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NANOTECHNOLOGY-BASED DRUG DELIVERY FOR TRIPLE-NEGATIVE BREAST CANCER: RECENT ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES

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ABSTRACT

Triple-negative breast cancer accounts for a minority of breast cancer diagnoses but a disproportionate share of early deaths, and the absence of oestrogen, progesterone and HER2 receptors removes the three targets on which the rest of the discipline is built. Cytotoxic chemotherapy therefore remains the backbone of treatment, and its ceiling is set less by tumour resistance than by what the patient can tolerate. Nanoscale carriers were proposed as the escape from that constraint, on the argument that leaky tumour vasculature would concentrate a circulating particle where free drug could not go. Two decades of work have complicated that argument considerably. This review synthesises the preclinical and clinical evidence for lipid, polymeric, inorganic and cell-derived carriers in triple-negative disease, the ligand and stimulus-responsive strategies developed to compensate for the loss of hormone-receptor targeting, and the record of what has actually reached patients. The pattern that emerges from the clinical data is consistent and is not the one the preclinical literature predicts: every nanoformulation that has succeeded in breast cancer did so by reshaping pharmacokinetics, solubilisation or toxicity rather than by concentrating drug in tumour tissue, and the formulations designed explicitly for tumour targeting have failed in randomised comparison. The review argues that the productive future for nanomedicine in this disease lies in three directions that do not depend on passive accumulation: carriage of cargo that cannot otherwise be administered, particularly nucleic acids and immunomodulators; exploitation of the active transport and dose-threshold behaviour that governs particle entry into tumours; and prospective stratification of patients by measured particle deposition rather than by tumour histology alone.

Keywords: Triple Negative Breast Neoplasms; Nanoparticle Drug Delivery Systems; Drug Carriers; Liposomes; Antibody-Drug Conjugates; Tumor Microenvironment; Translational Medical Research.

1. Introduction

Triple-negative breast cancer is defined by absence. Tumours in this group lack oestrogen and progesterone receptor expression and do not overexpress or amplify HER2, and that negative definition is the whole of the clinical problem: endocrine therapy and HER2-directed agents, which between them account for most of the survival gains in breast oncology over four decades, have nothing to bind. In the cohort study that established the disease's clinical profile, 180 of 1,601 consecutive breast cancer patients (11.2%) were triple-negative, and those patients carried a hazard ratio of 2.6 for distant recurrence and 3.2 for death within five years relative to the remainder.[1] The temporal pattern in that cohort is as informative as the magnitude. Risk of distant recurrence peaked at roughly three years after diagnosis and fell steeply afterwards, so the excess mortality is concentrated in a narrow early window rather than distributed across the survivorship period.

The label conceals substantial biological diversity. Transcriptional profiling of 587 triple-negative cases assembled from 21 datasets resolved six subtypes with distinct gene ontologies and distinct sensitivity to targeted agents,[2] a classification later refined to four when the immunomodulatory and mesenchymal stem-like groups were attributed to infiltrating lymphocytes and tumour-associated stroma rather than to tumour-cell-intrinsic programmes.[3] An independent genomic analysis of 198 tumours arrived at four stable groups by a different route, and found that the basal-like immunosuppressed group carried the worst disease-free and disease-specific survival while the basal-like immune-activated group carried the best (disease-free survival $p = 0.042$ and $p = 0.041$ respectively).[4] A third scheme derived from 465 primary Chinese tumours has since supported subtype-guided trial design.[5] No two schemes agree on boundaries, which matters for a delivery review because a carrier optimised against MDA-MB-231 cells is optimised against one point in a space that these studies show to be at least four-dimensional.

Chemosensitivity in this disease is not the deficit it is often described as. Among 1,118 patients receiving neoadjuvant chemotherapy, the 255 with triple-negative tumours achieved pathological complete response more often than the remainder, 22% against 11% ($p = 0.034$), yet had significantly worse three-year progression-free and overall survival.[6] Survival was equivalent between groups when pathological complete response was achieved and markedly worse for triple-negative patients when residual disease remained. The failure is therefore specific to the residual-disease subgroup, and any argument that chemotherapy is ineffective here is a misreading of the data.

Three additions to the cytotoxic backbone have changed outcomes since 2018. Adding pembrolizumab to neoadjuvant carboplatin and paclitaxel raised pathological complete response from 51.2% to 64.8% in early high-risk disease,[7] and at 75 months of follow-up translated into five-year overall survival of 86.6% against 81.7%, hazard ratio 0.66, $p = 0.00150$.[8] In

previously untreated metastatic disease with a PD-L1 combined positive score of 10 or above, the same agent extended median progression-free survival from 5.6 to 9.7 months, hazard ratio 0.65,[9] and median overall survival from 16.1 to 23.0 months.[10] Sacituzumab govitecan, an antibody-drug conjugate directed at Trop-2 and carrying an SN-38 payload, produced median progression-free survival of 5.6 against 1.7 months and overall survival of 12.1 against 6.7 months in refractory metastatic disease.[11] Adjuvant olaparib benefits the germline BRCA-mutated subgroup.[12] None of these dissolves the underlying constraint: for most patients, most of the time, the therapeutic effect still comes from a cytotoxic drug whose dose is limited by what healthy tissue will absorb.

That constraint is what nanoscale delivery was proposed to relieve, and one nanoformulation has been part of standard practice in this disease since 2005. Albumin-bound paclitaxel dispensed with the polyethoxylated castor oil vehicle that necessitates steroid premedication, and in a randomised phase III comparison delivered a 49% higher paclitaxel dose with a higher response rate (33% against 19%, $p = 0.001$), longer time to progression (23.0 against 16.9 weeks, hazard ratio 0.75, $p = 0.006$), and less grade 4 neutropenia (9% against 22%, $p < 0.001$).[13] That result is worth holding in mind through what follows, because the mechanism behind it is solubilisation and vehicle removal rather than tumour targeting, and the same distinction recurs at every subsequent point where a nanomedicine has succeeded or failed.

This review covers carrier platforms evaluated in triple-negative models, the targeting and stimulus-responsive strategies developed to substitute for the missing hormone receptors, the clinical record, and the barriers that separate the two literatures. It argues a specific position: that the field's dominant design rationale, passive accumulation through leaky vasculature, is the weakest part of its case, and that the strategies most likely to reach patients are those whose benefit does not depend on it.

2. The transport problem, reconsidered

The founding observation was that macromolecules accumulate in solid tumours and are retained there, a consequence of discontinuous tumour vasculature combined with impaired lymphatic drainage, and this enhanced permeability and retention effect became the justification for essentially every untargeted nanocarrier that followed.[14] The tumour microenvironment offers several features a carrier can exploit beyond vascular permeability. Extracellular pH in breast tumours falls to roughly 6.7 to 7.1 against 7.3 to 7.4 in normal tissue, while intracellular pH rises above 7.4, inverting the physiological gradient.[15] The intracellular glutathione concentration reaches approximately 10 mM against an extracellular range of 2 to 20 μM, a difference of three orders of magnitude that a disulfide bond can read.[16] Hypoxia, matrix metalloproteinase overexpression and dense desmoplastic stroma supply further contrasts. Sections 4.2 to 4.4 return to each as a trigger mechanism.

