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Targeting Is Not Delivery: A Compartment-Resolved Theory of Nanomedicine Transport from Administration to Intracellular Drug Release

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ABSTRACT

Nanomedicine is often evaluated through target affinity, tissue accumulation, cellular association, or carrier-triggered release, although none of these observations alone establishes that pharmacologically available drug has reached its intended site of action. This Original Transport Theory Article proposes Compartment-Resolved Delivery Theory as an organizing framework for separating the sequential transport states between administration and intracellular drug availability. The theory represents delivery as conditional movement through systemic, vascular, interstitial, cellular, vesicular, and pharmacological compartments, with competing losses possible at every transition. It distinguishes carrier location from payload state and treats overall delivery as dependent on stage-specific transfer efficiency rather than on a single targeting endpoint. Proposed quantitative metrics include available-dose fractions, transition efficiencies, retention and loss fractions, spatial coverage, payload integrity, and action-site availability. Validation would require matched measurements across adjacent compartments using physicochemical characterization, blood-interaction assays, pharmacokinetics, spatial biodistribution, vascular-crossing analysis, cellular trafficking measurements, release assays, and pharmacodynamic evidence. Concordance across in vitro systems, animal models, and human-relevant evidence would strengthen—but not independently prove—the theory's applicability. Important boundaries include route dependence, disease heterogeneity, species-specific biological identity, analytical ambiguity, carrier–payload dissociation, and the possibility that optimizing one stage merely relocates the dominant bottleneck. The original contribution is a non-empirical, testable architecture for defining what delivery claims mean, identifying unmeasured losses, and directing validation toward the compartment that limits terminal drug availability. It is not a validated predictive model, clinical recommendation, regulatory standard, or universally applicable design rule.

Key words: *Nanomedicine, Targeted drug delivery, Biological barriers, Intracellular release, Biodistribution, Protein corona*

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INTRODUCTION

Nanomedicine engineering has expanded control over carrier composition, payload protection, surface chemistry, biological interactions, and tissue exposure, yet clinical performance remains constrained by biological heterogeneity, incomplete transport, and translational requirements [1–3]. The persistence of these constraints suggests that formulation sophistication cannot substitute for evidence that a therapeutic payload has traversed the complete pathway from administration to its pharmacological site of action.

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A central conceptual problem is the compression of several non-equivalent observations into the term "delivery." Circulation time, organ accumulation, vascular proximity, receptor binding, cellular uptake, intracellular fluorescence, carrier degradation, and therapeutic response describe different material states and anatomical locations. Treating them as interchangeable can obscure where dose is lost, which mechanism is limiting, and whether the measured signal represents the nanocarrier, the payload, a label, or an active drug species.

This article develops Compartment-Resolved Delivery Theory, hereafter CRDT, as an original non-empirical contribution. CRDT defines delivery as conditional transport through operationally distinguishable compartments, each with specified entry events, exit events, competing losses, and measurement requirements. It further separates nanocarrier fate from payload fate so that accumulation of one cannot be interpreted automatically as availability of the other.

The objective is not to provide an exhaustive review or claim a universally valid transport model. Instead, the article integrates established barrier mechanisms into a proposed architecture for formulating testable propositions, stage-specific metrics, validation requirements, and decision boundaries. CRDT is intended to clarify claims and guide future experiments; it does not establish clinical effectiveness, regulatory acceptability, or deployment readiness.

Why target binding does not establish successful delivery

Ligand-mediated recognition cannot establish successful delivery when particles fail to enter the intended tissue, remain spatially inaccessible to target cells, or encounter competing biological sinks [4–6]. Binding affinity becomes relevant only after a sufficient fraction of the administered material reaches a biologically accessible receptor in an appropriate molecular state. Targeting is therefore conditional on upstream transport rather than an independent substitute for it.

