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A Targeted Nanocarrier Can Reach the Lesion Yet Fail Clinically Through Endosomal Sequestration, Payload–Carrier Decoupling, and Unmanageable Treatment Burden

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ABSTRACT

Targeted nanomedicine is often evaluated through evidence that a carrier reaches diseased tissue, accumulates within a lesion, or enters a target-cell population. These achievements are important, but each describes only one stage of a longer therapeutic problem. After lesion access, the carrier may acquire a different biological identity, enter the wrong cellular compartment, remain sequestered within endosomes or lysosomes, release its payload too early or too late, separate spatially from its payload, or generate intracellular exposure that is insufficient for pharmacodynamic activity. Even when these barriers are overcome, the resulting formulation may require dose intensity, administration procedures, toxicity surveillance, manufacturing complexity, or healthcare resources that constrain its clinical use. This Perspective examines the discordance between successful lesion-level targeting and clinically usable therapy. It distinguishes lesion accumulation, cellular entry, productive intracellular payload availability, pharmacodynamic action, toxicity, dose requirements, and treatment-delivery burden as separate evidentiary denominators. Particular attention is given to endosomal escape measurement, carrier–payload decoupling, and the possibility that improving one delivery property can worsen another. The central implication is that nanocarrier performance should be judged through linked but independently measured biological and practical outcomes. Lesion arrival can support therapeutic success, but it does not establish that the administered nanomedicine has delivered a usable treatment.

Keywords: Targeted nanomedicine, Endosomal escape, Intracellular drug delivery, Payload release, Pharmacodynamics, Clinical translation

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Introduction

Targeted nanomedicine has advanced from a predominantly localization-centered concept toward a broader problem of controlled biological exposure. Ligands, particle physicochemistry, surface engineering, responsive materials, and disease-specific design can all increase the probability that a carrier reaches a desired anatomical or cellular region. Yet the biological trajectory between administration and therapeutic effect contains several mechanistically distinct events. Contemporary analyses of targeted nanomedicine accordingly emphasize that systemic disposition, tissue access, cellular interaction, intracellular trafficking, payload release, and biological response cannot be assumed to move together simply because one of them has been optimized[1]. Precision nanoparticle engineering has made this separation increasingly important because designs intended for a specific

biological context encounter heterogeneous barriers whose consequences depend on disease state, particle composition, payload, and patient biology[2].

Cancer nanomedicine illustrates the problem particularly clearly. Targeting strategies can improve recognition or localization while leaving penetration, cell-specific uptake, intracellular routing, or drug action unresolved[3]. Even the familiar distinction between passive and active targeting does not define a single biological pathway to tumor accumulation; vascular transport, tissue architecture, receptor availability, particle characteristics, and microenvironmental conditions can alter how a detectable lesion-level signal is produced[4]. Experimental work has also challenged simplified descriptions of solid-tumor entry that attribute nanoparticle access primarily to static endothelial gaps. In several investigated models, active trans-endothelial processes contributed substantially to tumor entry, reinforcing the idea that a measured tumor signal does not itself disclose the route by which the material arrived or what subsequently happened to it[5].

The denominator becomes still more important when delivery efficiency is quantified. A physiologically based pharmacokinetic meta-analysis incorporating hundreds of published datasets found generally limited nanoparticle delivery to tumors and showed that measured delivery depends on time and nanoparticle characteristics[6]. Such analyses correctly focus attention on how little of an administered dose may reach a tumor. The converse problem deserves equal scrutiny: even when sufficient lesion arrival is demonstrated, the therapeutic chain can still fail after that point. A carrier may be present in diseased tissue but unavailable to the relevant cell, internalized but confined to an endolysosomal compartment, released from its payload before reaching the intended intracellular site, or associated with a pharmacologically inactive payload state. A formulation that overcomes those biological problems may nevertheless require a regimen whose toxicity, administration frequency, monitoring burden, manufacturing requirements, or resource demands weaken its clinical value.

The question for targeted nanomedicine is therefore not simply whether a carrier reaches a lesion. The more consequential question is whether lesion access is converted into biologically active exposure that can be delivered repeatedly and safely under realistic clinical conditions. Addressing that question requires independent attention to what is being measured at tissue, cellular, intracellular, pharmacodynamic, and treatment-delivery levels.