2.1 What the quantitative literature found instead

A survey of nanoparticle tumour delivery published between 2005 and 2015 reported a median delivered dose of 0.7% of the administered amount, with no improvement over the decade surveyed.[17] That figure has been quoted more than any other number in the field and is frequently presented as a verdict on nanomedicine. It should not be, for two reasons that the subsequent literature makes clear.

The first is methodological. Percent injected dose is a distribution metric, and a reanalysis using classical pharmacokinetic measures, tumour area under the curve and exposure relative to a small-molecule comparator, concluded that interpretation of nanoparticle pharmacokinetic results is markedly influenced by which metric is selected, and that the picture on classical measures is considerably more favourable than 0.7% implies.[18] A carrier that delivers a small fraction of dose but sustains tumour exposure for days may outperform a free drug that delivers a larger fraction and clears in hours.

The second is mechanistic, and is the more consequential finding. Detailed imaging of tumour vasculature established that inter-endothelial gaps, the 2,000 nm openings on which particle-size rationales were built, are rare, and that up to 97% of nanoparticle entry into solid tumours proceeds by active transcytosis through endothelial cells.[19] This does not deny that particles accumulate in tumours. It relocates the rate-limiting step from a passive geometric problem to an active cellular one, and in doing so invalidates a good deal of the design reasoning that treats particle diameter relative to a hypothetical pore as the primary variable.

A third result reframes the 0.7% figure as a saturation artefact rather than a ceiling. Hepatic Kupffer cell uptake competes with tumour delivery, and once the administered particle number exceeds roughly one trillion per mouse that uptake saturates; above the threshold, tumour delivery rose to as much as 12% of injected dose and the fraction of tumour cells reached approached 93%.[20] Delivery efficiency, on this evidence, is dose-dependent and not a fixed property of the carrier.

2.2 The consequence for targeting

Ligand functionalisation is the field's standard answer to poor delivery, and the aggregate evidence for it is narrower than its prevalence in the literature suggests. Across preclinical datasets, active targeting reliably increases cellular internalisation once a particle has reached the tumour interstitium but does not significantly increase total tumour localisation for carriers above about 50 nm.[21] Ligands change what happens after arrival, not how much arrives. This is not an argument against them, since intracellular delivery is exactly what a nucleic acid or a lysosomally activated prodrug requires. It is an argument against citing tumour accumulation as their justification, which much of the primary literature continues to do.

Human data on interpatient variability point the same way. Ferumoxytol magnetic resonance imaging was piloted as a companion

measurement of nanoparticle deposition in patients receiving nanoliposomal irinotecan, on the premise that deposition varies enough between individuals to be worth measuring before treating.[22] That premise is the one the preclinical literature almost never tests, since inbred mice bearing implanted tumours of uniform age remove precisely the variability that determines whether a given patient will benefit.

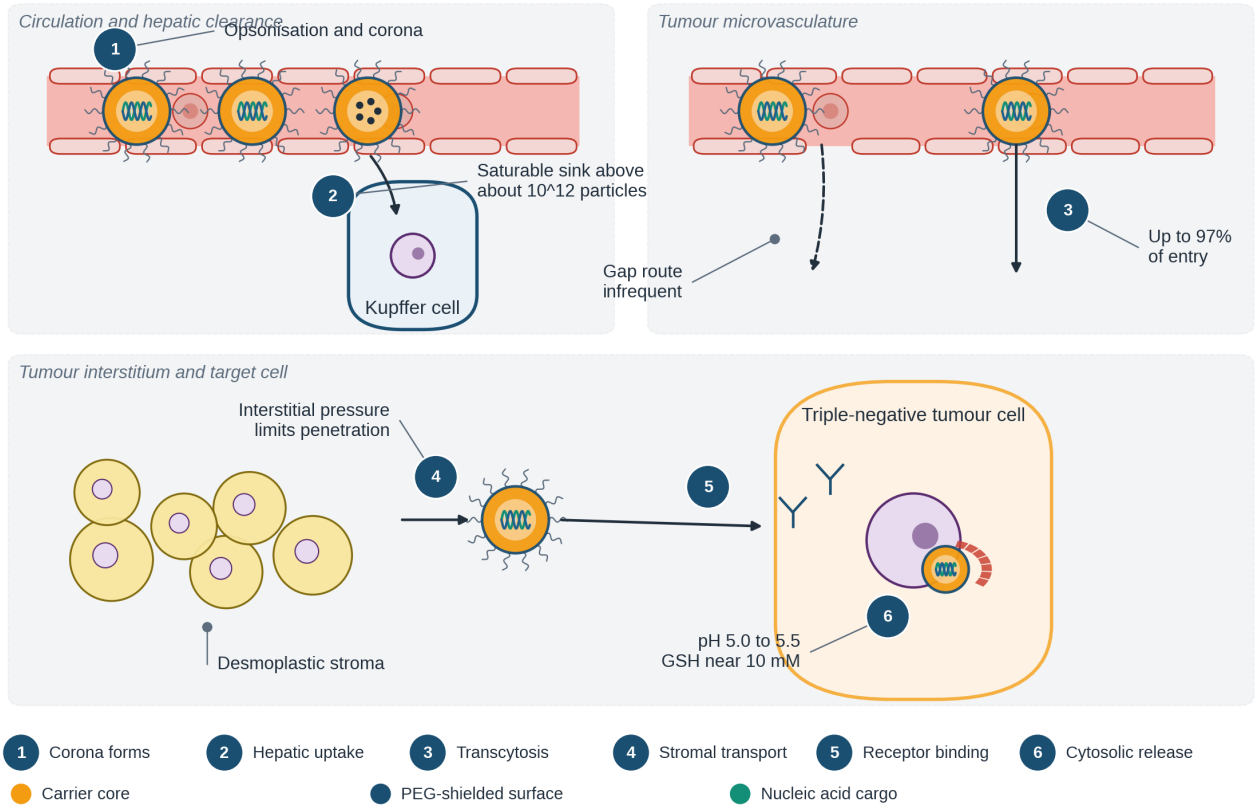

Figure 1. The delivery cascade for an intravenously administered nanocarrier in triple-negative breast cancer, showing the sequential losses that determine how much drug reaches a tumour cell.

3. Carrier platforms evaluated in triple-negative disease

The preclinical literature is large, uneven in quality, and dominated by two cell lines. MDA-MB-231 and murine 4T1 appear in the large majority of published studies, which constrains what can be generalised from them. Table 1 collects representative studies that reported physicochemical characterisation, a comparative cytotoxicity measure and an in vivo efficacy endpoint together, since studies reporting only one of the three are difficult to weigh.

3.1 Lipid-based carriers

Liposomes remain the most clinically credentialed nanocarrier class, and recent triple-negative work has moved away from simple encapsulation toward structural modification of the bilayer itself. Substituting cholesterol with the ginsenoside Rg3 produced docetaxel liposomes of 96.7 ± 4.5 nm against 136.8 ± 2.0 nm for the conventional comparator, with first-day leakage of 1.0% against 18.3% and a half-maximal inhibitory concentration of 0.8 ng/mL against 25.4 ng/mL in 4T1 cells.[23] The 30-fold

potency separation is larger than encapsulation alone explains, and the authors attribute it to Glut1-mediated uptake together with stromal remodelling, with alpha-smooth muscle actin reduced to one third and transforming growth factor beta approximately halved. Spheroid penetration depth rose from 66.7 ± 5.8 μm to 113.3 ± 5.8 μm, which is the more transferable observation, since penetration through a three-dimensional mass is closer to the clinical situation than potency against a monolayer.