Even after vascular exit, ligand-coated particles may remain within perivascular regions, extracellular spaces, phagocytic cells, stromal populations, or other non-target compartments. Cell-resolved analyses have shown that total tumour-associated material may not correspond to delivery into the intended malignant-cell population [4]. Consequently, whole-tissue accumulation can overstate the dose available for receptor engagement and downstream intracellular transport.

Targeting must also be distinguished from internalization. Surface association can arise through specific receptor binding, nonspecific adhesion, corona-mediated interactions, or incomplete removal of extracellular particles. Internalization, in turn, does not establish productive trafficking because particles may be recycled, exocytosed, degraded, or retained within vesicular compartments. These alternatives create mechanistically different explanations for the same bulk fluorescence or total-drug measurement.

CRDT therefore proposes that successful delivery be reserved for the presence of chemically and pharmacologically available payload at the intended action site. This definition does not diminish the value of ligand engineering; it limits the inference permitted by binding or uptake evidence. A targeting strategy may improve one transition while leaving circulation, vascular access, tissue penetration, intracellular trafficking, release, or target engagement unresolved.

Physiological and anatomical transport compartments

Nanomedicine transport traverses systemic, anatomical, tissue, cellular, and subcellular barriers whose relevance depends on the carrier, payload, route, and disease context [7–9]. These barriers should not be represented as a single obstacle because they operate through different mechanisms, occur at different spatial scales, and require different experimental measurements.

CRDT defines a compartment as an operational state characterized by location, material identity, entry conditions, residence, transformation, and possible exits. The initial compartment may be an injection site, gastrointestinal lumen, airway surface, mucosal depot, or circulating blood, depending on the route. Downstream compartments can include vascular plasma, clearance organs, endothelial interfaces, interstitial space, cell surfaces, endocytic vesicles, cytosol, organelles, and the molecular action site.

An anatomical compartment is not synonymous with an organ. A tumour, liver, lung, or lymph node contains vascular, extracellular, stromal, immune, parenchymal, and intracellular subcompartments that may have different access conditions. Likewise, a particle detected in an organ may be intravascular, endothelial, extracellular, membrane-associated, vesicular, degraded, or associated with released label. Spatial location and material state must therefore be reported together.

The proposed compartment boundaries are analytical rather than universally fixed. A payload acting on an extracellular receptor does not require cytosolic access, whereas nucleic-acid therapeutics generally require productive intracellular trafficking. Local administration may bypass part of systemic circulation but introduce depot retention or local clearance. CRDT consequently requires route-, payload-, carrier-, disease-, and time-specific adaptation without abandoning the principle that distinct transport states cannot substitute for one another.

Proposed compartment-resolved delivery theory

CRDT represents delivery as a sequence of conditional state transitions. At each stage, the available dose may move forward, remain temporarily retained, undergo transformation, return to an earlier accessible state, or enter an irreversible loss pathway. The theory does not assume that every formulation follows an identical anatomical route; it requires only that each claimed transition be defined and measured separately.

The proposed core pathway extends from administration through biological-identity transformation, circulation, vascular encounter, transvascular access, tissue penetration, target-cell association, internalization, vesicular trafficking, intracellular release, and pharmacological availability. **Figure 1** presents the original conceptual synthesis for sequential biological barriers from administration to intracellular release, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