Lesion accumulation is an incomplete denominator of delivery

A nanocarrier entering the circulation does not preserve a perfectly fixed biological identity. Interactions with proteins and other biomolecules can alter the interface that cells and tissues encounter, changing recognition, uptake, biodistribution, and downstream function[7]. The protein corona is particularly important because it can obscure engineered surface features, create new biological interactions, or modify how a nanoparticle is interpreted by the immune and vascular systems. This effect is not uniformly detrimental. Depending on the particle and serum environment, adsorbed proteins may interfere with targeting or contribute useful interactions that improve transport or recognition[8].

Attempts to engineer the corona demonstrate that this interface is modifiable, but they also reinforce its context dependence. Surface composition, particle properties, protein abundance, and biological milieu can be manipulated to influence the eventual corona and thereby alter targeting performance[9]. For an actively targeted carrier, the functional question is consequently broader than whether a targeting ligand was present at manufacture. Plasma exposure can modify ligand accessibility, receptor recognition, and subsequent fate, meaning that the effective targeting surface in vivo may differ from the nominal formulation surface[10].

This distinction becomes relevant even when lesion accumulation appears successful. A detectable tumor-associated signal may arise from particles whose surface identity, structural state, or functional accessibility has changed during circulation and tissue entry. Protein conformation and orientation within the corona can influence biological activity and receptor interactions, further separating manufactured carrier identity from the biological identity presented in vivo[11]. Thus, lesion accumulation should be interpreted as evidence of material presence within a defined anatomical denominator at a defined time. It cannot independently establish that the intended carrier configuration remains intact, that the payload is still coupled to that carrier, or that the detected material resides in the cell population whose pharmacology determines treatment response.

This distinction also clarifies why improving lesion accumulation does not automatically resolve the more clinically relevant question. A formulation may outperform a comparator in bulk tissue localization yet provide little additional intracellular active drug. Conversely, a formulation with modest whole-lesion accumulation could be pharmacologically effective if a larger fraction of the delivered payload reaches the relevant cells and

intracellular site. Bulk accumulation therefore remains an important pharmacokinetic observation, but its therapeutic interpretation depends on the biological denominator that follows it.

Cellular entry reshapes what lesion arrival can mean

The transition from lesion localization to cellular uptake introduces another change in denominator. Nanoparticles can associate with a cell surface, remain extracellular within tumor stroma, be taken up by nontherapeutic cell populations, or enter the intended target cell through different endocytic mechanisms. Methodological reviews of nanoparticle uptake have emphasized that commonly assigned routes of cellular entry are sometimes supported by limited or nonspecific evidence and that rigorous cell-biological analysis is necessary before a particular uptake mechanism is treated as established[12]. This matters because fluorescence associated with a tissue or cell is not equivalent to proof that intact carrier or active payload has reached the required intracellular compartment.

Intracellular trafficking can itself be treated as a design variable. Delivery systems have been engineered to influence endosomal processing, organelle localization, and subcellular distribution, illustrating that two particles with similar lesion and cell-associated exposure can have different intracellular fates[13]. The clinically relevant destination depends on payload mechanism. A molecule acting at the cell surface or within an endosomal compartment has different trafficking requirements from an siRNA that must reach the cytosol or a therapeutic whose action depends on nuclear, mitochondrial, or other organelle exposure.

For payloads requiring cytosolic access, endocytosis and productive release are separate events. A cell can internalize substantial carrier material without liberating enough payload from endosomal compartments to support the intended biological action[14]. This difference also changes what should be measured experimentally. Endosomal escape studies use diverse indirect and direct assays, and each assay answers a different question about membrane perturbation, compartmental redistribution, cytosolic access, or cargo function[15]. Interpretation therefore becomes stronger when tissue localization, target-cell internalization, intracellular compartment, payload state, and pharmacodynamic consequence are measured separately.

The central measurement problem can be summarized by comparing what each experimental denominator actually establishes.