Antibody conjugation to a liposome surface has produced smaller gains. Anti-lysyl-oxidase epirubicin liposomes reduced day-12 tumour volume to 810 ± 174 mm³ against 1039 ± 233 mm³ for the untargeted liposome and 1029 ± 203 mm³ for free drug,[24] a separation of roughly 22% that is modest against the 60% against 5% difference in tumour necrosis the same study reported. A large histological effect alongside a small volumetric one recurs throughout this literature and usually indicates that delivery, not potency, is limiting.

Covalent conjugation of drug to a lipid, rather than encapsulation within one, addresses the loading problem directly. A sphingomyelin-paclitaxel conjugate assembled into nanovesicles achieved drug loading of 16.2% to 18.4% against 0.89% for conventional liposomal paclitaxel, and raised the maximum tolerated dose from 20 mg/kg for solvent-based paclitaxel to 70 to 100 mg/kg.[25] A five-fold increase in tolerated dose is a larger therapeutic gain than most targeting strategies have produced, and it arises entirely from altered disposition.

Solid lipid nanoparticles and nanostructured lipid carriers occupy a middle position: cheaper and more scalable than liposomes, with lower loading capacity. Integrin-targeted paclitaxel solid lipid nanoparticles achieved encapsulation above 90% and an inhibitory concentration of 1.2 μg/mL against 3.4 μg/mL untargeted and 8.9 μg/mL free drug in 4T1 cells, with 82% tumour volume reduction and prevention of pulmonary metastasis.[26] Curcumin-loaded solid lipid nanoparticles increased intracellular doxorubicin retention five- to ten-fold relative to free curcumin in P-glycoprotein-overexpressing triple-negative cells, functioning as an efflux-reversal agent rather than as a cytotoxic carrier.[27] Quality-by-design optimisation of folate-functionalised nanostructured lipid carriers co-loading docetaxel and erlotinib gave entrapment near 95%, combination indices of 0.35 and 0.37 at a 1:3 molar ratio, and six-month stability at 4 °C,[28] the sort of formulation-development detail that most academic nanomedicine papers omit and every manufacturer requires.

Lipid nanoparticles for nucleic acid delivery represent the class with the strongest independent validation, since the platform is already in worldwide clinical use for messenger RNA vaccines. In triple-negative models the approach has been used both to deliver tumour-suppressor messenger RNA alongside cytotoxic drug and to silence oncogenic transcripts. Lipid nanoparticles built from a paclitaxel-amino-lipid carried 24 wt% paclitaxel with 88.7 ± 0.7% messenger RNA encapsulation, and co-delivery of p53 messenger RNA gave a combination index of

0.937 with efficacy exceeding both albumin-bound and liposomal paclitaxel comparators in orthotopic disease.[29] Selective organ targeting chemistry pushed lung accumulation from 1.2% to 16% and, combined with a MUC1 messenger RNA vaccine, produced 66.0% tumour growth inhibition against 46.8% for the silencing construct alone and 34.0% for the vaccine alone.[30] Additive rather than synergistic, but the direction is clear and the platform is manufacturable at scale.

3.2 Polymeric carriers

Poly(lactic-co-glycolic acid) is the default polymeric carrier because it is already approved as an excipient, and its triple-negative literature illustrates both the promise and the reproducibility problem of ligand targeting. Anti-EGFR-anchored paclitaxel nanoparticles in EGFR-high MDA-MB-468 xenografts reported a 93-fold higher tumour-to-plasma drug ratio than the free drug comparator,[31] while RGD-functionalised docetaxel nanoparticles in orthotopic 4T1 disease reported higher intratumoural accumulation on magnetic resonance imaging and, more usefully, substantially reduced cardiac toxicity on cardiac imaging relative to free docetaxel.[32] The second endpoint is the more credible contribution, since reduced off-target toxicity has translated clinically in this field and enhanced tumour accumulation largely has not.

Route of administration is an underexplored variable. A lipid-based combination nanoparticle co-loading gemcitabine and paclitaxel, administered subcutaneously to engage lymphatic transport, produced 100- to 140-fold greater tumour growth inhibition than equivalent free drug in axillary and sub-iliac tumours, with a tumour-to-plasma gemcitabine ratio at or above unity for 48 hours.[33] Effect sizes of that magnitude in vivo are uncommon and warrant independent replication, but the underlying logic, that regional lymphatic delivery sidesteps the systemic distribution problem entirely, deserves more attention than it receives.

Chitosan carriers exploit the polymer's cationic character for nucleic acid complexation and its derivatisation for CD44 targeting. Hyaluronic-acid-coated thiolated chitosan nanoparticles carrying 5-fluorouracil gave an inhibitory concentration of 42.1 ± 0.11 μg/mL in MDA-MB-231 against 51.3 ± 0.04 μg/mL in MCF-10A normal mammary epithelium.[34] That selectivity ratio of about 1.2 is honest reporting and also a caution: a carrier that is only marginally more toxic to tumour than to normal epithelium has not solved the therapeutic index problem. A more sophisticated use of the same polymer co-delivered 5-fluorouracil with three microRNAs, on the rationale that 5-fluorouracil itself suppresses miR-1275, miR-615-5p and Let-7i while activating JAK/STAT and PI3K/Akt/mTOR signalling, so that the carrier repairs the resistance mechanism the drug creates.[35] Release was approximately 40% at pH 7.4 against 80% at pH 5.5 over 72 hours.

Polymeric micelles have the longest clinical history of any research-stage polymer platform and the most instructive record. Among academic systems, a hyaluronic-acid-dasatinib

prodrug micelle encapsulating olaparib achieved 72.31% tumour growth inhibition against 56.53% for the free drug combination, with olaparib half-life extended 2.46-fold and area under the curve 3.22-fold,[36] while RGD-modified lipid-core docetaxel micelles raised area under the curve 3.2-fold and half-life from 5.57 ± 0.51 to 13.25 ± 2.54 hours.[37] Both improvements are pharmacokinetic. In the clinic, the methoxy-poly(ethylene glycol)-poly(D,L-lactide) micelle Genexol-PM raised objective response rate against Cremophor-based paclitaxel in 212 patients with HER2-negative advanced breast cancer without improving progression-free or overall survival,[38] a pattern section 6 shows to be characteristic of the field.

Dendrimers offer defined architecture and high surface valency at the cost of charge-related toxicity. PEGylated dendritic polylysine co-delivering paclitaxel and AXL-silencing small interfering RNA restored sensitivity in paclitaxel-resistant 4T1 cells with 84.69% encapsulation at 49.6 ± 5.9 nm.[39] Carrier-free self-assembly of two drugs, dispensing with the excipient entirely, produced paclitaxel-curcumin nanodrugs with 80.36% tumour growth inhibition and release of 33.3% at pH 7.4 against 83.2% at pH 5.5 over 48 hours,[40] which is a useful reminder that not every delivery problem requires a delivery vehicle.

3.3 Inorganic and carbon-based platforms

Inorganic carriers bring capabilities the organic classes cannot match, principally photothermal conversion, catalytic activity and imaging contrast, and bring a persistence problem the organic classes do not have.