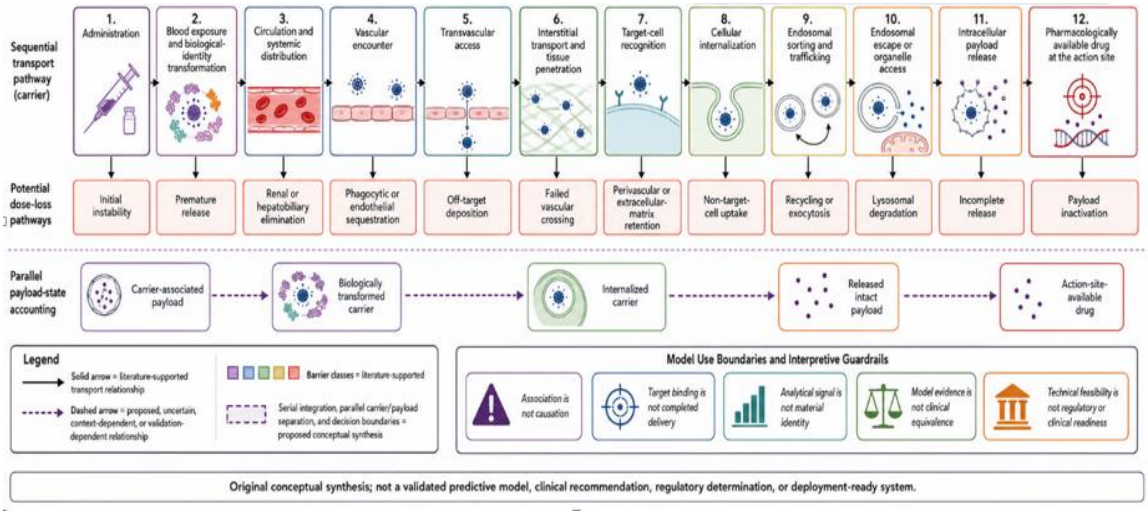

Figure 1. Sequential Biological Barriers from Administration to Intracellular Release.

The figure is an original conceptual synthesis developed for "Targeting Is Not Delivery: A Compartment-Resolved Theory of Nanomedicine Transport from Administration to Intracellular Drug Release." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. Literature-supported barrier classes include systemic exposure, biological-identity transformation, clearance, vascular access, tissue transport, cellular uptake, intracellular trafficking, and payload release. Their integration into one serial architecture, the parallel separation of carrier and payload states, and the assignment of explicit decision boundaries are proposed components requiring empirical validation. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

CRDT further proposes parallel accounting for the nanocarrier and its payload. A carrier can remain structurally intact while losing payload, degrade while the payload remains chemically active, or produce a detectable label after both carrier and drug have changed state. Mechanistic discussions of nanomedicine similarly span carrier design, biological interactions, cellular transport, and release, but these stages require separate evidence rather than a single composite delivery claim [10].

For conceptual analysis, the available dose entering compartment i may be represented as Di, and the fraction successfully transferred to the next required compartment as ηi. The downstream available dose is therefore expressed as $D_{i+1} = D_i \times \eta_i$. End-to-end availability can be represented conceptually as the administered dose multiplied by the conditional efficiencies of all required transitions. These expressions define accounting relationships only; they are not validated pharmacokinetic equations or numerical predictors.

The theory also introduces a bottleneck principle. The most consequential stage-specific attrition defines the current limiting transition, but improving that transition may expose a different downstream limitation. Organ-selective nanoparticle composition demonstrates that distribution can be redirected at one stage without

establishing later cellular or intracellular delivery [11]. CRDT therefore evaluates design changes by whether they increase terminal payload availability while preserving safety and manufacturability, not merely by whether they improve one intermediate targeting metric [12].

Circulation, opsonization, clearance, and vascular access

Blood exposure changes the interface through which a nanocarrier interacts with biological systems. Adsorbed proteins can mask engineered ligands, introduce new receptor interactions, alter colloidal stability, and change recognition by immune or endothelial cells [13]. CRDT therefore treats the formulated surface and the acquired biological identity as related but non-equivalent material states.

Clearance is not a single terminal event. Hepatic endothelial uptake, phagocytic sequestration, renal filtration, splenic retention, and hepatobiliary elimination may remove different carrier fractions through formulation- and host-dependent mechanisms. Stab2-mediated uptake demonstrates that a defined scavenger pathway can substantially redirect biodistribution, although the magnitude and dominance of that pathway cannot be generalized across carriers or species [14].

Vascular persistence only preserves an opportunity for access. A circulating particle must still encounter an appropriate vascular region, interact with the endothelial interface, and cross into the target tissue. Paracellular transport, endothelial transcytosis, vascular fenestration, and inflammation-associated permeability represent distinct routes with different determinants and evidential requirements [15]. Whole-blood exposure or organ signal cannot establish successful transvascular movement.