Table 1. Experimental denominators separating lesion arrival from intracellular pharmacological function

Experimental denominator	What the observation establishes	Carrier state resolved?	Payload state resolved?	Intracellular compartment resolved?	Pharmacological readout needed for stronger inference	Common false inference
Bulk lesion-associated signal	Carrier label, payload label, or both are detectable within sampled diseased tissue	Sometimes	Usually incomplete	No	Target engagement or downstream response	Lesion signal equals therapeutically available drug
Spatial carrier localization within lesion	Carrier-associated material occupies defined lesion regions	Yes, if carrier-specific assay is valid	Not necessarily	No	Independent payload localization and activity	Carrier position defines payload position
Target-cell-associated signal	Material is associated with the therapeutically relevant cell population	Partly	Partly	Usually no	Internalization-sensitive assay and compartment analysis	Cell association proves intracellular delivery
Confirmed intracellular carrier uptake	Carrier-associated material is inside the target cell	Intracellular location, not necessarily structural integrity	Not necessarily	Partly	Payload-specific trafficking measurement	Internalized carrier proves productive cargo delivery
Endosomal or lysosomal localization	Internalized material occupies vesicular compartments	Vesicular location, not necessarily structural integrity	Only if independently tracked	Yes	Cytosolic or destination-compartment payload assay	Uptake alone is sufficient for intracellular pharmacology

Cytosolic or destination-compartment payload	Payload reaches the compartment required for its mechanism	Carrier may no longer be informative	Yes	Yes	Target engagement, gene modulation, enzyme inhibition, or other payload-specific response	Cytosolic presence guarantees adequate biological activity
Pharmacodynamic target engagement	Payload has produced a defined molecular or cellular action	Not required	Functionally supported	Mechanism-dependent	Exposure–response and toxicity assessment	Molecular response guarantees a clinically feasible regimen

The table preserves a critical distinction: advancing to a more informative denominator does not invalidate measurements made earlier in the delivery sequence. Lesion accumulation, cellular uptake, and vesicular trafficking each provide useful information. Their limitation is inferential. Each supports a narrower statement than is often implied when carrier localization is used as shorthand for therapeutic delivery.

Endosomal sequestration separates uptake from cytosolic availability

Endosomal sequestration is one of the clearest examples of post-targeting failure because it can occur after both lesion entry and target-cell internalization have been achieved. This problem has become especially visible in lipid nanoparticle delivery of nucleic acids. Recent analyses describe endosomal escape as a major bottleneck for LNP-mediated therapeutics while also emphasizing that its mechanism, location within the endocytic pathway, and quantitative efficiency remain incompletely resolved[16]. The challenge is therefore simultaneously biological and methodological.

More direct measurement approaches have begun to reduce this ambiguity. Split-luciferase-based quantification can distinguish cytosolic delivery from simple uptake and has demonstrated substantial formulation-dependent differences in escape efficiency[17]. Such assays show why carrier internalization should not be used as the denominator for payload availability. A formulation can enter cells efficiently yet release only a limited fraction of its cargo into the cytosol. Conversely, modest uptake may still yield useful delivery if the fraction undergoing productive escape is high.

Reporter choice can nevertheless reshape the apparent result. Calcein and related probes are widely used because redistribution of a fluorescent reporter can indicate endosomal membrane perturbation, but the relationship between reporter leakage, vesicle damage, payload release, and productive cytosolic delivery is not always straightforward[18]. Orthogonal measurements become especially important when a mechanistic claim depends on distinguishing transient membrane permeability from durable payload availability.

A functional readout can strengthen this inference. In a porphyrin-containing lipid nanoparticle system, light-triggered endosomal disruption increased measured escape and improved siRNA-mediated knockdown, directly linking a trafficking intervention to payload function in the tested setting[19]. This constitutes a positive example of post-uptake rescue: in this system, altering the intracellular barrier improved payload function after cellular entry. The result remains system-specific because the intervention requires a particular formulation and external activation condition.

The opposite result is equally informative. Engineering ionizable lipid–siRNA conjugates to increase endosomal escape potential produced undesirable biological effects and in-vivo toxicity in the investigated system[20]. The implication is that endosomal escape cannot be optimized as an isolated maximum. Membrane disruption, lipid activity, tissue distribution, cargo release, and toxicity are coupled. A formulation may move more payload into the cytosol while simultaneously narrowing the dose range within which that gain can be used safely.