Gold nanostructures dominate the photothermal literature. EpCAM-directed silver-coated gold nanorods achieved 4.5-fold higher tumour accumulation than untargeted particles at 24 hours, though the absolute figures, 1.4% against 0.3% of injected dose, place the whole comparison inside the low-single-digit range that section 2 identified. More recent work uses heating to provoke immunity rather than to ablate: solamargine-functionalised gold nanoparticles combined with PD-L1 blockade eradicated distant untreated tumours in all treated animals, with increased CD8-positive T cells and natural killer cells and a raised M1 to M2 macrophage ratio.[42] A layer-by-layer gold nanorod and nanocluster composite reached 52 °C after ten minutes at 808 nm and 400 mW/cm², reducing three-dimensional spheroid viability below 5% against 29% without irradiation, with no *in vivo* data reported.[43]

Mesoporous silica provides high loading capacity with gateable pores; aptamer capping against MUC1 has been used to make release conditional on receptor engagement.[44] Iron oxide carriers have moved from magnetic guidance toward catalytic chemistry. Magnetic composite nanoparticles carrying docosahexaenoic acid and doxorubicin re-sensitised doxorubicin-resistant MDA-MB-231 cells by suppressing PI3K/AKT/mTOR signalling and glutathione peroxidase 4, driving ferroptosis in cells selected for apoptotic resistance.[45] IR-780-loaded superparamagnetic carriers combining magnetic

guidance, photothermal therapy and radiotherapy eradicated tumours completely in three of five animals, with 25% recurrence at two weeks.[46] Reporting both the complete response fraction and the recurrence fraction is uncommon and should be standard.

Catalytic nanomedicine has produced the largest single-agent effects in this literature. An iron(II) metal-organic framework nanozyme loaded with actinomycin D depleted glutathione by 25.5% at 24 hours and reported a tumour inhibition rate of 91.89% in orthotopic 4T1 disease.[47] A porphyrinic framework combining photodynamic therapy with checkpoint blockade raised dendritic cell maturation 1.5- to 1.9-fold and tumour-infiltrating cytotoxic lymphocytes 2- to 2.5-fold, with significant inhibition of distant untreated tumours.[48] Folate-functionalised carbon dot micelles reduced the doxorubicin inhibitory concentration roughly ten-fold.[49]

Against these, the safety data are the weaker half of the record. PEGylated gold nanoparticles cleared more than 80% from circulation within 24 hours but showed an elimination half-life of 57.0 hours, a whole-body mean residence time of 74.6 hours, and roughly 74% of residual gold held in liver between days 7 and 28, with altered lipid metabolism and liver injury markers still present at 28 days.[50] Silica nanoparticles similarly concentrate in liver and spleen, with degradation and clearance governed by size, shape, porosity and surface modification, and safety identified as the principal translational barrier.[51] Quantum dot cytotoxicity tracks surface chemistry, diameter and exposure duration rather than core composition, so cadmium-free substitution alone does not resolve it.[52,53] Graphene oxide produces lung DNA double-strand breaks whose resolution depends on lateral size, dose and inflammatory profile, followed to day 84.[54] Carbon nanotube toxicity is systematically overstated by monolayer culture relative to spheroids,[55] which cuts both ways: it inflates apparent efficacy in the same assays.

The mismatch is straightforward to state. Efficacy studies in this section observed animals for 14 to 28 days. Gold, silica and carbon materials persist for months. No triple-negative efficacy study identified for this review followed clearance beyond 28 days.

3.4 Cell-derived and biomimetic systems

Coating a synthetic core with a biological membrane transfers that membrane's surface identity to the particle, which is a more economical route to immune evasion and homotypic targeting than synthetic ligand chemistry. Successful coating is verifiable: zeta potential shifts from −58.7 ± 1.02 mV to −27.8 ± 0.67 mV on application of a red blood cell and fibroblast hybrid membrane, and the coated particle released 58.47% over ten hours against 90.40% in four hours for free drug.[56]

Exosome-sheathed porous silica co-delivering 3,3'-diindolylmethane and doxorubicin reduced inhibitory concentrations from 48 μM and 22 μM for the free drugs to 0.77 μM and 0.31 μM, and reversed the epithelial-mesenchymal transition that doxorubicin alone induced, where N-cadherin rose to 65.7% in MDA-MB-231 cells.[57]

That a cytotoxic drug drives the mesenchymal programme it is meant to suppress is an argument for combination carriage rather than for higher dose. Cancer cell membrane-coated albumin particles carrying indocyanine green and perfluorotributylamine reduced tumour hypoxia from 87.4% before injection to 8.3% at 24 hours,[59] addressing the oxygen dependence that limits photodynamic therapy, while tumour-derived vesicles loaded with paclitaxel and melanin raised tumour-infiltrating CD8-positive lymphocytes from 6.3% to 11.2% under irradiation[58] and platelet membrane coating eliminated tumours completely with no recurrence over 18 days.[60] Bacterial outer membrane vesicles contribute intrinsic immunostimulation: hybridised with cancer cell membrane they supported sonodynamic therapy of bone metastasis with 100% two-week survival against 50% for control,[61] and cloaking cerium oxide nanozymes in outer membrane vesicles produced radiosensitisation that spared normal fibroblasts, with gamma-H2AX signal exceeding a 10 Gy positive control at 4 Gy and no detectable lung metastases.[62]

The manufacturing objection to this class is serious and rarely addressed in the primary papers. A source cell line, a membrane extraction, a coating step and a characterisation panel for membrane orientation and protein retention constitute a biological product process appended to a chemical one, and no regulatory precedent exists for it.

Table 1. Representative nanocarrier studies in triple-negative breast cancer models reporting physicochemical characterisation, comparative cytotoxicity and an in vivo endpoint together.

Carrier	Cargo	Model	Size / EE	Key comparative outcome	Ref
Ginsenoside Rg3 liposome	Docetaxel	4T1, orthotopic BALB/c	96.7 ± 4.5 nm; loading 7.1 ± 0.1%	IC50 0.8 vs 25.4 ng/mL (conventional liposome); spheroid penetration 113.3 vs 66.7 µm	[23]
Anti-LOX liposome	Epirubicin	MDA-MB-231, nude mice	156-171 nm; EE 60%	Day-12 tumour 810 ± 174 vs 1039 ± 233 mm³; necrosis 60% vs 5%	[24]
Sphingomyelin-paclitaxel nanovesicle	Paclitaxel (conjugated)	4T1-Luc2 orthotopic	Loading 16.2-18.4%	Maximum tolerated dose 70-100 vs 20	[25]

