiphilic block copolymers such as polyethylene glycol–poly(D,L-lactide) self-assemble in aqueous media into micelles with a hydrophobic core capable of solubilising poorly water-soluble drugs. Genexol-PM, a Cremophor-free micellar paclitaxel approved in South Korea in 2007, permits higher paclitaxel doses without solvent-related hypersensitivity reactions. Biodegradable polymers such as poly(lactic-co-glycolic acid) are also widely studied for sustained release, since their degradation products are metabolised through normal pathways.

Protein-Based Nanoparticles

Nanoparticle albumin-bound paclitaxel (Abraxane) consists of paclitaxel non-covalently bound to human serum albumin in particles of approximately 130 nm. The formulation removes the need for the solvent Cremophor EL and is thought to exploit albumin transport pathways, including the gp60 receptor on endothelium and the albumin-binding protein SPARC in tumour stroma. Abraxane is approved for metastatic breast cancer, non-small cell lung cancer and metastatic pancreatic adenocarcinoma.

Inorganic Nanoparticles

Gold, iron oxide, mesoporous silica and hafnium oxide nanoparticles offer optical, magnetic or radiation-interacting properties that organic carriers do not possess. Superparamagnetic iron oxide nanoparticles have been applied to magnetic hyperthermia, and hafnium oxide nanoparticles, because of their high atomic number, amplify the local absorbed dose of radiotherapy when injected directly into a tumour.

Lipid Nanoparticles for Nucleic Acids

Ionisable lipid nanoparticles protect fragile RNA from nuclease degradation and promote its escape from endosomes into the cytoplasm. Following clinical validation of the platform with patisiran, a small interfering RNA therapeutic approved in 2018, and with the messenger RNA vaccines developed during the COVID-19 pandemic, lipid nanoparticles are now being applied to individualised cancer vaccines, in vivo chimeric antigen receptor engineering and gene editing.

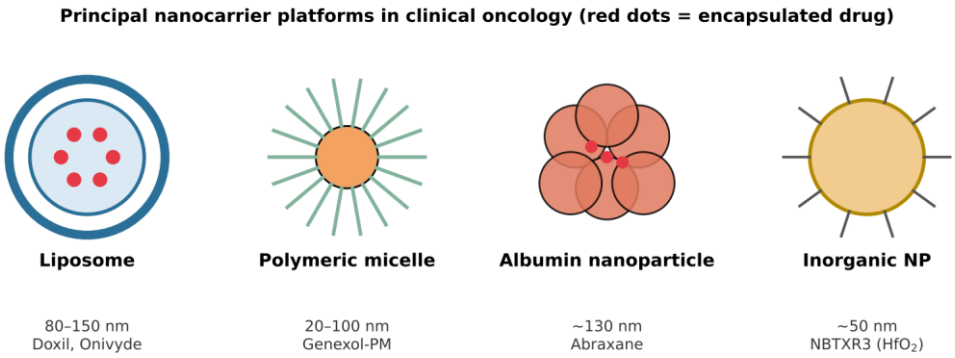


Fig 2: Schematic representation of the principal nanocarrier platforms in clinical oncology, with typical particle sizes and representative products.

Table 1: Selected approved nanomedicines for cancer therapy

Product	Platform	Drug	Main indication(s)	Approval
Doxil / Caelyx	PEGylated liposome	Doxorubicin	Ovarian cancer, Kaposi sarcoma, multiple myeloma	FDA 1995
DaunoXome	Liposome	Daunorubicin	HIV-associated Kaposi sarcoma	FDA 1996
Myocet	Non-PEGylated liposome	Doxorubicin	Metastatic breast cancer	EMA 2000
Abraxane	Albumin nanoparticle	Paclitaxel	Breast, non-small cell lung, pancreatic cancer	FDA 2005
Genexol-PM	Polymeric micelle	Paclitaxel	Breast cancer, non-small cell lung cancer	Korea 2007
Marqibo	Liposome	Vincristine	Ph-negative acute lymphoblastic leukaemia	FDA 2012
Onivyde	Liposome	Irinotecan	Metastatic pancreatic adenocarcinoma	FDA 2015
Vyxeos	Liposome (1:5 molar ratio)	Daunorubicin and cytarabine	Therapy-related and MRC acute myeloid leukaemia	FDA 2017

Product	Platform	Drug	Main indication(s)	Approval
Hensify (NBTXR3)	Hafnium oxide nanoparticle	Radio-enhancer	Locally advanced soft-tissue sarcoma	CE mark 2019

Mechanisms of Tumour Targeting

Passive Targeting and the EPR Effect

Passive targeting relies on the enhanced permeability and retention effect, first described by Matsumura and Maeda in 1986[5]. Rapidly growing tumours induce disorganised angiogenesis, producing vessels with endothelial fenestrations that may extend to several hundred nanometres, and they frequently lack functional lymphatic drainage. Particles in the approximate range of 10 to 200 nm can therefore extravasate into tumour interstitium and are retained there, whereas they are largely excluded from healthy tissue with intact endothelial junctions. Prolonged circulation is a prerequisite for this process, which explains why pegylation, near-neutral surface charge and avoidance of rapid renal clearance are recurring design features.

