



Review Article

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What Clinical Translation Has Taught Us About Nanocarrier Targeting

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ABSTRACT

Nanocarrier targeting has often been framed as a problem of increasing affinity for a disease-associated receptor or exploiting preferential vascular permeability. Clinical translation has exposed the incompleteness of that interpretation. A nanocarrier must survive systemic disposition, avoid or tolerate competing biological sinks, reach an accessible tissue compartment, retain a functional biological identity, release or present its payload appropriately, and produce a clinically relevant effect. These requirements are influenced by carrier composition, protein adsorption, immune recognition, administration route, particle dose, manufacturing process, disease context, and measurement scale. This State-of-the-Art Review examines how biodistribution studies, tumour and non-tumour targeting experiments, active-versus-passive targeting comparisons, barrier biology, dose-scaling studies, manufacturing investigations, and clinical experience have reshaped the targeting paradigm. The evidence supports a shift away from affinity-centred interpretation toward a multistage translational view in which tissue access and functional payload availability must be demonstrated independently of receptor recognition. Particular attention is given to why targeting effects observed in preclinical models contract in humans and why seemingly similar formulations may not remain biologically equivalent after scale-up. The review develops an evidence-bounded translational logic for distinguishing carrier accumulation, cellular access, payload availability, and clinical consequence without treating any one level as a surrogate for the others.

Keywords: Nanocarrier targeting, Biodistribution, Biological identity, Active targeting, Lipid nanoparticles, Translational nanomedicine

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INTRODUCTION

Nanomedicine has moved well beyond a purely experimental field, yet its clinical footprint remains small relative to the scale of biomedical development. A recent registry-level analysis identified thousands of nanomedical clinical trials across a much larger global trial landscape, showing both substantive clinical activity and persistent selectivity in what reaches human testing [1]. Clinical cancer nanomedicine provides a similar lesson: some products have achieved meaningful development or approval, but the success of individual platforms does not validate nanocarriers as a uniformly superior therapeutic class [2].

Clinical translation also exposes failure modes that are only weakly represented by receptor-binding diagrams. Formulation scale-up can alter product attributes, while animal models can exaggerate or misrepresent the biological conditions governing human disposition [3]. Consequently, a targeting claim cannot be evaluated only by asking whether a ligand binds its intended receptor. Precision delivery depends on coordinated control of carrier properties, biological transport, tissue access, cell interaction, intracellular handling, and pharmacologically meaningful payload exposure [4].

This review therefore treats targeting as a multistage translational problem. The central proposed interpretation is that successful targeting requires alignment among product identity, acquired biological identity, systemic access, local tissue access, cellular interaction, payload availability, and clinically relevant consequence. These levels are analytically separable: evidence at one level can support, but cannot automatically establish, success at the next.

Evolution of the targeting paradigm

Early targeting narratives often contrasted passive accumulation with active ligand-mediated recognition. That distinction remains useful, but it is insufficient when interpreted as a complete explanation of delivery. Receptor-directed binding can operate only after the carrier has remained available in circulation, reached the relevant tissue compartment, encountered accessible target molecules, and retained a surface state compatible with recognition [5].

Tumour delivery illustrates why the passive-versus-active dichotomy has become increasingly unstable. Enhanced permeability and retention remains relevant in selected settings, but vascular transport cannot always be reduced to passive leakage. Active transport and transcytotic processes may contribute under particular tumour conditions, although their relative importance is not established uniformly across tumour types, carrier systems, doses, or species [6]. The relevant translational question is therefore not whether the EPR effect is “true” or “false,” but which transport mechanism is operating strongly enough, in which biological context, to make the downstream targeting step possible.

Affinity itself is also conditional. Multivalent nanocarriers can display nonlinear relationships among ligand density, receptor density, geometry, avidity, and selectivity [7]. Increasing ligand number or binding strength may improve attachment under one receptor configuration while narrowing discrimination between target and non-target cells under another. Clinical translation has thus shifted the targeting problem from maximizing affinity toward matching an engineered interaction to the biological access conditions in which that interaction can actually occur.

Lessons from biodistribution

Biodistribution is the first major reality check on a targeting hypothesis. A large circulating dose does not imply a large accessible target dose because nanocarriers are continuously partitioned among blood, liver, spleen, mononuclear phagocyte populations, kidneys, vascular interfaces, target tissue, and other competing compartments [8]. Targeting efficiency therefore needs to be interpreted against the entire disposition field rather than against tumour signal alone.

Mouse meta-analysis reinforces this point. Across heterogeneous nanoparticle datasets, liver and spleen frequently account for substantial exposure while tumour delivery remains variable and relatively limited [9]. Such distributions do not mean that tumour delivery is impossible; they mean that tumour accumulation is one outcome of a competition among compartments. Reporting only the target compartment can obscure whether an apparent targeting gain results from improved access, reduced off-target clearance, altered circulation time, or a change in how the carrier is being measured.

Measurement itself can produce another inferential error. Analytical methods that track a polymeric component, fluorescent label, lipid, radionuclide, drug, or nucleic-acid payload do not necessarily measure the same biological object. PEG-based LC-MS/MS approaches, for example, can provide useful quantitative biodistribution information for appropriate PEG-containing systems, but a carrier marker cannot automatically establish that the intact carrier and pharmacologically available payload remain co-localized [10].