Within CRDT, circulation, clearance, and vascular access are upstream conditional gates rather than proxies for complete delivery. Increasing circulation time may enlarge the encounter window, but it may also prolong off-target exposure or shift the dominant loss to another compartment. **Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in targeting is not delivery..

Table 1. Definitions, components, relationships, and intended uses in Targeting Is Not Delivery.

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Biological identity	Engineered surfaces may not remain biologically recognizable as designed	Surface chemistry, plasma composition, exposure time, host state	Protein adsorption modifies receptor interactions and clearance behaviour [13]	Separates formulated identity from in vivo identity	Corona composition, stability, receptor-interaction and uptake measurements	Ex vivo corona may not reproduce in vivo transformation	Corona composition alone does not predict delivery
Circulating available dose	Administered dose may overstate material capable of reaching tissue	Route, stability, release, clearance and distribution	**Proposed:** only intact or functionally relevant circulating material remains available downstream	Defines the denominator for vascular access	Pharmacokinetics with carrier and payload discrimination	Labels may persist after carrier transformation	Blood persistence is not tissue delivery
Clearance and sequestration	Non-target uptake reduces downstream opportunity	Size, charge, corona, scavenger pathways and organ physiology	Clearance pathways compete with forward transport; specific pathways may dominate in defined systems [14]	Identifies upstream dose sinks	Organ-, cell- and receptor-resolved disposition evidence	Species and formulation dependence	Avoid universal clearance rankings

Vascular access	Organ exposure may not establish tissue entry	Vascular anatomy, flow, endothelial state and particle properties	Vascular encounter precedes paracellular or transcellular crossing [15]	Separates circulation from extravascular exposure	Intravascular–extravascular discrimination and spatial imaging	Residual blood signal can mimic tissue accumulation	Organ signal is not proof of extravasation
Target recognition	Binding is often treated as completed delivery	Accessible receptor density, ligand state and competing interactions	**Proposed:** binding contributes only after sufficient dose reaches an accessible interface	Limits interpretation of targeting assays	Binding specificity, accessibility and downstream trafficking evidence	Nonspecific adhesion or corona-mediated recognition	Affinity is not terminal delivery
Intended use of CRDT	Intermediate outcomes are conflated	Compartment definitions and matched measurements	**Proposed:** claims are restricted to the last directly demonstrated transport state	Improves claim precision and experiment design	Adjacent-compartment measurements	Missing states may remain hidden	CRDT is an organizing theory, not a validated predictor

Tissue penetration and extracellular transport

Crossing the vascular wall does not establish distribution throughout the tissue. Extravasation deposits material within an extravascular region, whereas infiltration requires subsequent movement through interstitial fluid, extracellular matrix, stromal structures, pressure gradients, and cellular obstacles [16]. CRDT therefore treats vascular exit and tissue penetration as separate transitions.

Transcellular transport may provide an alternative to passive extracellular movement. Experimental evidence indicates that nanomedicine can undergo transcytosis and propagate through tumour tissue in defined systems [17]. This finding supports the existence of active penetration routes but does not establish that transcytosis is dominant in every tumour, organ, disease state, or formulation.

Particle size, morphology, charge, deformability, surface interactions, degradation, and stimulus responsiveness can influence spatial penetration [18]. However, an intervention that increases mobility may reduce retention, cellular association, payload protection, or stability. Penetration must consequently be assessed as a distribution pattern and not reduced to mean tissue concentration.

CRDT defines tissue-accessible dose as material that has crossed the vascular boundary and remains capable of reaching the intended cellular interface. Suitable evidence includes distance-from-vessel analysis, three-dimensional localization, intact-carrier assessment, and discrimination among extracellular, stromal, immune-cell, and target-cell compartments. A larger extravascular signal is not sufficient when spatial coverage or payload integrity remains unknown.