Intracellular fate can remain complex after endocytosis. LNP-delivered mRNA has been shown to participate in extracellular-vesicle-associated transfer after internalization, demonstrating that internalized material can enter additional trafficking routes that are not captured by a simple retained-versus-escaped binary[21]. Super-resolution imaging has also enabled direct visualization of endosomal rupture and siRNA release in defined polyplex systems, providing a mechanistic level of evidence that conventional colocalization cannot supply[22].

Chemical or pharmacological manipulation of endolysosomal trafficking adds another layer of context dependence. Cationic amphiphilic compounds can enhance lysosomal escape of small nucleic-acid therapeutics,

but the magnitude and even usefulness of that effect depend on the associated nanocarrier[23]. Recent analyses of polycation chemistry similarly show that endosomal escape behavior reflects polymer structure, protonation characteristics, membrane interactions, and assay definition; no single mechanistic explanation accounts cleanly for all systems[24].

These observations support a specific interpretation of post-targeting failure. Endosomal sequestration matters because it creates discordance between an apparently successful upstream event—cellular uptake—and the downstream exposure required by a particular payload. It should therefore be quantified with the payload's site of action in mind and interpreted together with pharmacodynamic and toxicity measurements.

Figure 1 depicts diverging post-targeting states across lesion access, uptake, escape, and intracellular function; these states need not occur in an obligatory linear sequence.

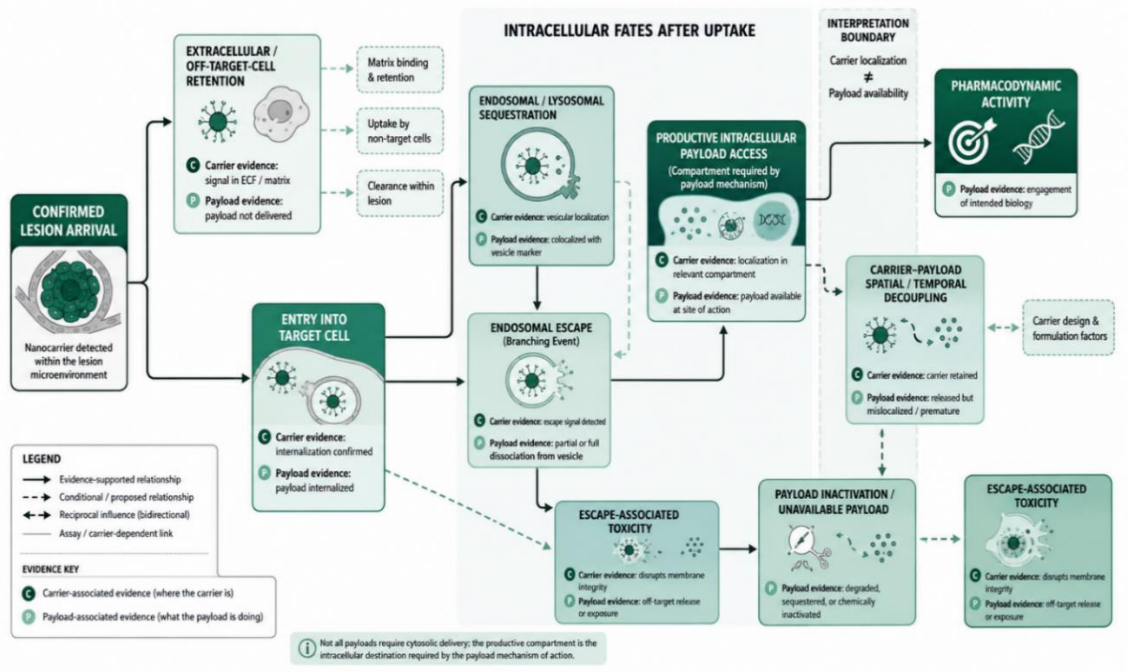

Figure 1. Divergent post-targeting states after confirmed lesion access

Payload–carrier coupling can fail after tissue access

The carrier is often easier to visualize than the pharmacologically relevant state of its cargo. This creates a further source of discordance because carrier localization can persist after payload release, whereas a payload can diffuse, degrade, react, or become activated at a location and time that no longer correspond to the carrier signal. Controlled-release research has therefore increasingly focused on temporal and microenvironmental triggers intended to reduce premature release while improving availability at the intended site[25]. These strategies make an important point even when they remain preclinical: payload release is an independent variable, not an automatic consequence of successful targeting.