				mg/kg for solvent-based paclitaxel	
Integrin-targeted solid lipid nanoparticle	Paclitaxel	4T1, MDA-MB-231; 4T1 mice	EE >90%	IC50 1.2 vs 3.4 vs 8.9 μg/mL; 82% tumour volume reduction	[26]
Paclitaxel-amino-lipid nanoparticle	Paclitaxel + p53 mRNA	MDA-MB-231 orthotopic	163.2 ± 0.9 nm; mRNA EE 88.7 ± 0.7%	Combination index 0.937; exceeded albumin-bound and liposomal paclitaxel	[29]
SORT lipid nanoparticle	siMETTL16 + MUC1 mRNA	4T1, BALB/c	131.86 nm; EE 95.2%	TGI 66.0% vs 46.8% (siRNA alone) vs 34.0% (vaccine alone)	[30]
Anti-EGFR PLGA nanoparticle	Paclitaxel	MDA-MB-468 xenograft	336.3 nm; entrapment 85.58 ± 1.2%	93-fold higher tumour-to-plasma drug ratio vs free drug	[31]
Lymphatic-targeting lipid nanoparticle	Gemcitabine + paclitaxel	4T1 orthotopic; MDA-231-HM	~60 nm; drug association 98% / 75%	100-140x greater TGI than equivalent free drug	[33]
Hyaluronic acid-dasatinib micelle	Dasatinib + olaparib	MDA-MB-231, nude mice	56.18 ± 1.29 nm	TGI 72.31% vs 56.53% (free combination); olaparib AUC x3.22	[36]
Iron(II) metal-organic framework nanozyme	Actinomycin D	4T1 orthotopic	~50 nm	GSH depletion 25.5% at 24 h; tumour inhibition rate 91.89%	[47]
Superparamagnetic iron oxide carrier	IR-780 (PTT + radiotherapy)	4T1, nude mice	41.21 ± 4.8 nm; EE >92%	Complete eradication in 3/5 animals; 25% recurrence	[46]

				at 2 weeks	
Exosome-sheathed porous silica	Diindolylmethane + doxorubicin	MDA-MB-231, 4T1 orthotopic	80-150 nm; EE ~84% / ~81%	IC50 0.77 / 0.31 µM vs 48 / 22 µM free; reversed doxorubicin-induced EMT	[57]
Cancer cell membrane-coated albumin particle	Indocyanine green + perfluorotributylamine (PDT)	4T1 xenograft	131.3 ± 1.08 nm	Tumour hypoxia 87.4% to 8.3% at 24 h	[59]
Cerium oxide nanozyme in outer membrane vesicle	Radiosensitiser	Bilateral orthotopic 4T1	191.3 nm	4T1 viability to 60% at 4 Gy with fibroblast sparing; no lung metastases	[62]

4. Targeting and stimulus-responsive design

4.1 The surface target landscape

Losing three receptors does not leave a tumour featureless. It leaves a set of candidate targets that are less prevalent, less specific and considerably less validated than the ones the rest of breast oncology uses, and a delivery review should be explicit about the arithmetic. Table 2 assembles the reported prevalences from immunohistochemical cohorts.

Trop-2 is the strongest candidate on prevalence alone, expressed in 86% of 685 triple-negative tumours, although only 16.5% at high intensity and 58.2% at low.[63] Folate receptor alpha follows at 71% of 384 centrally confirmed cases, where its expression associated with improved disease-free survival.[64] PD-L1 was positive in 44.3% of 88 tumours at baseline, and, notably for anyone designing a targeted carrier around it, 52.9% of initially positive cases lost expression after neoadjuvant therapy.[65] Transferrin receptor was positive in 43% of 23 specimens,[66] CD44 in 40% of 50,[67] and mesothelin in 36% of 226, correlating with basal-like phenotype and distant metastasis.[68] EGFR, which appears in the delivery literature more often than any of these, was positive in 18.7% of 150 tumours with high-level expression in only 2.7%,[68].

Two consequences follow. First, no single target covers the disease, so a ligand-targeted product would require companion diagnostic selection, which changes the commercial calculation. Second, the field's target selection is inverted relative to prevalence: EGFR, the least prevalent marker in this table, is the most frequently used ligand target in published triple-negative nanocarriers, while Trop-2 is used least often outside the antibody-drug conjugate literature. That inversion is a legacy of which antibodies were available rather than of which targets are present.

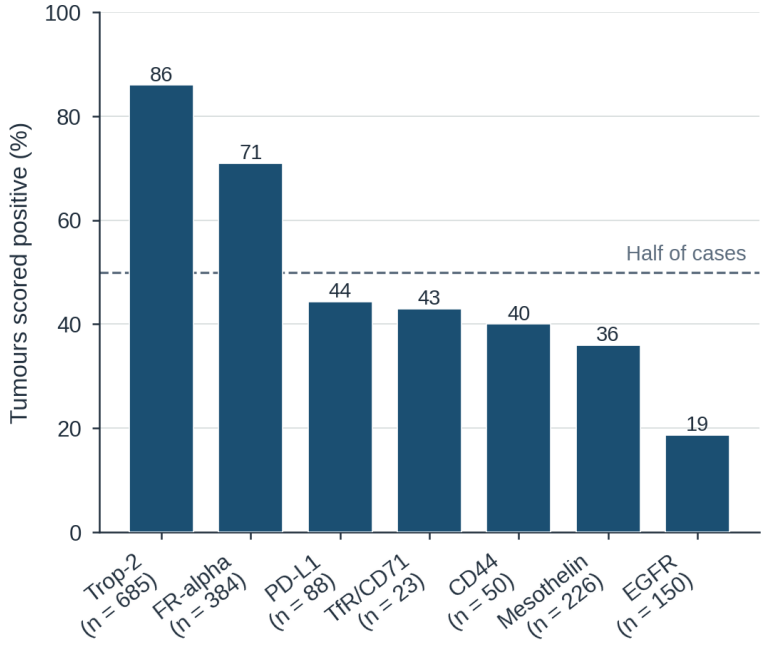

Figure 2. Reported positivity for candidate surface targets in triple-negative breast cancer, ordered by prevalence, with the size of the cohort supplying each estimate.

Table 2. Candidate surface targets for ligand-directed nanocarriers in triple-negative breast cancer, with prevalence as reported in immunohistochemical cohorts.

Target	Reported prevalence	Cohort	Ligand classes used in nanocarriers	Ref
Trop-2	86% (589/685); high intensity 16.5%	685 TNBC	Antibody (antibody-drug conjugate)	[63]
Folate receptor alpha	71% (274/384)	384 TNBC	Folic acid	[64]
Luteinising hormone-releasing hormone receptor	>50%	TNBC specimens	LHRH peptide	[72]
PD-L1	44.3% at baseline; 52.9% of positives lost expression after neoadjuvant therapy	88 TNBC	Small-molecule inhibitor cargo, antibody	[65]
Transferrin receptor (CD71)	43% (10/23)	23 TNBC	Transferrin, ferritin	[66]
CD44	40% (20/50)	50 TNBC	Hyaluronic acid, chitosan oligosaccharide	[67]
Mesothelin	36% (82/226)	226 TNBC	Antibody	[68]

EGFR	18.7% (28/150); high level 2.7%	150 TNBC	Nanobody, antibody, peptide	[69]
Integrin alpha-v beta-3	Not established by a prevalence cohort in this review	-	RGD, iRGD peptide	[32,37,71]
Nucleolin	Not established by a prevalence cohort in this review	-	AS1411 aptamer	[73,74]

4.2 Ligand classes and what each contributes

Antibody fragments give the highest affinity and the largest manufacturing burden. An anti-EGFR nanobody on quantum dot theranostic micelles carrying aminoflavone produced EGFR-specific uptake and tumour regression in orthotopic MDA-MB-468 disease.[70] Peptides trade affinity for cost and immunogenicity: iRGD-modified red blood cell membrane-camouflaged silica particles gave 86.29 ± 5.12% tumour growth inhibition with apoptosis of 71.1% against 27.7% for the untargeted comparator,[71] and luteinising hormone-releasing hormone conjugates of prodigiosin and paclitaxel reduced tumour volume by approximately 95.6% and 91% at 21 days.[72]

Aptamers are the class with the best recent data and the least clinical precedent. An AS1411 aptamer-triptolide conjugate with an acid-labile acetal ester linker gave inhibitory concentrations of 18.31 ± 0.42 nM in MDA-MB-231, 21.23 ± 1.61 nM in MDA-MB-468 and 22.09 ± 1.21 nM in 4T1 cells, with approximately 11-fold tumour accumulation, 83.7% tumour growth inhibition, a 40% cure rate, and plasma half-life extended 29-fold to 7.32 hours.[73] A companion construct pairing the same aptamer with paclitaxel through a redox-cleavable thioether and a fluorouracil modification gave synergistic activity with reduced in vivo toxicity.[74] Consistency across two linker chemistries and three cell lines from the same group is encouraging; independent replication is the missing element.