Competing clearance mechanisms are similarly informative. Experimental depletion of Kupffer cells increased nanoparticle tumour delivery in mice, demonstrating that hepatic macrophage uptake can materially constrain the accessible dose [11]. Yet removal of that sink did not abolish the remaining delivery problem. The observation is therefore more useful as evidence for a failure hierarchy than as evidence that one clearance compartment fully explains poor targeting.

These distinctions are difficult to compare consistently in prose alone. **Table 1** therefore organizes the manuscript-derived biodistribution failure states according to where the targeting inference becomes unreliable and what additional observation is required before translation can be claimed.

Table 1. Biodistribution patterns that can produce misleading conclusions about nanocarrier targeting

Observed configuration		Mechanism and competing diagnosis	Corrective discrimination
Misleading pattern / Dominant barrier or sink	Transport or uptake event being inferred	Biological-compartment transition / Plausible competing diagnosis	Corrective test / Residual translational consequence
Misleading pattern: Long circulation interpreted as effective targeting Dominant barrier or sink: Persistent systemic clearance competition	Product remains available long enough to enter target tissue	Biological-compartment transition: Blood → target tissue Plausible competing diagnosis: Extended blood residence without meaningful extravasation	Corrective test: Quantify time-resolved target entry relative to circulating and off-target pools Residual translational consequence: Circulation remains necessary but insufficient evidence of access
Misleading pattern: Increased tumour-associated signal interpreted as successful delivery Dominant barrier or sink: Liver/spleen sequestration and vascular heterogeneity	Carrier crosses the tumour vascular boundary	Biological-compartment transition: Blood → tumour interstitium Plausible competing diagnosis: Reduced competing clearance or extracellular retention	Corrective test: Resolve intravascular, interstitial and cellular fractions Residual translational consequence: Bulk tumour signal does not establish cellular delivery
Misleading pattern: Cellular fluorescence interpreted as intact therapeutic delivery Dominant barrier or sink: Membrane trafficking and probe dissociation	Nanocarrier reaches the intended cellular compartment	Biological-compartment transition: Interstitium → target cell Plausible competing diagnosis: Free label, degraded carrier, or extracellular probe persistence	Corrective test: Orthogonal carrier and payload measurements Residual translational consequence: Apparent uptake may overstate functional payload availability
Misleading pattern: Reduced hepatic uptake interpreted as removal of the main bottleneck Dominant barrier or sink: Residual non-hepatic barriers	More administered dose becomes target-accessible	Biological-compartment transition: Blood → reticuloendothelial sink Plausible competing diagnosis: Redistribution to other sinks or persistent poor tissue entry	Corrective test: Whole-body mass-balance and target-access analysis Residual translational consequence: Removing one sink can expose a different rate-limiting step

Tumour and non-tumour targeting

The expanding LNP literature shows that targeting cannot be defined solely by tumour accumulation. Reformulation of LNP composition can alter both organ accumulation and functional mRNA translation, emphasizing that where a carrier is detected and where its cargo functions are related but non-identical outcomes [12]. This distinction is especially important for nucleic-acid delivery, where tissue accumulation without productive cellular entry, endosomal escape, or translation can exaggerate the practical meaning of “targeting.” Non-tumour systems reinforce the importance of organ-specific biology. Lung-directed LNP formulations have produced preferential pulmonary delivery and therapeutic effects in preclinical fibrosis models [13], whereas fine adjustments in LNP composition have been used to redirect mRNA delivery toward the colon [14]. These examples demonstrate that organ tropism can be engineered, but they do not establish a universal formulation rule. The relevant proteins, vascular interfaces, immune populations, extracellular environments, and cellular uptake pathways differ across organs.

Some targeting behaviour may also emerge only after exposure to biological fluids. In a kidney-tumour model, adsorbed endogenous proteins contributed to tumour-directed interactions, illustrating that the biologically active surface presented in vivo can differ substantially from the surface designed during formulation [15]. Such findings complicate the conventional assumption that the synthetic ligand is always the dominant targeting determinant.

Composition-driven organ targeting is particularly clear in selective organ targeting LNP systems, where formulation changes redirected functional mRNA delivery among tissues in mice [16]. This strategy is mechanistically distinct from simply appending an external receptor ligand. It suggests that the formulation itself can influence which biological interactions become dominant after administration. However, the translation of these organ-tropism rules to humans remains a separate validation problem.

Active versus passive targeting

Direct comparison of active and passive strategies is most informative when relative improvement and absolute delivery are considered together. A recent meta-analysis of actively targeted polymeric nanocarriers in mouse solid-tumour models found an increase in median tumour delivery from approximately 0.4% to 0.9% of the injected dose in the included systems [17]. The relative improvement is meaningful, but the low absolute delivery also shows why a twofold preclinical gain should not be interpreted automatically as a clinically transformative targeting effect.

The problem is further complicated by inconsistent endpoint definitions. “Targeting” may refer to organ accumulation, tumour extravasation, cellular uptake, intracellular trafficking, organelle localization, target engagement, or pharmacological response. LNP research increasingly distinguishes these levels explicitly [18]. An active ligand may enhance cellular uptake among particles that have already reached a tissue while having little influence on the fraction of the administered dose that enters that tissue in the first place. Active and passive processes are therefore better treated as interacting levels of access and recognition than as mutually exclusive labels.