Tumor-activated prodrug nanoparticles provide a complementary example. Their design attempts to connect lesion localization with local conversion of a relatively inactive precursor into a therapeutically active state[26]. Such systems are useful counterexamples to the strongest version of the article's thesis. Post-targeting failure is not inevitable. When carrier stability, tumor activation, cellular uptake, and payload pharmacology are well aligned, lesion access can be converted into useful biological action. The scientific requirement is to demonstrate that alignment rather than infer it from localization.

Multistage formulations illustrate how those claims can be separated experimentally. Mannosylated redox-responsive prodrug nanocolloids have been investigated through distinct measurements of receptor-associated targeting, cellular internalization, stimulus-sensitive release, and antitumor activity in preclinical colon-cancer models[27]. A system of this kind does not prove that active targeting will translate clinically, but it demonstrates the value of treating recognition, uptake, payload release, and biological response as different experimental questions.

Payload-specific pharmacology can impose still more downstream constraints. Cisplatin nanomedicine, for example, is affected by intracellular drug concentration, molecular deactivation, DNA-associated pharmacology, resistance pathways, toxicity, and other post-accumulation processes[28]. A carrier that increases tumor localization may therefore yield limited additional benefit if the active drug does not reach the relevant intracellular target in a useful chemical state or if resistance mechanisms dominate once it arrives.

The practical consequence is that carrier tracking and payload tracking should not be interchangeable. Their spatial relationship may remain stable for one formulation and diverge rapidly for another. Their temporal relationship may also change as the carrier disassembles or the payload is activated. Apparent failure can additionally be created by measurement itself—for example, when a fluorescent carrier label persists after drug release or when a payload-associated signal does not distinguish intact active compound from degraded or sequestered material.

The most important payload–carrier discordance patterns are summarized below as experimentally distinguishable states.

Table 2. Payload–carrier discordance states that can persist despite successful lesion localization

Observed delivery pattern	Carrier state	Plausible payload state	Mechanistic origin to resolve	Measurements needed to discriminate the state	Pharmacological interpretation
Lesion-localized carrier with weak active-payload signal	Carrier remains detectable within lesion	Payload released prematurely, degraded, cleared, or chemically unavailable	Release kinetics; carrier stability; extracellular degradation	Independent carrier and payload quantification over time; chemical-state analysis	Carrier accumulation may overestimate usable drug delivery
Intact carrier retained within target cell	Carrier remains associated with intracellular vesicles	Payload remains trapped within carrier or vesicular lumen	Insufficient carrier disassembly or membrane escape	Compartment-resolved imaging plus cytosolic/destination-compartment payload assay	Cellular uptake may occur without productive intracellular exposure
Carrier signal declines while pharmacological activity increases	Carrier disassembles or clears	Payload has been successfully released and reaches its site of action	Programmed disassembly or activation	Time-resolved carrier tracking, active-payload assay, target engagement	Loss of carrier signal can coexist with therapeutic success
Carrier and payload separate spatially after uptake	Carrier persists in one intracellular region	Payload redistributes to another compartment	Release, diffusion, trafficking, or transporter activity	Dual carrier/payload tracking with compartment markers	Carrier localization no longer predicts payload localization
High intracellular payload signal with weak pharmacodynamic effect	Carrier may have delivered payload successfully	Payload is inactive, inaccessible to target, insufficiently concentrated, or opposed by resistance	Chemical inactivation; target availability; resistance; insufficient exposure duration	Active-chemical-species measurement plus target engagement and downstream response	Intracellular presence is insufficient evidence of usable pharmacology
Improved payload release accompanied by increased toxicity	Carrier/release chemistry enhances cytosolic access	More payload or membrane-active material reaches sensitive compartments	Escape chemistry, membrane injury, off-target exposure, dose	Cytosolic-delivery assay together with toxicity and exposure–response analysis	A higher intracellular-delivery fraction can reduce therapeutic usability

Persistent carrier fluorescence after payload loss	Carrier label remains stable	Therapeutic payload is no longer co-localized with the tracked label	Label stability and decoupled release	Orthogonal label validation; direct payload measurement	Imaging can create an artificial impression of intact drug delivery
Targeted activation in the lesion with preserved payload function	Carrier and payload transitions are appropriately coordinated	Payload becomes active at the intended site and time	Tumor-responsive chemistry or enzymatic/redox activation	Activation-state assay plus pharmacodynamic confirmation	Demonstrates a productive countercase in which lesion access converts into useful therapy