4.3 Reading the microenvironment

The gradients described in section 2.1 become useful when a bond is chosen to break under one condition and hold under the other. Dual-responsive designs perform better than single-trigger ones because they can encode a logical conjunction. Hyperbranched nanoparticles responsive to both pH and glutathione released 10% over 120 hours at pH 7.4 with 10 μM glutathione and 100% at pH 6.4 with 10 mM glutathione, while shrinking from 227.0 ± 73.6 nm to 32.10 ± 5.9 nm and reversing surface charge, so that a long-circulating particle converts into a small penetrating one only inside the tumour.[75] Apoptosis rose to 71.5 ± 2.8% against 42.3 ± 3.1% for free docetaxel.

Enzyme-responsive release offers the sharpest specificity available. Self-assembled peptide nanofibers combining a cell-penetrating sequence with an EGFR-binding motif and a matrix metalloproteinase-9-cleavable

doxorubicin linker released approximately 85% of payload within 90 minutes of exposure to activated enzyme and matched free doxorubicin's antiproliferative effect at a 6.7-fold lower dose, 7.5 μM against 50 μM, while sparing keratinocytes.[76] Redox and CD44 targeting combine in disulfide-crosslinked hyaluronic acid micelles co-loading paclitaxel with ritonavir as an efflux inhibitor, where paclitaxel release rose from 43.5% at pH 7.4 to 98.2% at pH 6.8 in serum.[77] A simpler lipid-polysaccharide construct with disulfide crosslinks reduced the doxorubicin inhibitory concentration three-fold in MDA-MB-231 and two-fold in MDA-MB-468 cells with no change in MCF-10A normal epithelium,[78] the selectivity profile the chitosan example in section 3.2 did not achieve.

Hypoxia is the trigger with the clearest tumour specificity and the least developed chemistry. A niosome-encapsulated dendrimer carrying tirapazamine reduced the inhibitory concentration under 1% oxygen to 14.14 μM against 71.37 μM for the dendrimer alone and 143.3 μM for free prodrug,[79] and hypoxia-activated TH302 combined with a photosensitiser in CD44-targeted liposomes reduced MDA-MB-231 viability to 11.08 ± 0.79% under irradiation.[80] Both exploit a feature that healthy tissue does not have, which is a stronger starting position than pH or glutathione gradients that differ from normal tissue by degree rather than in kind.

4.4 Resistance and anatomical sanctuaries

Nanocarriers address P-glycoprotein efflux by two distinct routes that are often conflated. The Transcytosis-promoting design applies to both tumour penetration and the blood-brain barrier, which matters because central nervous system relapse is common in this disease. A transcytosable peptide-paclitaxel prodrug with acid- and esterase-sensitive linkers released 57.02 ± 0.51% at pH 6.8 with esterase over 48 hours and improved tumour inhibition to 43.24% against 28.47% for free drug[81,82], and iRGD-coated nanoworms reduced experimental brain metastasis when given early in metastatic progression.[83] Evidence in this area remains thin, and no triple-negative-specific brain-penetrant nanocarrier with survival data was identified for this review.

5. Combination and immunomodulatory nanomedicine

The strongest argument for a carrier is not that it takes a drug somewhere new but that it takes two or more agents to the same cell in a fixed ratio. Free drugs given together distribute independently, so the ratio at the tumour is not the ratio in the syringe; co-encapsulation fixes it. This is the mechanism behind the only ratio-controlled liposome approved anywhere in oncology, and it applies with particular force in a disease where combination is already standard.

Multi-agent carriers have accordingly grown more ambitious. A pH-responsive micelle carrying paclitaxel, the CXCR4 antagonist AMD3100 and the PD-L1 inhibitor BMS-1 addressed the cytotoxic, stromal and immune-checkpoint axes at once, releasing 23.1% of paclitaxel at pH 7.4 against 58.7% at pH 5.0, and

produced approximately 57% tumour inhibition with 83% inhibition of lung metastasis and 70% survival at day 51.[84] Whether three agents in one particle is developable is a separate question from whether it works in mice.

Macrophage repolarisation can be achieved without any drug at all: polyaniline-coated iron oxide particles reduced tumour volume by 50% and weight by 30% with a significant reduction in lung metastases ($p = 0.0163$)[85,86,87]. Copper and iron coordination systems inducing cuproptosis and ferroptosis under near-infrared-II irradiation release approximately 93% of copper in the tumour microenvironment against 38% in plasma,[88] engaging death pathways distinct from the apoptotic route that resistant cells have already learned to block.

The clinical evidence for nano-immunotherapy in this disease is early but is no longer absent. An individualised neoantigen vaccine formulated as an intravenous RNA-lipoplex, carrying up to 20 mutations across two RNA molecules, induced vaccine-specific T cell responses in all 14 evaluable patients treated in the adjuvant setting, with 12 of 14 measurable by ex vivo ELISpot and nine responding to five or more neoantigens; 11 patients remained relapse-free for up to six years.[89] A single-arm phase 1 study cannot establish efficacy, and adjuvant triple-negative patients who reach that setting after standard therapy include many who would not have relapsed. What the study does establish is that a lipid nanoparticle can deliver a personalised, manufactured-per-patient payload systemically and produce durable measurable immunity, which is a capability no small molecule possesses.

6. What has actually reached patients

Nanoformulations that succeeded did so by changing pharmacokinetics or toxicity. Liposomal encapsulation of doxorubicin with cyclophosphamide reduced cardiotoxicity from 21% to 6% while preserving antitumour efficacy[90], and the pegylated formulation was developed on and marketed for the same rationale.[91] Albumin-bound paclitaxel, discussed in section 1, works by eliminating a toxic vehicle. The fixed 5:1 cytarabine to daunorubicin liposome works by holding a molar ratio.[92,93] Not one of these five is a targeting technology.

Nanoformulations designed for tumour targeting have not succeeded. NK105, a paclitaxel-incorporating polymeric micelle, entered a 436-patient phase III non-inferiority trial against paclitaxel and produced median progression-free survival of 8.4 months against 8.5 months, hazard ratio 1.255 (95% CI 0.989 to 1.592), breaching the predefined non-inferiority margin of 1.215.[94] The formulation was better tolerated, with grade 3 or higher peripheral sensory neuropathy of 1.4% against 7.5%, and that advantage was not what the trial measured. BIND-014, a prostate-specific membrane antigen-targeted docetaxel nanoparticle and the most prominent actively targeted product to reach clinical testing, completed phase 2 without establishing benefit, and its sponsor did not survive commercially.[95] Genexol-PM improved

response rate without improving time-to-event endpoints.