Biological barriers

Once a carrier enters biological fluids, its engineered surface is modified by adsorbed biomolecules. The resulting protein corona can alter receptor accessibility, cellular recognition, clearance, and tissue interaction, meaning that the biological entity encountered by cells may not be equivalent to the synthetic particle characterized before administration [19]. This transition from designed to acquired identity is a central barrier to translating affinity measured under simplified experimental conditions.

The corona is not uniformly detrimental. Depending on composition and host environment, adsorbed biomolecules can inhibit designed targeting interactions, produce new receptor interactions, or change trafficking in ways that may be exploitable [20]. The translational challenge is therefore not simply to “eliminate” the corona but to understand how a particular carrier acquires biological identity under clinically relevant exposure conditions.

Strategies intended to reduce nonspecific adsorption can mitigate some of these effects, but complete and durable suppression of biomolecular association is not a general property of current nanoparticle surfaces [21]. Taken together, the evidence indicates that corona formation, targeting-ligand accessibility, and stealth behaviour should be treated as conditional states rather than fixed material characteristics [19-21].

Different organs also impose qualitatively different access problems. Brain delivery is constrained by the blood-brain barrier, disease-dependent vascular and cellular changes, and potentially time-dependent physiological variables that do not resemble tumour leakiness [22]. A design principle inferred from a peripheral tumour model therefore cannot be transferred directly to the central nervous system without re-establishing the access mechanism.

Host history adds another level of variability. Anti-PEG immunity can modify pharmacokinetics, safety, and efficacy for PEG-containing nanomedicines, although the clinical consequences vary among products, exposure histories, and patients [23]. The same nominal formulation may therefore encounter different biological conditions in different individuals.

These interacting barriers are better represented as state transitions with feedback and validation gates than as a sequential list. **Figure 1** summarizes the proposed manuscript-derived architecture linking synthetic carrier identity, acquired biological identity, competing systemic sinks, local tissue access, cellular processing, and functional payload availability.

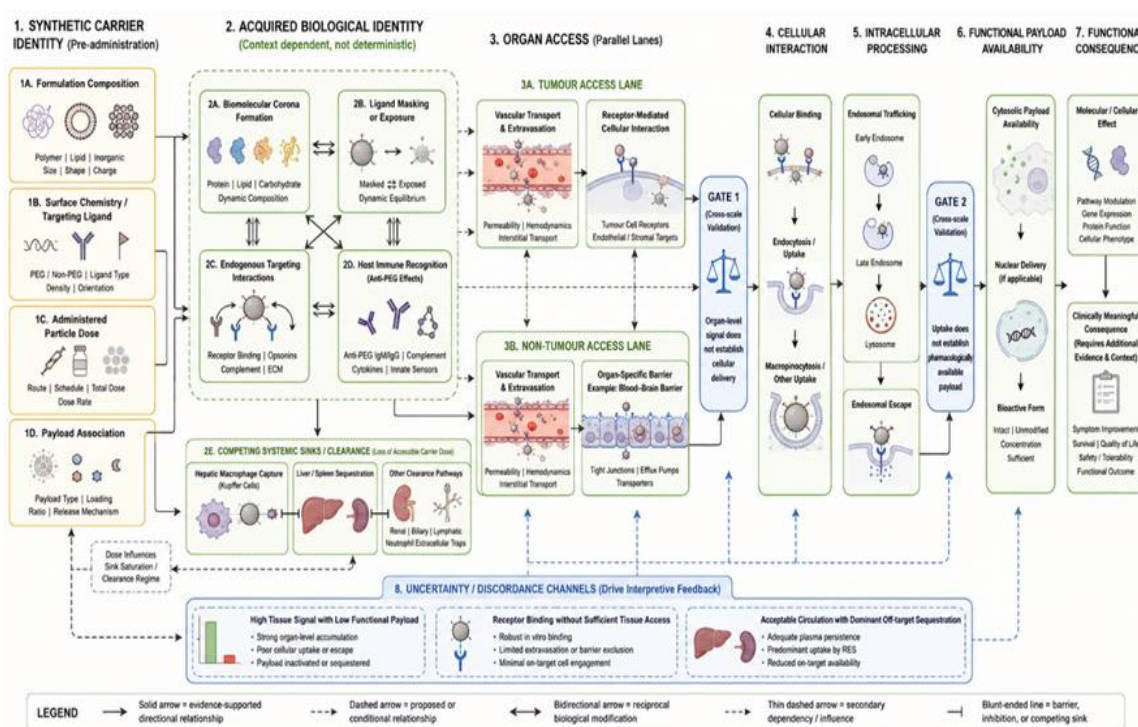


Figure 1. Biological barriers reshape nanocarrier identity before targeting can become functionally meaningful

Dose and scale effects

Dose is not only a scalar measure of how much nanocarrier is administered; it can alter the biological regime governing disposition. In mice, sufficiently high particle numbers saturated Kupffer-cell uptake and increased tumour delivery, demonstrating nonlinear interaction between dose and clearance [24]. The result is mechanistically important but translationally bounded: the reported particle threshold is not a human dosing rule and cannot be transferred across formulations without validation.