Payload–carrier decoupling is therefore best treated as a measurable relationship between two evolving states rather than as a single formulation defect. In some systems it represents failure: the carrier reaches the lesion while the therapeutically relevant payload does not. In others, carrier disappearance is part of successful release. The interpretation depends on whether the payload reaches the compartment required for its mechanism, remains pharmacologically competent, and produces the intended biological response within an acceptable exposure range.

Biological activity must survive the efficacy–toxicity–dose-intensity trade-off

Clinical translation applies a stricter denominator than tissue or intracellular delivery. The relatively small set of nanoparticle technologies that has reached routine or advanced clinical use shows that successful formulation requires more than favorable preclinical localization[29]. Development reviews similarly identify representative models, trial design, safety, regulation, manufacturing, and sponsorship as determinants of whether a nanomedicine can become usable therapy[30].

Clinical-stage diversity also argues against a single formulation solution. Marketed and investigational nanomedicines vary widely in carrier composition, payload, indication, administration, and development maturity[31]. In oncology, persistent translation gaps show that strong preclinical performance can lose value when heterogeneity, toxicity, dosing requirements, or clinical context change the exposure–response relationship[32]. A useful intracellular-delivery gain must therefore survive comparison with the dose needed to produce it and the adverse effects generated at that dose. This is especially important when a membrane-active or release-enhancing modification increases cytosolic exposure but also increases toxicity, as already illustrated by escape-enhancing chemistry[20].

Treatment delivery burden is part of nanomedicine feasibility

Manufacturing complexity, scale-up, production cost, regulatory demands, and tumor heterogeneity remain substantial barriers to cancer-nanomedicine translation[33]. Translational guidance consequently emphasizes integrating biological performance with chemistry, manufacturing, reproducibility, safety, regulation, and development strategy from an early stage[34]. These constraints matter clinically because a formulation cannot provide benefit if the required product cannot be supplied reproducibly or administered at the dose and schedule needed to sustain its pharmacology.

Administration itself can create additional demands. Infusion reactions associated with some nanomedicines may require prevention, modified infusion procedures, monitoring, or acute management, although their occurrence and mechanism are product- and patient-dependent[35]. Patient selection, drug choice, and rational integration with existing regimens are likewise central to translating sophisticated nanomedicines into useful treatments[36]. The practical relationships should therefore remain visible alongside molecular performance.

Table 3. Clinical-feasibility dimensions that can modify the value of successful nanocarrier delivery

Dimension	Question after biological delivery succeeds	Evidence needed before claiming feasibility	Potential burden if unfavorable
Dose intensity	What exposure is required to sustain pharmacodynamic activity?	Exposure–response and toxicity data	Higher dose or repeated administration

Administration	Can the regimen be delivered predictably in routine care?	Route, frequency, duration, premedication data	Longer or more frequent treatment encounters
Safety monitoring	What surveillance accompanies the usable dose?	Product-specific adverse-event and monitoring evidence	Observation, laboratory testing, rescue capability
Manufacturing/logistics	Can the formulation be produced and supplied reproducibly?	Scale-up, stability, quality, and supply evidence	Specialized handling or restricted availability
Patient/service demand	Does incremental benefit justify the care required to deliver it?	Comparative clinical and implementation evidence	Time, travel, coordination, and healthcare-resource demand

These dimensions should not be converted into a universal burden score. Direct patient-reported burden evidence remains limited in the selected nanomedicine literature, so practical demands must be distinguished from demonstrated patient experience.

Figure 2 relates carrier state, payload pharmacology, and treatment delivery while retaining the distinct evidence required for each.