The most instructive episode in the field concerns a formulation that was never itself the variable under test. Atezolizumab combined with albumin-bound paclitaxel extended median progression-free survival in PD-L1-positive metastatic triple-negative disease from 5.0 to 7.5 months, hazard ratio 0.62, with median overall survival of 25.0 against 15.5 months in that subgroup, and this supported accelerated approval.[96,97] The confirmatory trial substituted solvent-based paclitaxel with the steroid premedication it requires, kept everything else, and missed its primary progression-free survival endpoint in the PD-L1-positive population.[98] The indication was voluntarily withdrawn on 27 August 2021.[99] Whether the difference lay in the nanoparticle formulation itself or in the corticosteroids that solvent-based paclitaxel obliges cannot be settled from two trials, and the most defensible reading is that the immunosuppressive premedication is the more likely culprit. Either way, the episode demonstrates that formulation choice can determine whether an immunotherapy combination succeeds, which is a stronger claim for nanoformulation than the tumour-targeting literature has ever substantiated.

Antibody-drug conjugates deserve separate treatment because they are frequently claimed for nanomedicine and are not nanoparticles. Sacituzumab govitecan achieved a hazard ratio of 0.48 for overall survival in refractory metastatic disease trastuzumab deruxtecan produced median overall survival of 23.4 against 16.8 months in HER2-low disease including a hormone-receptor-negative cohort,[100] and datopotamab deruxtecan extended progression-free survival to 6.9 against 4.9 months with grade 3 or higher adverse events of 21% against 45% for chemotherapy.[101,102] These are molecularly defined single entities with a defined drug-to-antibody ratio, manufactured as biologics. They validate targeted intracellular payload delivery in this disease decisively; they do not validate nanoparticles.

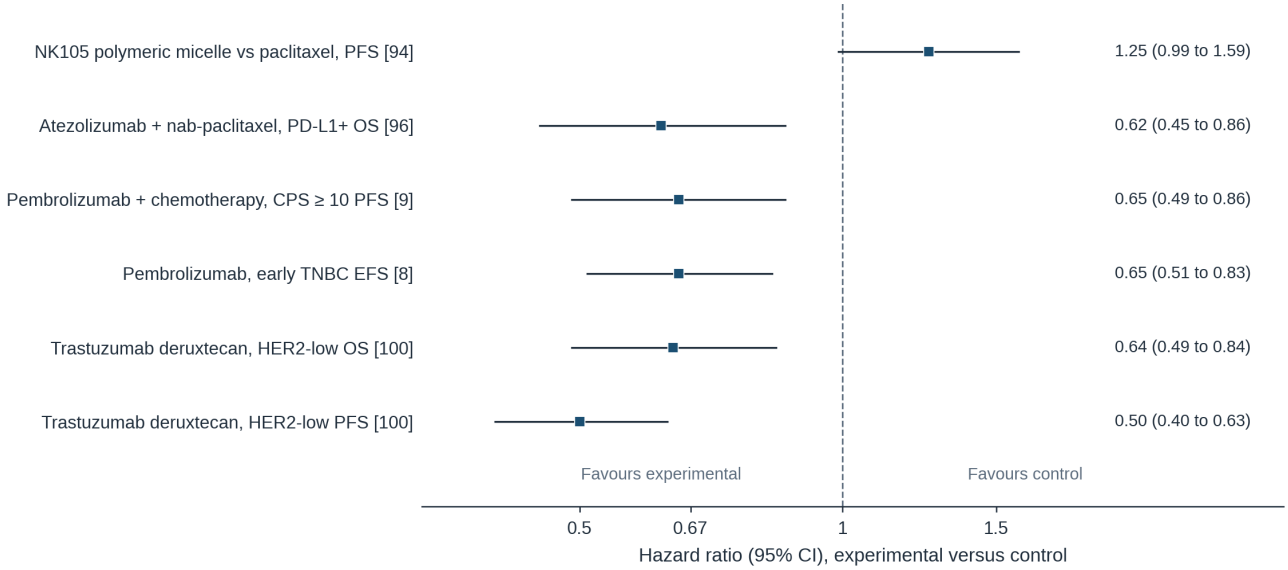

Figure 3. Randomised effect estimates in triple-negative and related breast cancer settings, plotted on a logarithmic hazard ratio scale with 95% confidence intervals.

Table 3. Clinical evidence for nanoformulations and targeted macromolecular carriers relevant to triple-negative breast cancer.

Agent (platform)	Phase / registration	Population	Key result	Status
Albumin-bound paclitaxel (albumin nanoparticle)	III (n = 454)	Metastatic breast cancer	ORR 33% vs 19%, p = 0.001; time to progression 23.0 vs 16.9 weeks, HR 0.75; grade 4 neutropenia 9% vs 22%	Approved; standard of care
Liposomal doxorubicin + cyclophosphamide (non-pegylated liposome)	III	Metastatic breast cancer	Cardiotoxicity 6% vs 21% with comparable antitumour efficacy	Approved
Pegylated liposomal doxorubicin (pegylated liposome)	III	Metastatic breast cancer, first line	Reduced cardiotoxicity with comparable efficacy vs conventional doxorubicin	Approved
Atezolizumab + albumin-bound paclitaxel	III, NCT02425891 (n = 902)	Untreated advanced TNBC	PD-L1-positive PFS 7.5 vs 5.0 months, HR 0.62; OS 25.0 vs 15.5 months, HR	Accelerated approval withdrawn 27

			0.62	Aug 2021
Atezolizumab + solvent-based paclitaxel	III	Untreated advanced TNBC	Primary PFS endpoint not met in the PD-L1-positive population	Confirmatory trial; triggered withdrawal
Genexol-PM (polymeric micelle)	III (n = 212)	HER2-negative advanced breast cancer	ORR 39.1% vs 24.3%, p = 0.016; PFS 8.0 vs 6.7 months, p = 0.26; OS 28.8 vs 23.8 months, p = 0.52	Approved in some jurisdictions
NK105 (polymeric micelle)	III, NCT01644890 (n = 436)	Metastatic or recurrent breast cancer	PFS 8.4 vs 8.5 months, HR 1.255 (0.989-1.592); non-inferiority margin 1.215 breached	Failed
BIND-014 (PSMA-targeted polymeric nanoparticle)	II, NCT01812746	Metastatic castration-resistant prostate cancer	No survival advantage established	Discontinued; sponsor insolvent
Liposomal irinotecan (liposome)	Ib, NCT04728035 (n = 119)	mTNBC after two or more prior chemotherapy lines	ORR 25.3% (22/87); PFS 4.8 months; OS 14.1 months	Completed
Individualised RNA-lipoplex neoantigen vaccine (lipid nanoparticle)	Phase I, NCT02316457 (n = 14 evaluable)	Adjuvant TNBC	T cell responses in 14/14; 12/14 ELISpot-positive; 11 relapse-free up to 6 years	Reported 2026
Sacituzumab govitecan (antibody-drug conjugate)	III, NCT02574455 (n = 529)	Refractory mTNBC	PFS 5.6 vs 1.7 months, HR 0.41; OS 12.1 vs 6.7 months, HR 0.48; ORR 35% vs 5%	Approved
Trastuzumab deruxtecan (antibody-drug conjugate)	III, NCT03734029 (n = 557)	HER2-low advanced breast cancer including hormone-receptor-negative cohort	PFS 9.9 vs 5.1 months, HR 0.50; OS 23.4 vs 16.8 months, HR 0.64	Approved