Scale also includes geometry and administration route. Polymeric nanocarriers administered intraperitoneally displayed size-dependent differences in translocation and lymphatic transport [25]. Such findings demonstrate that size effects are conditional on the anatomical route through which the carrier encounters tissues. A size–distribution relationship observed after intraperitoneal administration cannot simply be imposed on an intravenous system.

For LNPs, route interacts with formulation chemistry. Changes in ionizable lipid identity and administration by intravenous versus subcutaneous routes produced different pharmacokinetic and biodistribution profiles [26]. Thus, the same physicochemical descriptor can have a different translational meaning when exposure route changes the sequence of biological interfaces encountered by the carrier.

Model-based approaches can help distinguish competing explanations. Mechanistic PBPK modelling has been used to test the contribution of active transcytosis to tumour delivery and to examine how dose may affect the relative importance of transport processes [27]. Such analysis can strengthen or weaken a mechanistic interpretation, but model agreement remains conditional on parameterization and validation. It does not convert an inferred mechanism into direct clinical observation.

Machine-learning work similarly indicates that nanoparticle biodistribution is not equally predictable across compartments. Models trained on mouse datasets can perform differently for individual organs, with tumour delivery presenting a particularly difficult prediction problem [28]. Translational evaluation should therefore avoid a single global performance claim when the clinically relevant compartment may be the least predictable part of the model.

Table 2 converts these dose- and scale-dependent observations into a claim-to-test structure so that a targeting interpretation is not accepted until the minimum supporting observation and its strongest alternative explanation have been separated.

Table 2. Adjudicating dose- and scale-dependent targeting claims before translational interpretation

Evidence configuration		Interpretive alternatives	Adjudication requirement
Inference scenario / Local biological identity	Measurement scale / Minimum observation	Strongest alternative explanation	Discriminating test / Design lever or dose dependence / Interpretation permitted after testing
Inference scenario: Higher dose produces greater tumour accumulation Local biological identity: Dose-conditioned systemic state	Measurement scale: Whole body → tumour Minimum observation required: Tumour gain accompanied by quantified redistribution across major sinks	Clearance saturation rather than improved target affinity	Discriminating test: Dose-resolved mass balance with liver/spleen and tumour compartments Design lever or dose dependence: Particle number and dosing schedule Interpretation permitted after testing: Dose may alter accessible fraction; affinity cannot be inferred alone
Inference scenario: Smaller or larger carrier changes lymphatic delivery Local biological identity: Route-conditioned carrier state	Measurement scale: Injection site → lymphatic compartment Minimum observation required: Size-dependent transport confirmed over time	Route-specific drainage kinetics	Discriminating test: Repeat across relevant routes or anatomical settings Design lever or dose dependence: Particle size and administration route Interpretation permitted after testing: Size effect is valid only within the tested route context
Inference scenario: LNP reformulation changes organ exposure Local biological identity: Composition-conditioned biological identity	Measurement scale: Systemic → organ Minimum observation required: Organ accumulation and functional expression measured separately	Altered clearance or translation efficiency rather than access alone	Discriminating test: Paired carrier, cargo and functional readouts Design lever or dose dependence: Ionizable lipid and administration route Interpretation permitted after testing: Formulation alters disposition, but mechanism remains endpoint specific
Inference scenario: Model identifies active transcytosis as dominant Local biological identity: Model-defined tissue state	Measurement scale: Computational → tissue Minimum observation required: Model improvement under explicit mechanistic alternatives	Parameter compensation or incomplete competing mechanism	Discriminating test: External validation with mechanism-discriminating measurements Design lever or dose dependence: Dose and transport parameters Interpretation permitted after testing: Mechanism may be supported conditionally, not clinically proven
Inference scenario: Predictive model performs well overall Local biological identity: Dataset-defined carrier state	Measurement scale: Dataset → organ/tumour Minimum observation required: Compartment-specific out-of-sample performance	Strong performance driven by easier non-target organs	Discriminating test: External target-compartment validation Design lever or dose dependence: Descriptor set and training domain Interpretation permitted after testing: Predictive utility must be stated for the actual target compartment

Manufacturing and reproducibility

Targeting performance can change before a product ever reaches a patient if manufacturing alters the state of the carrier. Peptide-modified LNPs produced through different incorporation or conjugation strategies can display distinct biological behaviour even when routine particle measurements appear broadly comparable [29]. This finding is important because particle size, polydispersity, charge, or total ligand content may not fully describe ligand orientation, accessibility, membrane organization, or functional presentation.

Scale-up creates the same problem at a larger process level. Microfluidic manufacture of lipid-based nanoparticles depends on mixing conditions, flow parameters, chip geometry, composition, concentration, and downstream processing. Translation therefore requires an explicit relationship between critical process parameters, critical quality attributes, and biological performance rather than an assumption that increasing batch size preserves the original product state [30].

Manufacturing reproducibility is consequently part of targeting validity. A targeting hypothesis tested with one laboratory product cannot be considered unchanged if scale-up produces a carrier with a different surface organization, encapsulation state, colloidal behaviour, or acquired biological identity. Conventional release testing remains essential, but translational targeting requires selected functional assays capable of detecting biologically important differences that routine physical characterization may miss.