Cellular uptake, endosomal trafficking, and intracellular release

Cellular uptake measurements must distinguish surface association from internalization. Washing procedures, temperature shifts, fluorescence quenching, microscopy, flow cytometry, and biochemical recovery answer different questions and may generate different estimates of uptake [19]. CRDT requires the assay to specify which material state and cellular location are actually measured.

Following internalization, carriers may enter clathrin-dependent, caveolar, macropinocytic, phagocytic, or other pathways. They may then be retained, recycled, transported, degraded, or redirected among intracellular compartments [20]. Internalized dose is therefore divided conceptually into productive and non-productive trafficking fractions.

Endosomal escape is especially vulnerable to overinterpretation. Diffuse fluorescence, toxicity, altered reporter expression, or total intracellular signal may suggest—but does not independently prove—cytosolic delivery. Escape assessment requires complementary methods with appropriate spatial resolution and controls for carrier disruption, probe dissociation, and endosomal damage [21].

CRDT defines productive trafficking according to the payload's required destination. Cytosolic nucleic acids, lysosome-active drugs, nuclear agents, mitochondrial therapeutics, and membrane-directed compounds have

different terminal pathways. No intracellular compartment is universally desirable, and the relevant success criterion must be specified before uptake or escape is evaluated.

Drug availability at the site of pharmacological action

Release is not equivalent to availability. A payload may leave its carrier prematurely, remain chemically bound, precipitate, degrade, bind extracellular components, enter an inaccessible cellular pool, or fail to reach its molecular target. CRDT therefore separates carrier-associated payload, released payload, chemically intact free payload, and pharmacologically available drug.

Conventional release measurements may also misidentify the governing process. Dialysis-based assays can be influenced by membrane transport and sink conditions, causing the measured profile to differ from the intrinsic release behaviour of the nanocarrier [22]. Release evidence must identify the carrier state, external transport resistance, analytical recovery, and chemical integrity of the payload.

Stimuli-responsive systems add further transitions. Exposure to light or another stimulus, activation of a responsive element, carrier transformation, payload liberation, intracellular distribution, and target engagement are distinct events. Remotely controlled delivery systems demonstrate the feasibility of conditional release, but stimulus response does not itself establish action-site availability [23].

CRDT reserves the strongest delivery claim for evidence that intact, pharmacologically competent drug reaches the required molecular environment. **Table 2** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for targeting is not delivery.

Table 2. Testable propositions, evidence requirements, and validation criteria for Targeting Is Not Delivery.

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Conditional targeting	Establish receptor interaction after access	Vascularly and spatially accessible carrier to target-associated carrier	Depends on all upstream transport stages	Specific binding plus accessible-dose and downstream-state evidence	High affinity with negligible accessible dose	Investigators must distinguish affinity, accessibility and uptake	Binding evidence supports targeting, not completed delivery
Multiplicative attrition	Represent cumulative stage losses	**Proposed:** $D_{i+1} = D_i \times \eta_i$	Every required transition limits terminal availability	Matched denominators across adjacent compartments	Incompatible assays or unreconciled material	Analytical teams must document recovery and state identity	Conceptual equation is not a validated pharmacokinetic model
Bottleneck displacement	Identify the currently limiting transition	Stage-specific transfer, retention and loss evidence	Improvement at one stage may expose another	Prospective comparison before and after redesign	Optimizing a surrogate while terminal delivery is unchanged	Design teams must reassess the full pathway	No universal bottleneck ranking
Carrier–payload separation	Prevent carrier signal from substituting for drug availability	Carrier-associated, released, intact and active payload states	Connects trafficking with release and pharmacology	Orthogonal carrier and payload measurements	Label dissociation or payload degradation	Investigators must validate label fidelity and chemical integrity	Carrier accumulation cannot establish active-drug exposure
Productive trafficking	Deliver payload to its required intracellular destination	Internalized carrier to destination-accessible payload	Depends on uptake route and vesicular processing	Destination-specific localization and functional evidence [21]	Recycling, lysosomal degradation or false-positive escape	Cell-biological and analytical teams share responsibility	Uptake is not productive intracellular delivery
Release validity	Establish genuine payload liberation	Carrier-associated to released intact payload	Influenced by assay transport and environment	Method controls excluding membrane-	Apparent release reflects	Formulation scientists must justify method fitness	In vitro release does not alone establish in vivo availability