Datopotamab deruxtecan (antibody-drug conjugate)	III, NCT05104866 (n = 732)	Pretreated hormone receptor-positive, HER2-negative disease	PFS 6.9 vs 4.9 months, HR 0.63; grade 3 or higher adverse events 21% vs 45%	Active, not recruiting
Pembrolizumab + chemotherapy (immunotherapy comparator)	III, NCT03036488 (n = 1174)	Early high-risk TNBC	pCR 64.8% vs 51.2%; 5-year OS 86.6% vs 81.7%, HR 0.66	Approved

7. Why the two literatures diverge

7.1 Biology

The preclinical-to-clinical gap is not principally a translation problem in the usual sense of insufficient rigour. It is a problem of what the standard model system measures. Inbred mice bearing subcutaneous or orthotopic implants of a single cell line, grown to a defined volume over two to four weeks, have vasculature that is younger, more uniform and more permeable than a human tumour that has developed over years. The mechanistic finding that entry is predominantly transcytotic rather than gap-mediated[19] compounds this, since transcytotic capacity is an endothelial phenotype that need not scale between species. Interpatient variability, which the ferumoxytol imaging work was designed to measure[22], is engineered out of the mouse experiment by design. A carrier optimised in that system is optimised against a version of the transport problem that patients do not have.

7.2 Chemistry, manufacturing and controls

A nanomedicine is a heterogeneous population characterised by distributions rather than by a structure. Size, polydispersity, surface charge, encapsulation efficiency, drug-to-lipid ratio, free against encapsulated fraction and release kinetics all require specification, validated methods and stability data. Novel lipid excipients attract regulatory data packages comparable to those for active pharmaceutical ingredients, against limited specific global guidance, with lipid impurity control, oxidative degradation, excipient-payload interaction and manufacturing scale-up all unresolved at the level of consensus expectation.[103] The academic literature reviewed in section 3 almost never reports batch-to-batch reproducibility across independently manufactured lots, which is the parameter a manufacturing site cares about most.

7.3 Regulation

No unified nanomedicine pathway exists in either major jurisdiction. The US guidance for liposome drug products covers chemistry, manufacturing and controls, human pharmacokinetics and bioavailability, and labelling, and explicitly excludes drug-lipid complexes, vaccine adjuvant formulations and biologics.[104] Follow-on liposomal products in the European Union must demonstrate comparability across liposome morphology, mean size and size distribution, aggregates, encapsulated fraction

and release rate, together with comparative tissue distribution, immune reactogenicity, and clinical pharmacokinetics of total, encapsulated and unencapsulated drug with 90% confidence intervals for maximum concentration and area under the curve within 80 to 125%.[105] That is a development programme, not an abbreviated filing, and the consequence is that nanomedicine generics arrive late and expensive, so originator pricing persists long after patent expiry.

7.4 Safety

Two classes of risk are specific to this modality. Complement activation-related pseudoallergy is an innate hypersensitivity reaction triggered by particulate carriers, documented for approved liposomal products,[106] and it is not predicted by conventional toxicology. Persistence of non-degradable inorganic cores is the second, and section 3.3 set out the mismatch between 14- to 28-day efficacy observation and multi-month tissue residence.[50,51] A survey of which cancer nanomedicines were approved and which failed frames both as recurring rather than incidental contributors to attrition.[107]

7.5 What the reporting standard should be

Several improvements are within the reach of any laboratory publishing in this area and would raise the informativeness of the literature immediately. Report the untargeted carrier alongside the targeted one and the free drug, not only the free drug, since the targeted-against-free comparison confounds the carrier with the ligand. Report tumour delivery as percent injected dose per gram alongside efficacy, so that a mechanistic claim can be checked against a delivery measurement. Extend the safety observation window to match the persistence of the material rather than the duration of the efficacy experiment. Test in at least one model beyond MDA-MB-231 and 4T1, ideally a patient-derived xenograft, given the subtype heterogeneity established in section 1. Report the reproducibility of the formulation across independent batches. None of these requires new technology, and their absence is the main reason the preclinical literature cannot be pooled quantitatively.

8. Future perspectives

Design for cargo that has no alternative route. The clearest case for a nanocarrier is a payload that cannot be given any other way. Small interfering RNA, messenger RNA, microRNA and gene-editing components are degraded in plasma and do not cross membranes unaided, so the carrier is not an enhancement but a precondition. The adjuvant RNA-lipoplex vaccine study[89] and the paclitaxel-plus-p53-messenger-RNA co-delivery work both exploit this, and the manufacturing platform is now proven at global scale. Cytotoxic reformulation, by contrast, competes against a free drug that already works, which is why the margin of victory has been so consistently thin.

Treat dose as a design variable. The saturation threshold finding implies that particle number, not only drug amount, determines delivery efficiency, and that a nanomedicine trial dosed by milligrams of active per square metre may sit

below the threshold at which the carrier does anything useful. Deliberately administering unloaded carrier to saturate hepatic uptake before the therapeutic dose is a testable clinical hypothesis that has not been tested.

Industrialise the manufacture. Parallelised microfluidic production of lipid nanoparticles addresses the reproducibility and scale-up barrier of section 7.2,[109] and continuous manufacture with in-line characterisation would convert a batch specification problem into a process control problem, the transition every mature pharmaceutical modality has made. Machine learning offers a route through a design space, of lipid composition, ratio, ligand density, size and charge, that combinatorial synthesis cannot cover, but its constraint is training data, and the literature reviewed here supplies little of it in usable form.[110]

The last point is worth stating plainly. A field that reports its formulations inconsistently, tests them in two cell lines, and observes safety for a fraction of the material's residence time cannot train a model, cannot pool its results and cannot tell a regulator what its product is. These are solvable problems, and they are more likely to determine the next decade than any new carrier chemistry.

9. Conclusion

Nanotechnology has already changed how triple-negative breast cancer is treated, through albumin-bound paclitaxel and liposomal anthracyclines, and it did so by solving formulation and toxicity problems rather than by delivering drug selectively to tumour. The tumour-targeting rationale that motivates most of the preclinical literature has not survived quantitative scrutiny: passive accumulation is inefficient, dose-dependent and mechanistically different from what was assumed, and ligand functionalisation improves cellular uptake without improving how much particle arrives. The preclinical results assembled here are frequently impressive and are generated in a model system that removes the variable, interpatient heterogeneity in particle deposition, most likely to decide whether a given patient benefits.

The productive path forward does not require the targeting argument to be rescued. It requires carriers to be built for payloads that have no alternative route into a cell, dosed above the threshold at which hepatic clearance saturates, tested in patients selected by measured deposition rather than by histology alone, and manufactured to a specification a regulator can accept. Each of those is a concrete, testable programme. Together they describe a version of this field that would be judged on what reaches patients rather than on what accumulates in mice.

Declarations

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