This interaction between product reproducibility and biological access is summarized in **Figure 2** as an access-versus-affinity decision landscape. The figure emphasizes that strong receptor affinity has little translational value when the manufactured product cannot reproducibly achieve the biological state required for tissue access.

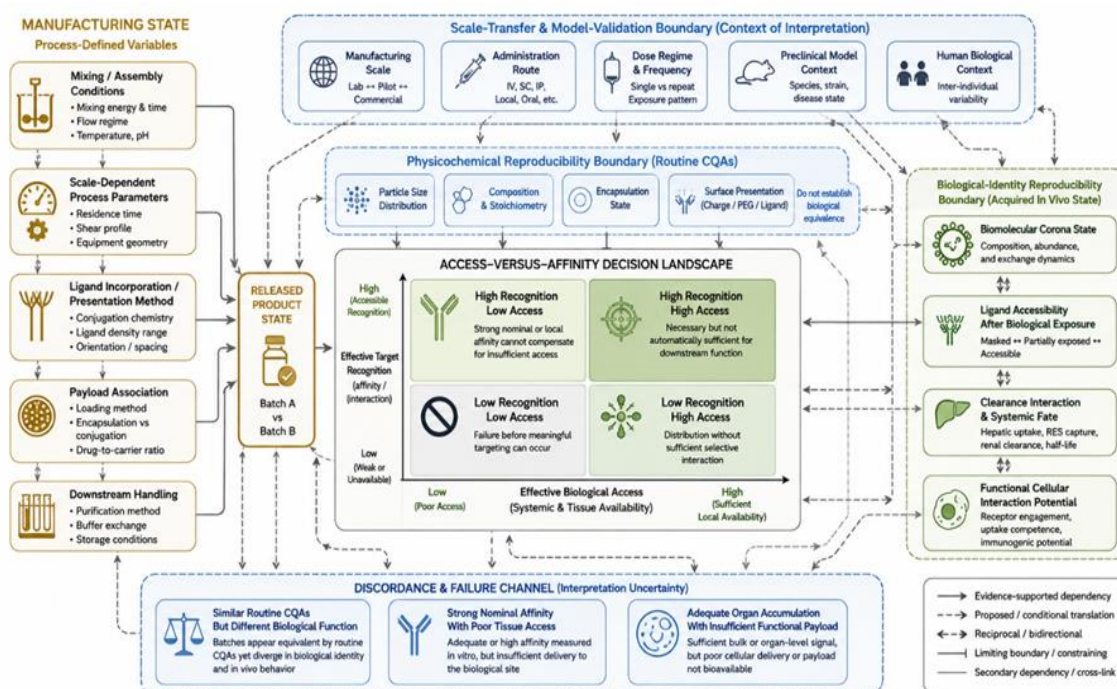


Figure 2. Manufacturing reproducibility determines whether targeting affinity remains biologically accessible

Clinical trial experience

Clinical experience clarifies an important distinction: a nanocarrier can succeed therapeutically without validating the most elaborate version of a targeting hypothesis. Patisiran provides the clearest example. In hereditary transthyretin amyloidosis, hepatic LNP delivery of siRNA produced clinically meaningful gene silencing and treatment benefit in a randomized phase III trial [31]. Its importance for targeting science lies partly in what it does **not** require: successful delivery exploited a biologically accessible organ and an appropriate carrier–payload system rather than depending on highly specific tumour–ligand recognition.

Target-directed oncology products illustrate a different evidentiary problem. MM-302, a HER2-targeted liposomal doxorubicin formulation, reached clinical dose-escalation testing in patients with advanced HER2-positive breast cancer, generating human safety and pharmacokinetic information [32]. That experience establishes clinical feasibility but does not by itself prove that receptor-directed delivery produced superior intratumour payload exposure or clinical outcome.

BIND-014 similarly entered phase II evaluation as a PSMA-targeted docetaxel nanoparticle and demonstrated clinical activity in metastatic castration-resistant prostate cancer [33]. Yet activity within a single-arm study cannot isolate the causal contribution of PSMA-directed targeting from nanoparticle pharmacokinetics, docetaxel exposure, tumour biology, or patient heterogeneity. Taken together, these programs show why clinical activity, pharmacokinetic feasibility, target expression, and mechanistic validation should remain separate evidentiary categories [31-33].

Why preclinical targeting effects contract in humans

The contraction of preclinical targeting effects in humans is unlikely to have one universal cause. Industry experience has repeatedly identified interacting biological, formulation, manufacturing, regulatory, clinical-development, and commercial constraints that intervene between experimental proof-of-concept and viable nanomedicine products [34]. A carrier may therefore lose translational advantage even when its original molecular targeting premise remains plausible.

Human translation also exposes scale-dependent differences that are difficult to reproduce simultaneously in animal models. Blood volume, immune composition, macrophage activity, vascular architecture, tumour

perfusion, stromal structure, disease heterogeneity, prior treatment, administration schedule, and host protein composition can all change the environment in which the carrier acquires biological identity. Nanotheranostic development demonstrates the same cross-scale problem: strong preclinical imaging or targeting signals require independent validation of product state, measurement meaning, safety, tissue access, and clinical utility [35].