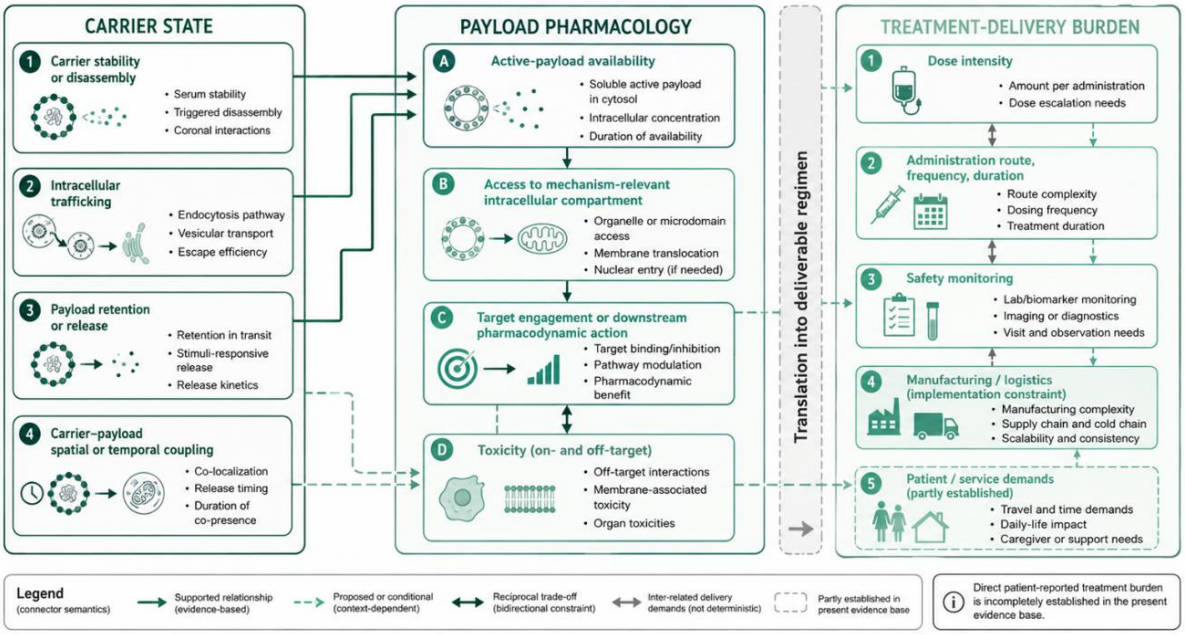

Figure 2. Coupling carrier performance, payload pharmacology, and treatment delivery

Results and Discussion

The evidence supports treating lesion accumulation, target-cell entry, intracellular payload availability, pharmacodynamic action, toxicity, and clinical feasibility as linked measurements with different inferential limits. No single surrogate should automatically stand for every downstream state. Carrier imaging is informative about carrier location; escape assays inform a narrower intracellular question; target engagement adds pharmacological evidence; and clinical feasibility introduces dose, safety, manufacturing, and treatment-delivery constraints.

This interpretation changes experimental priorities. Carrier and payload should be tracked independently when their coupling can change, and intracellular assays should match the compartment required by payload mechanism. Orthogonal measurement is particularly important when endosomal escape is inferred from membrane-perturbation reporters[15]. Improvements in one denominator should also be tested against downstream consequences: enhanced escape can improve functional delivery in one system[19] while introducing toxicity in another[20]. Release engineering likewise has value only when the active payload remains available at the right site and time[25].

Three propositions follow. First, among carriers with comparable lesion accumulation, direct intracellular payload availability and pharmacodynamic engagement should explain response heterogeneity better than bulk carrier signal alone. Second, greater intracellular exposure need not increase clinically usable benefit if it requires materially greater dose intensity, toxicity management, or treatment resources. Third, independent carrier and payload tracking should reveal spatial or temporal discordance in at least some formulations. Consistent one-to-one concordance across diverse systems would weaken the third proposition.

The practical implication is not to replace targeting with another universal optimization metric. Development should instead preserve the denominator of each claim and identify where the therapeutic chain actually loses usable exposure or feasibility.

Conclusion

Successful lesion arrival is an important achievement in targeted nanomedicine, but its meaning is conditional. Therapy can still fail through incorrect cellular destination, endosomal sequestration, payload–carrier decoupling, inadequate pharmacodynamic activity, toxicity, excessive dose requirements, or impractical treatment delivery. Conversely, well-aligned systems can convert lesion access into useful therapy. Stronger translation therefore depends on measuring carrier location, payload state, intracellular availability, biological action, and practical treatment demands separately enough to determine where success is gained or lost.

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