				limited artefacts [22]	dialysis transport		
Action-site availability	Link transport to pharmacological opportunity	Intact free drug to molecular target environment	Terminal outcome of required transport stages	Drug-state, localization and target-engagement evidence	Total concentration without active fraction	Pharmacology teams must define the relevant action site	Availability does not automatically establish clinical benefit

Quantitative metrics for stage-specific delivery efficiency

Stage-specific measurement begins with a defined denominator. Depending on the question, the denominator may be administered dose, circulating intact carrier, organ-associated material, extravascular material, target-cell-associated payload, internalized dose, or released drug. These denominators cannot be exchanged without changing the meaning of the efficiency estimate.

Imaging can connect whole-body, organ-level, tissue-level, and temporal observations, but the signal must be related to a specified material state [24]. Radiolabels, fluorescent probes, elemental signatures, and chemical assays differ in their ability to distinguish intact carrier, degradation products, released label, and payload. Orthogonal measurements are therefore preferable when feasible.

Comparative biodistribution analyses show that apparent delivery depends on formulation, organ, tumour model, measurement time, and denominator [25]. CRDT accordingly proposes reporting stage-transfer efficiency, stage retention, competing loss, spatial coverage, payload integrity, and action-site availability rather than relying on one accumulation percentage.

These metrics are proposed definitions, not validated thresholds. Their purpose is to expose missing transitions and permit reconciliation between adjacent compartments. A stage-specific estimate should report material identity, location, time, biological model, analytical recovery, uncertainty, and denominator. Unrecovered material should remain unassigned rather than being assumed to have moved forward.

Validation across in vitro, animal, and human evidence

Validation should proceed through linked evidence rather than through a single "representative" model. The DELIVER framework emphasizes coordinated attention to design, characterization, manufacturing, preclinical evidence, clinical development, regulation, and implementation [26]. CRDT adds a transport-specific requirement: each major claim should be tied to the compartment and material state directly measured.

In vitro systems can isolate protein adsorption, endothelial interaction, matrix transport, cellular uptake, trafficking, release, and target engagement. Their value lies in controlled mechanism testing, not in automatic prediction of organism-level delivery. Increasingly complex co-cultures, organoids, microphysiological systems, and patient-derived materials may improve relevance while introducing additional variability.

Animal studies can connect pharmacokinetics, whole-organ distribution, vascular crossing, cellular localization, safety, and pharmacodynamics. The clinical development of a nucleic-acid nanomedicine illustrates that translation depends on alignment among formulation, scalable manufacturing, pharmacology, safety, and clinical context rather than on targeting performance alone [27]. Product-specific success nevertheless does not validate a universal transport theory.

Human validation may require imaging, tissue analysis, pharmacokinetics, biomarkers, target engagement, and clinical pharmacology appropriate to the product. Concordance across adjacent compartments and model levels would strengthen confidence without proving universal applicability. **Table 3** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for failure modes, boundary conditions, governance needs, and implementation priorities for targeting is not delivery..

Table 3. Failure modes, boundary conditions, governance needs, and implementation priorities for Targeting Is Not Delivery.