This review therefore proposes a targeting-effect contraction stack rather than a single translation barrier. A preclinical advantage may diminish through sequential or interacting losses in manufactured-product equivalence, systemic availability, biological identity, tissue access, cellular access, payload release, pharmacological sensitivity, or clinical detectability. The stack is an interpretive synthesis, not a validated universal mechanism. Its value is to prevent a disappointing human result from being attributed automatically to failed receptor affinity when the limiting event may have occurred much earlier in the delivery chain.

Translational design principles

Clinical translation suggests that carrier design should begin with the biological state that must be reproduced, not only with the molecular target that can be bound. Individual formulation components may participate directly in that state. Recent work on SORT LNPs showed that phospholipid identity can influence membrane interaction, intracellular processing, and organ-level delivery, supporting the interpretation that nominally “supporting” excipients may become mechanistic determinants of biological performance [36].

A translation-ready targeting claim should consequently be decomposed into discriminable questions. Is the manufactured carrier reproducibly the intended product? Does it acquire a biological identity compatible with the proposed mechanism? Does sufficient material reach the relevant tissue compartment? Is the measured signal associated with intact carrier, payload, or both? Does the carrier contact the intended cell population? Is the payload released or expressed in a pharmacologically useful form? Finally, does that molecular or cellular effect produce a clinically meaningful consequence?

This sequence should not be interpreted as a mandatory linear pipeline. Barriers interact: dose can alter clearance, corona composition can modify affinity, manufacturing can alter ligand presentation, and tissue access can determine whether receptor specificity matters at all. The more defensible principle is therefore mechanism discrimination. Competing explanations should be designed into experiments before an apparent targeting advantage is accepted.

Table 3 formalizes this proposed logic by separating what is observed from what is inferred and identifying the experiment required to distinguish competing interpretations.

Table 3. Mechanism-discrimination matrix for translational nanocarrier targeting claims

Scientific configuration	Observable support	Mechanistic test and consequence
Carrier–barrier encounter / Inference that must remain separate	Directly observable state	Strong competing explanation / Discriminating experiment / Pharmaceutical decision consequence
Carrier–barrier encounter: Manufactured carrier → biological fluid Inference that must remain separate: Biological equivalence	Reproducible physical and compositional attributes	Strong competing explanation: Different corona or ligand presentation despite similar routine CQAs Discriminating experiment: Compare biological identity and functional interaction across batches Pharmaceutical decision consequence: Do not advance scale-up based on physicochemical comparability alone
Carrier–barrier encounter: Circulation → target tissue Inference that must remain separate: Improved tissue access	Increased target-associated signal	Strong competing explanation: Longer circulation or reduced competing clearance Discriminating experiment: Time-resolved whole-body and compartment-resolved biodistribution Pharmaceutical decision consequence: Optimize access before increasing ligand complexity
Carrier–barrier encounter: Tissue → target cell Inference that must remain separate: Receptor-mediated productive uptake	Cellular association	Strong competing explanation: Nonspecific uptake or extracellular retention Discriminating experiment: Receptor perturbation plus spatially resolved uptake analysis Pharmaceutical decision consequence: Retain ligand only if selective cellular interaction is demonstrated

Carrier–barrier encounter: Cell → functional payload Inference that must remain separate: Pharmacologically available cargo	Carrier internalization	Strong competing explanation: Endosomal trapping, carrier degradation, or probe dissociation Discriminating experiment: Orthogonal carrier, payload, and functional readouts Pharmaceutical decision consequence: Optimize intracellular processing rather than surface affinity
Carrier–barrier encounter: Functional payload → clinical effect Inference that must remain separate: Clinical targeting superiority	Molecular or cellular response	Strong competing explanation: Disease biology, exposure, or comparator differences Discriminating experiment: Prospectively designed clinical comparison with mechanism-relevant biomarkers Pharmaceutical decision consequence: Claim clinical advantage only at the evidentiary level actually demonstrated

Research priorities

The next phase of nanocarrier targeting research should place greater emphasis on human-relevant mechanism discrimination. Biodistribution studies should report target exposure together with competing organ sinks, carrier identity, payload identity, administered particle dose, route, and time. High tissue signal should not be accepted as a surrogate for intact carrier delivery or pharmacologically available payload.

Predictive models also require stronger external validation. PBPK and machine-learning approaches can help identify mechanistic hypotheses and likely distribution patterns, but their value will depend on prospective testing in biological systems that reproduce clinically relevant product states, dose regimes, and tissue environments. Model performance should be reported for the compartment that actually matters to the therapeutic hypothesis rather than only as a global average.

Manufacturing development should likewise be integrated earlier with targeting studies. Functional comparability assays should accompany conventional physicochemical characterization when process changes can plausibly alter biological identity or cellular behaviour. The combined evidence indicates that formulation mechanism, scalable production, and translational validation cannot be treated as independent late-stage tasks [34-36].

Finally, increasingly elaborate carrier decoration should not substitute for access evidence. The most informative future studies will compare competing mechanisms directly, quantify absolute as well as relative delivery, preserve null results, and identify the conditions under which a targeting strategy ceases to work. Such evidence would make negative translation scientifically useful rather than merely disappointing.