Active Targeting

Active targeting adds ligands to the nanoparticle surface so that the carrier binds receptors overexpressed on malignant cells or on tumour vasculature. Antibodies and antibody fragments, peptides, aptamers, folate and transferrin have all been used, directed against targets such as HER2, the epidermal growth factor receptor, folate receptor alpha and integrin alpha-v beta-3. An important qualification is that ligands mainly improve cellular internalisation and intratumoural retention once the particle has already reached the tumour; they do not substantially increase the total quantity of nanoparticle that accumulates there, which remains governed by circulation time and extravasation.

Stimuli-Responsive Release

Stimuli-responsive carriers are engineered to release their payload in response to characteristics of the tumour microenvironment, such as acidic extracellular pH, elevated intracellular glutathione or overexpressed enzymes including matrix metalloproteinases, or in response to externally applied triggers such as heat, light, ultrasound and magnetic fields. Thermosensitive liposomal doxorubicin combined with radiofrequency ablation illustrates the approach, although its pivotal phase III trial in hepatocellular carcinoma did not meet its primary endpoint, underlining the difficulty of translating elegant release chemistry into clinical benefit.

Clinical Evidence and Recent Advances

Approved nanomedicines have improved the therapeutic index of established cytotoxic drugs, principally by reducing toxicity and, in several cases, by improving efficacy. Table 2 summarises the outcomes of key randomised trials[2–4,7,9–12], and Figure 3 compares overall survival for three liposomal formulations against their respective comparators.

Table 2: Key clinical trial outcomes of nanoformulations in oncology

Trial / formulation	Setting	Comparator	Main reported outcome
Doxil (O'Brien et al., 2004)	Metastatic breast cancer, first line	Conventional doxorubicin	Comparable progression-free survival (6.9 vs 7.8 months); markedly lower cardiotoxicity
Abraxane (Gradishar et al., 2005)	Metastatic breast cancer	Solvent-based paclitaxel	Response rate 33% vs 19%; less grade 4 neutropenia
MPACT (Von Hoff et al., 2013)	Metastatic pancreatic cancer	Gemcitabine alone	Median overall survival 8.5 vs 6.7 months
NAPOLI-1 (Wang-Gillam et al., 2016)	Pancreatic cancer after gemcitabine	5-fluorouracil and leucovorin	Median overall survival 6.1 vs 4.2 months
Vyxeos (Lancet et al., 2018)	Secondary AML, ages 60–75	Standard 7+3 regimen	Median overall survival 9.56 vs 5.95 months
NAPOLI-3 (Wainberg et al., 2023)	Metastatic pancreatic cancer, first line	Nab-paclitaxel and gemcitabine	Median overall survival 11.1 vs 9.2 months
Act.In.Sarc (Bonvalot et al., 2019)	Soft-tissue sarcoma, pre-operative radiotherapy	Radiotherapy alone	Pathological complete response 16% vs 8%
KEYNOTE-942 (mRNA-4157/V940)	Resected high-risk melanoma	Pembrolizumab alone	Approximately 44% reduction in risk of recurrence or death

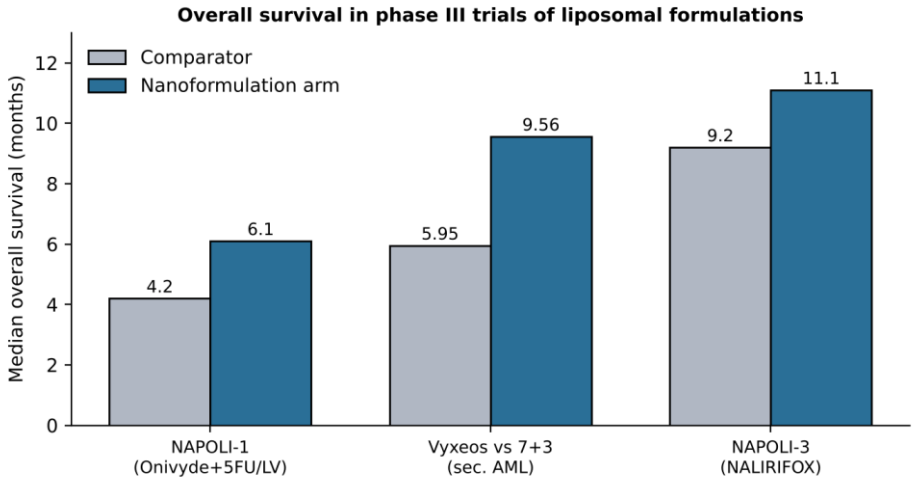


Fig 3: Median overall survival reported in phase III trials of liposomal formulations compared with their comparator regimens.