Decision scenario or design trade-off	Trigger or context	Competing objective	Evidence threshold	Uncertainty treatment	Corrective or escalation action	Expected implication	What cannot be concluded
Increase ligand density	Weak measured	Stealth, stability and tissue transport	Demonstrated accessible receptor binding	Report corona and	Compare multiple densities	May identify a conditional optimum	Greater affinity does not establish greater

	target association		and preserved upstream transport	accessibility uncertainty	across the complete pathway		terminal delivery
Extend circulation	Rapid blood clearance	Off-target exposure and delayed elimination	Intact carrier and payload pharmacokinetics with organ-resolved disposition	Separate label persistence from intact material	Investigate the responsible clearance route	May preserve vascular-encounter opportunity	Longer circulation does not prove tissue entry
Increase tissue penetration	Perivascular retention	Local retention, payload protection and safety	Spatial distribution with intact-payload evidence	Report model-specific matrix and vascular features	Modify size, surface or transformation only after bottleneck confirmation	May improve spatial coverage	Penetration in one model is not universal
Promote uptake	Low cellular internalization	Nonspecific uptake and degradative trafficking	Binding–internalization discrimination and destination tracking	Quantify non-target-cell uptake	Redesign uptake mechanism or intracellular routing	May improve internalized dose	Uptake does not prove productive trafficking
Trigger release	Incomplete intracellular liberation	Premature release and systemic toxicity	Trigger exposure, carrier response, intact release and target-site evidence	Model trigger heterogeneity	Adjust trigger sensitivity or carrier stability	May improve payload availability	Trigger activation does not establish clinical benefit
Translate between models	Discordant in vitro and animal results	Mechanistic control versus physiological complexity	Prespecified adjacent-compartment concordance	Preserve disagreement rather than averaging it away	Escalate to human-relevant systems or revise the claim	Clarifies model domain	Cross-model similarity is not clinical equivalence
Scale manufacture	Batch or process change	Reproducibility, cost and biological performance	Comparability of critical material and stage-specific transport attributes	Propagate manufacturing uncertainty into biological interpretation	Recharacterize affected transitions	Protects mechanistic comparability	Physicochemical similarity alone does not prove biological equivalence
Strengthen reporting	Irreproducible or ambiguous findings	Experimental burden	Minimum material, biological, analytical and contextual reporting [28]	Declare missing information explicitly	Restrict claims or repeat critical measurements	Improves interpretability	Complete reporting does not itself validate efficacy
Standardize methods	Assay-dependent conclusions	Flexibility for product-specific methods	Fit-for-purpose quality and safety methods [29]	Report intermethod disagreement	Use orthogonal methods and qualified controls	Improves evidence robustness	Standardization is not regulatory approval

Limitations and boundary conditions

CRDT is limited by the quality of measurements assigned to its compartments. Incomplete characterization of material properties, biological conditions, analytical procedures, and experimental context can prevent comparison or reconstruction of a delivery claim [28]. Formal compartment labels cannot correct an assay that measures the wrong material state.

Methodological standardization is also incomplete. Quality, safety, and comparability assessments may require product-specific methods, reference materials, controls, and acceptance logic [29]. CRDT can identify where evidence is missing, but it does not supply validated assays or universally transferable acceptance criteria.

The architecture may require modification for local administration, extracellular drug targets, immune-cell carriers, depot systems, mucosal transport, central nervous system delivery, degradable materials, or payloads intended to remain in endosomal compartments. Compartments can merge, branch, or become irrelevant depending on the therapeutic mechanism.

Causality remains another boundary. Association between a stage metric and pharmacological response may reflect correlated formulation properties, disease biology, exposure, or measurement bias. Prospective perturbation of a defined transition is needed to test whether that stage is causally limiting. CRDT is therefore hypothesis-generating and claim-restricting rather than self-validating.

Implications for nanocarrier design

CRDT redirects design from maximizing isolated attributes toward resolving an experimentally demonstrated bottleneck. A stronger ligand is useful only when receptor access limits delivery; increased stability is useful only when premature transformation is consequential; and enhanced escape is useful only when sufficient intact payload reaches the relevant vesicular compartment.

Cell-membrane coatings illustrate how biological interfaces may provide combinations of immune evasion, adhesion, recognition, or homotypic interaction that are difficult to reproduce with one synthetic ligand [30]. Hybrid erythrocyte–platelet membrane coatings further demonstrate the feasibility of integrating complementary cellular functions within one carrier [31]. These platforms remain subject to source, manufacturing, safety, and context-dependent uncertainties.