CONCLUSION

Clinical translation has changed the meaning of nanocarrier targeting. Target affinity remains relevant, but it operates within a larger system of product identity, biological identity, systemic disposition, tissue access, cellular processing, payload availability, and disease response. Failure at any of these levels can weaken or erase an apparent preclinical targeting advantage.

The central implication is that accumulation, recognition, uptake, payload activity, and clinical benefit should not be treated as interchangeable endpoints. A convincing targeting claim should establish the relevant transition between these levels and actively test competing explanations. Dose, route, host biology, organ-specific barriers, manufacturing state, and measurement method must remain explicit parts of interpretation.

The resulting translational standard is more demanding than demonstrating preferential binding or increased target-associated signal, but it is also more informative. Nanocarrier targeting is most likely to progress when design begins with reproducible biological access and mechanism discrimination, and when molecular affinity is treated as one layer of a changing exposure–response system rather than as the definition of targeting itself.

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REFERENCES

1. Gultepe E, Valluru R, Brown NB, Sridhar S. The landscape of nanomedical clinical trials. *Nano Today*. 2026;66:102898. doi:10.1016/j.nantod.2025.102898
2. Pallares RM, Barmin RA, Wang A, Kiessling F, Lammers T. Clinical cancer nanomedicines. *J Control Release*. 2025;385:113991. doi:10.1016/j.jconrel.2025.113991
3. Kelly OM, Hanna AR, Byrne AK, Green JA, Viotti Perisse I, Wells KD, et al. Towards clinical translation of nanomedicines: Formulation scale-up and model systems. *Adv Drug Deliv Rev*. 2026;234:115862. doi:10.1016/j.addr.2026.115862
4. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov*. 2021;20(2):101-24. doi:10.1038/s41573-020-0090-8
5. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. Progress and challenges towards targeted delivery of cancer therapeutics. *Nat Commun*. 2018;9(1):1410. doi:10.1038/s41467-018-03705-y
6. Dasgupta A, Sofias AM, Kiessling F, Lammers T. Nanoparticle delivery to tumours: From EPR and ATR mechanisms to clinical impact. *Nat Rev Bioeng*. 2024;2(9):714-6. doi:10.1038/s44222-024-00203-3
7. Woythe L, Tito NB, Albertazzi L. A quantitative view on multivalent nanomedicine targeting. *Adv Drug Deliv Rev*. 2021;169:1-21. doi:10.1016/j.addr.2020.11.010
8. Cabral H, Li J, Miyata K, Kataoka K. Controlling the biodistribution and clearance of nanomedicines. *Nat Rev Bioeng*. 2024;2:214-32. doi:10.1038/s44222-023-00138-1
9. Chen Q, Yuan L, Chou WC, Cheng YH, He C, Monteiro-Riviere NA, et al. Meta-analysis of nanoparticle distribution in tumors and major organs in tumor-bearing mice. *ACS Nano*. 2023;17(20):19810-31. doi:10.1021/acsnano.3c04037
10. Hyldbakk A, Hansen T, Hak S, Borgos SEF. Polyethylene glycol (PEG) as a broad applicability marker for LC-MS/MS-based biodistribution analysis of nanomedicines. *J Control Release*. 2024;366:611-20. doi:10.1016/j.jconrel.2024.01.016
11. Tavares AJ, Poon W, Zhang YN, Dai Q, Besla R, Ding D, et al. Effect of removing Kupffer cells on nanoparticle tumor delivery. *Proc Natl Acad Sci U S A*. 2017;114(51):E10871-E10880. doi:10.1073/pnas.1713390114
12. Su K, Shi L, Sheng T, Yan X, Lin L, Meng C, et al. Reformulating lipid nanoparticles for organ-targeted mRNA accumulation and translation. *Nat Commun*. 2024;15(1):5659. doi:10.1038/s41467-024-50093-7
13. Cheng M, Yu X, Qi S, Yang K, Lu M, Cao F, et al. Development of organ targeting lipid nanoparticles with low immunogenicity and their application in the treatment of pulmonary fibrosis. *Angew Chem Int Ed Engl*. 2024;63(44):e202407398. doi:10.1002/anie.202407398
14. Rampado R, Naidu GS, Karpov O, Goldsmith M, Sharma P, Ezra A, et al. Lipid nanoparticles with fine-tuned composition show enhanced colon targeting as a platform for mRNA therapeutics. *Adv Sci (Weinh)*. 2025;12(3):e2408744. doi:10.1002/advs.202408744
15. Vaidya A, Sung YC, Toffessi Tcheuyap V, Zhang C, Butti R, Mal A, et al. Endogenous targeting of lipid nanoparticles to kidney tumors. *ACS Nano*. 2025;19(34):30860-71. doi:10.1021/acsnano.5c05370
16. Cheng Q, Wei T, Farbiak L, Johnson LT, Dilliard SA, Siegwart DJ. Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing. *Nat Nanotechnol*. 2020;15(4):313-20. doi:10.1038/s41565-020-0669-6
17. Sousa-Oliveira I, Duarte BPM, Coelho JFJ, Fonseca AC, Veiga F, Concheiro A, et al. Optimizing intravenous solid tumour treatment through active targeting approaches and polymeric micelles engineering: A meta-analysis in mouse models. *J Control Release*. 2026;396:115103. doi:10.1016/j.jconrel.2026.115103
18. Sato Y, Nakamura T, Yamada Y, Harashima H. The impact of, and expectations for, lipid nanoparticle technology: From cellular targeting to organelle targeting. *J Control Release*. 2024;370:516-27. doi:10.1016/j.jconrel.2024.05.006
19. Chou WC, Lin Z. Impact of protein coronas on nanoparticle interactions with tissues and targeted delivery. *Curr Opin Biotechnol*. 2024;85:103046. doi:10.1016/j.copbio.2023.103046
20. Salvati A. The biomolecular corona of nanomedicines: Effects on nanomedicine outcomes and emerging opportunities. *Curr Opin Biotechnol*. 2024;87:103101. doi:10.1016/j.copbio.2024.103101
21. Barz M, Parak WJ, Zentel R. Concepts and approaches to reduce or avoid protein corona formation on nanoparticles: Challenges and opportunities. *Adv Sci (Weinh)*. 2024;11(34):e2402935. doi:10.1002/advs.202402935