Several developments are currently reshaping the field. **First**, ratiometric co-delivery, demonstrated clinically by Vyxeos, maintains a synergistic five-to-one molar ratio of cytarabine to daunorubicin in plasma and bone marrow, a degree of pharmacokinetic control that cannot be achieved with free drugs administered separately. **Second**, nanoparticles are increasingly combined with radiotherapy and immunotherapy: hafnium oxide nanoparticles are being evaluated together with immune checkpoint inhibitors, and carriers delivering stimulator of interferon genes agonists or Toll-like receptor ligands aim to convert immunologically cold tumours into inflamed ones. **Third**, individualised neoantigen messenger RNA vaccines formulated in lipid nanoparticles have shown clinically meaningful benefit in resected melanoma and have progressed to phase III evaluation. **Fourth**, biomimetic carriers coated with erythrocyte or cancer cell membranes, and vehicles derived from extracellular vesicles, are being developed to reduce immune clearance and to improve homing to specific tissues.

Clinical Challenges

Despite these successes, the number of approved cancer nanomedicines remains modest in relation to the very large volume of preclinical literature. Several interconnected barriers help to explain this gap, and they are summarised in Table 3.

- **Low delivery efficiency.** A frequently cited meta-analysis of 117 published studies by Wilhelm and colleagues[13] reported that a median of only about 0.7 per cent of the injected nanoparticle dose reaches solid tumours in murine models, with modest differences between passive and active targeting and between organic and inorganic materials, as shown in Figure 4.
- **Heterogeneity of the EPR effect.** The enhanced permeability and retention effect is pronounced in rapidly growing mouse xenografts but highly variable in human disease, differing between patients, between tumour types and even between regions of a single lesion. Dense desmoplastic stroma and elevated interstitial fluid pressure, characteristic of pancreatic adenocarcinoma, further restrict penetration beyond the perivascular space.
- **Protein corona and immune clearance.** Plasma proteins adsorb onto nanoparticle surfaces within seconds of administration, forming a corona that can mask targeting ligands and redefine the biological identity of the particle. Repeated dosing of pegylated carriers may elicit anti-polyethylene glycol antibodies, accelerated blood clearance and complement activation-related pseudoallergy.
- **Emergence of new toxicities.** Altered biodistribution redistributes rather than abolishes toxicity. Pegylated liposomal doxorubicin substantially reduces cardiotoxicity but introduces palmar-plantar erythrodysaesthesia, or hand-foot syndrome, and mucositis as dose-limiting effects.
- **Manufacturing and characterisation.** Reproducible control of particle size, polydispersity, drug loading, surface chemistry, stability and sterility at industrial scale is demanding, and minor process changes can alter in vivo performance. Generic versions must demonstrate equivalence of a complex system rather than of a single molecule, an issue highlighted by the Doxil supply shortage of 2011 to 2012.
- **Regulatory and translational gaps.** Regulatory frameworks for complex drug products continue to evolve, and conventional preclinical models rarely reproduce the vascular biology, stroma and immune context of human tumours, contributing to high attrition in phase II and phase III studies.

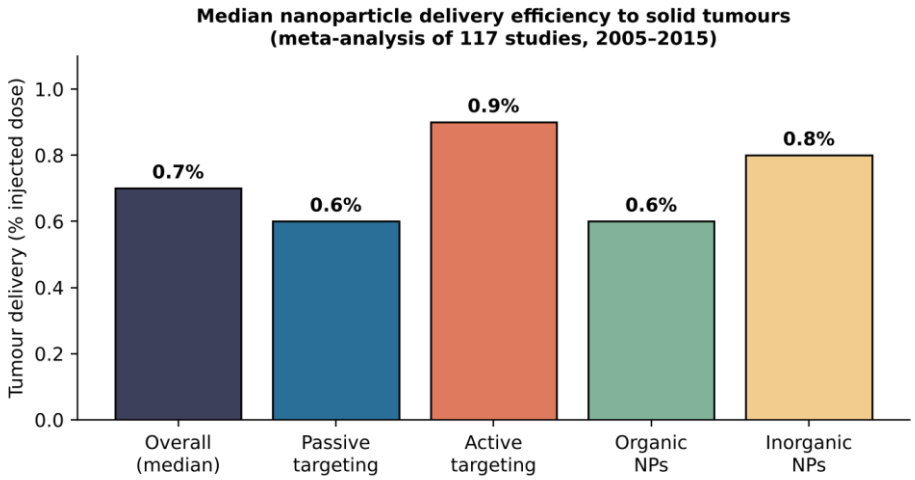


Fig 4: Median delivery efficiency of nanoparticles to solid tumours, expressed as percentage of injected dose, by targeting strategy and material class (data reported by Wilhelm et al., 2016).