Figure 2 presents the original conceptual synthesis for compartment-resolved accounting of nanomedicine dose loss, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

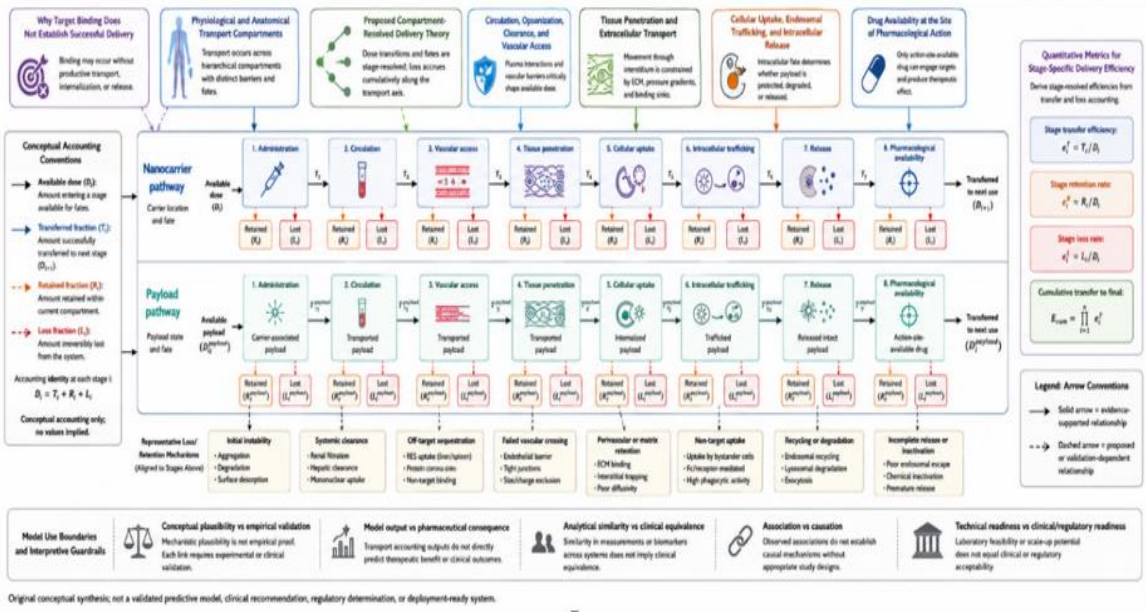

Figure 2. Compartment-Resolved Accounting of Nanomedicine Dose Loss.

The figure is an original conceptual synthesis developed for "Targeting Is Not Delivery: A Compartment-Resolved Theory of Nanomedicine Transport from Administration to Intracellular Drug Release." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

The design implication is a stage-matched optimization rule. Candidate changes should be evaluated against the compartment they are intended to improve, all adjacent transitions that may be disrupted, terminal payload availability, safety, and manufacturability. A higher intermediate metric should justify progression only when it produces interpretable improvement without transferring unacceptable loss or uncertainty elsewhere.

CONCLUSION

This Original Transport Theory Article proposes CRDT to distinguish targeting from completed delivery by representing nanomedicine transport as a sequence of non-substitutable compartments with explicit transfer, retention, transformation, and loss. Its central contribution is the separation of carrier fate from payload fate and the restriction of each claim to the last material state and location directly demonstrated. The theory generates testable propositions concerning conditional targeting, cumulative attrition, bottleneck displacement, state-specific measurement, and cross-model validation. Its applicability remains conditional on administration route, carrier and payload properties, disease anatomy, host biology, analytical validity, manufacturing comparability, and evidence across adjacent transport stages. CRDT is not empirically validated, clinically prescriptive, regulator-approved, universally applicable, or deployment-ready; it is a bounded conceptual architecture for designing more discriminating experiments and more defensible delivery claims.

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