22. Pineiro-Alonso L, Rubio-Prego I, Lobytseva A, González-Freire E, Langer R, Alonso MJ. Nanomedicine for targeting brain neurodegeneration: Critical barriers and circadian rhythm considerations. *Adv Drug Deliv Rev.* 2025;222:115606. doi:10.1016/j.addr.2025.115606
23. Chen Y, Su YC, Roffler SR. Polyethylene glycol immunogenicity in nanomedicine. *Nat Rev Bioeng.* 2025;3:742-60. doi:10.1038/s44222-025-00321-6
24. Ouyang B, Poon W, Zhang YN, Lin ZP, Kingston BR, Tavares AJ, et al. The dose threshold for nanoparticle tumour delivery. *Nat Mater.* 2020;19(12):1362-71. doi:10.1038/s41563-020-0755-z
25. Cai Y, Zhang Z, Liu C, Tai Z, Zhu Q, Qi J, et al. Size-dependent translocation and lymphatic transportation of polymeric nanocarriers post intraperitoneal administration. *J Control Release.* 2024;376:553-65. doi:10.1016/j.jconrel.2024.10.032
26. Ren Y, Lin L, Abdallah M, Zhu X, Liu H, Fabb SA, et al. Impact of ionizable lipid type on the pharmacokinetics and biodistribution of mRNA-lipid nanoparticles after intravenous and subcutaneous injection. *J Control Release.* 2025;384:113945. doi:10.1016/j.jconrel.2025.113945
27. Zhu J, Lin H, Wang K, Zhang S, He H, Hao K. Translational m-PBPK modeling reveals active transcytosis as the pivotal mechanism for nanoparticle tumor delivery: Implications for dose optimization. *J Control Release.* 2026;392:114684. doi:10.1016/j.jconrel.2026.114684
28. Mi K, Chou WC, Chen Q, Yuan L, Kamineni VN, Kuchimanchi Y, et al. Predicting tissue distribution and tumor delivery of nanoparticles in mice using machine learning models. *J Control Release.* 2024;374:219-29. doi:10.1016/j.jconrel.2024.08.015
29. Miyasaki K, Han S, Carton O, Kandell RM, Gunn J, Kwon EJ. Formulation methods for peptide-modified lipid nanoparticles. *J Control Release.* 2025;385:114030. doi:10.1016/j.jconrel.2025.114030
30. Abostait A, Abdelkarim M, Nikdoost A, Chavrier P, El Hamri M, Andrieux K, et al. A toolbox to optimize and scale up microfluidic production of lipid-based nanoparticles. *Adv Drug Deliv Rev.* 2026;115946. doi:10.1016/j.addr.2026.115946
31. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
32. Munster P, Krop IE, LoRusso P, Ma C, Siegel BA, Shields AF, et al. Safety and pharmacokinetics of MM-302, a HER2-targeted antibody-liposomal doxorubicin conjugate, in patients with advanced HER2-positive breast cancer: A phase 1 dose-escalation study. *Br J Cancer.* 2018;119(9):1086-93. doi:10.1038/s41416-018-0235-2
33. Autio KA, Dreicer R, Anderson J, Garcia JA, Alva A, Hart LL, et al. Safety and efficacy of BIND-014, a docetaxel nanoparticle targeting prostate-specific membrane antigen for patients with metastatic castration-resistant prostate cancer: A phase 2 clinical trial. *JAMA Oncol.* 2018;4(10):1344-51. doi:10.1001/jamaoncol.2018.2168
34. Hare JI, Lammers T, Ashford MB, Puri S, Storm G, Barry ST. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Adv Drug Deliv Rev.* 2017;108:25-38. doi:10.1016/j.addr.2016.04.025
35. Gawne PJ, Ferreira M, Papaluca M, Grimm J, Decuzzi P. New opportunities and old challenges in the clinical translation of nanotheranostics. *Nat Rev Mater.* 2023;8(12):783-98. doi:10.1038/s41578-023-00581-x
36. Guerrero ED, Vaidya A, Santelli J, Tian Z, Pazzi GA, Siegwart DJ. Investigating the functional contributions of phospholipids in selective organ targeting lipid nanoparticles. *Biomaterials.* 2026;326:123671. doi:10.1016/j.biomaterials.2025.123671