Table 3: Major barriers to clinical translation and proposed strategies

Barrier	Consequence	Proposed strategy
Low tumour accumulation (~0.7% of injected dose)	Limited efficacy gain over free drug	Prolonged circulation, transcytosis-mediated transport, intratumoural or locoregional delivery
Variable EPR effect in patients	Inconsistent clinical response	Patient stratification using companion imaging, for example ferumoxytol-enhanced MRI
Protein corona formation	Loss of targeting specificity, altered fate	Corona-aware design, zwitterionic and protein-resistant coatings
Anti-PEG immunity	Accelerated clearance, hypersensitivity	PEG alternatives such as polysarcosine or poly(2-oxazoline)s
Stromal and interstitial pressure barriers	Poor penetration into the tumour core	Stroma-modulating combination therapy, size-switchable or charge-switchable particles
Scale-up and quality control	Batch-to-batch variability, high cost	Microfluidic continuous manufacturing, quality-by-design frameworks
Incomplete regulatory guidance	Longer development timelines	Harmonised characterisation standards and reference materials

Future Perspectives

The next generation of cancer nanomedicines is likely to be defined less by novel materials than by better biological reasoning about where particles actually go and why. Three directions appear particularly promising. The first is patient selection. If the enhanced permeability and retention effect varies widely between individuals, then imaging agents able to predict nanoparticle accumulation could identify those patients most likely to benefit, converting nanomedicine into a stratified rather than an empirical therapy. The second is the shift from cytotoxic payloads to immunological and genetic ones. Lipid nanoparticles carrying messenger RNA do not depend on killing every malignant cell directly; they instruct the immune system, so that modest delivery efficiency may still produce a durable systemic response. The third is the integration of nanocarriers with other modalities, including radiotherapy, focused ultrasound and checkpoint blockade, where the nanoparticle acts as a local amplifier rather than as the sole therapeutic agent.

In parallel, the field would benefit from greater methodological rigour. Standardised reporting of physicochemical characterisation, routine use of orthotopic and patient-derived models, and transparent reporting of delivery efficiency expressed as percentage of injected dose per gram of tissue would make preclinical results more comparable and more predictive. Advances in microfluidic manufacturing and in computational modelling of nanoparticle transport are also expected to shorten the path from design to clinical batch.

Conclusion

Nanotechnology has already changed clinical oncology in concrete ways. Pegylated liposomal doxorubicin reduced the cardiotoxicity that had long limited anthracycline use, albumin-bound paclitaxel removed a toxic solvent from the regimen, and liposomal irinotecan and the fixed-ratio daunorubicin and cytarabine formulation have extended survival in diseases where incremental gains are difficult to obtain. At the same time, the field has had to confront a sobering quantitative reality: most of an injected nanoparticle dose does not reach the tumour, and the enhanced permeability and retention effect on which passive targeting depends is far less reliable in patients than in mice. Progress will therefore depend less on continued proliferation of new carrier chemistries and more on understanding the biological barriers that govern delivery, on selecting the patients and tumour types in which these carriers can work, and on building manufacturing and regulatory pathways robust enough to support complex products. Approached in this way, nanomedicine is best understood not as a replacement for existing cancer therapy but as a means of making established and emerging agents safer, better targeted and more durable in effect.

References

1. Barenholz Y. Doxil® — the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):117–134.
2. Bonvalot S, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue

sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial. Lancet Oncol. 2019;20(8):1148–1159.
3. Gradishar WJ, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794–7803.
4. Lancet JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary AML. J Clin Oncol. 2018;36(26):2684–2692.
5. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy. Cancer Res. 1986;46(12):6387–6392.
6. Mitchell MJ, et al. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101–124.
7. O'Brien MER, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004;15(3):440–449.
8. Sung H, et al. Global Cancer Statistics: GLOBOCAN estimates of incidence and mortality worldwide. CA Cancer J Clin. 2021;71(3):209–249.
9. Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–1703.
10. Wainberg ZA, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3). Lancet. 2023;402(10409):1272–1281.
11. Wang-Gillam A, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1). Lancet. 2016;387(10018):545–557.
12. Weber JS, et al. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942). Lancet. 2024;403(10427):632–644.
13. Wilhelm S, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater. 2016;1:16014.