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Targeted Delivery Should Be Designed Around Competing Biological Sinks

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ABSTRACT

Targeted drug delivery is usually framed as a problem of increasing affinity for a desired tissue or cell. That framing is incomplete because an administered carrier is simultaneously exposed to biological compartments that remove, retain, transform, redistribute, or consume it before and after target contact. These competing sinks include the mononuclear phagocyte system, liver and spleen, renal and pulmonary pathways, adsorbed proteins, nontarget cellular populations, and finite receptor pools at the intended destination. Their influence is dynamic rather than fixed: formulation composition, acquired biological identity, administration route, dose, tissue state, receptor abundance, and time can change the relative strength of each pathway. This Systems Perspective argues that targeted delivery should therefore be designed as an exposure-allocation problem. Target accumulation represents only one term in a broader system of competing fluxes, retention processes, capacity limits, and exit routes. Evidence from nanomedicine biodistribution, tumor transport, lipid nanoparticles, renal and pulmonary targeting, protein-corona biology, and receptor-density studies is used to distinguish established mechanisms from a proposed competing-sinks interpretation. Particular attention is given to conditions in which apparently improved targeting redistributes exposure toward another organ, increases nonproductive cellular binding, saturates clearance, perturbs receptor availability, or introduces a new safety liability. The resulting perspective does not provide a validated quantitative predictor. Instead, it proposes a mass-balance-oriented design logic in which target exposure must be interpreted against simultaneous changes in competing biological sinks and verified using measurements that preserve tissue, cellular, temporal, dose, and translational boundaries.

Keywords: *Nanomedicine, Targeted drug delivery, Biodistribution, Biological sinks, Protein corona, Receptor capacity*

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INTRODUCTION

Targeted delivery is often evaluated through a local question: how much carrier, drug, or functional payload reaches the intended tissue relative to a comparator? Yet the biological fate of a systemically administered nanomedicine is determined before, during, and after this target-facing event. Clearance processes, vascular access, plasma-protein adsorption, phagocytic capture, liver and spleen sequestration, renal elimination, pulmonary extraction, cell binding, intracellular processing, and target-tissue egress collectively determine how much administered material remains available for productive delivery. Contemporary analyses of nanomedicine biodistribution and clearance therefore support treating disposition as a coupled design problem rather than as an isolated optimization of target affinity [1]. Precision nanoparticle engineering similarly demonstrates that carrier

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size, composition, surface chemistry, mechanics, route of administration, biological interactions, and disease context can modify delivery simultaneously [2].

A broader design framework is consequently required. Delivery systems traverse sequential biological barriers, but those barriers are not merely obstacles arranged in a linear path. They can act as competing destinations, reservoirs, transformation sites, or elimination routes, and their relative importance can change as the carrier itself changes state after administration [3]. The present article therefore advances a proposed competing-biological-sinks interpretation: target tissue is one consumer of available carrier exposure among several biologically active alternatives. The framework is intended as an organizing systems perspective rather than a prospectively validated pharmacokinetic model.

The need for such a perspective is especially clear in tumors, where access itself remains mechanistically heterogeneous. Contemporary intravital analyses challenge an interpretation in which nanoparticle accumulation can always be represented by a single permeability or enhanced-permeability-and-retention term; active endothelial transport, immune-cell-associated transport, lymphatic escape, and tumor-specific microvascular organization can all contribute under particular experimental conditions [4]. Targeting efficiency should therefore be interpreted as a balance among access, competing capture, residence, exit, and productive intracellular delivery rather than as a single percentage of injected dose reaching a nominal anatomical destination.

Target tissue as one competitor among many

The intended tissue becomes pharmacologically relevant only after the carrier has remained available long enough to encounter an accessible vascular or tissue interface. Even within one tumor, this access is heterogeneous. Experimental and modelling work has shown that nanoparticle passage into studied solid tumors can involve active endothelial processes rather than occurring predominantly through static inter-endothelial gaps, and that a restricted endothelial-cell subset may contribute disproportionately to transvascular entry [5, 6]. These findings do not establish one universal entry mechanism for all nanocarriers or all malignancies. They do establish a more limited but important principle: anatomical presence of a target does not imply uniform access capacity.

This distinction changes how “target tissue” should be represented in a systems model. A tumor, inflamed tissue, kidney compartment, pulmonary vascular bed, or other intended destination should not be treated as an unlimited absorbing compartment. Access can be spatially restricted, temporally variable, phenotype-dependent, and carrier-dependent. In the proposed competing-sinks interpretation, target entry is therefore a flux whose magnitude is conditioned by both the carrier state and the local biological interface. A formulation that increases affinity after extravasation may provide little benefit if upstream target access remains limiting, whereas rapid vascular capture can potentially outperform slower affinity-dependent processes when systemic scavenging is fast.

Target accumulation is also not equivalent to irreversible retention. Nanoparticles can exit solid tumors through lymphatic routes and return to the circulation, with the importance of exit varying with particle characteristics [7]. Target-tissue exposure should therefore include both inward and outward terms. A high measurement at one time point may represent transient residence rather than durable local availability, while a lower late measurement may reflect redistribution rather than failed entry. This temporal distinction becomes particularly important when biodistribution measurements are used as surrogates for functional payload delivery.

Cellular capture within the target adds a further complication. Tumor-associated macrophages can actively redistribute extravasated nanoparticles after vascular entry rather than acting only as terminal phagocytic sinks [8]. Thus, a cell population usually categorized as off-target may sometimes behave as a secondary transport vector within the intended tissue. The proposed model therefore avoids assigning a fixed biological meaning to every sink. A sink is defined operationally by how it alters the availability of carrier or payload for the article’s intended delivery objective. The same macrophage population can represent loss, temporary storage, redistribution, or potentially payload transfer depending on carrier properties, tumor organization, and time.

Mononuclear phagocyte system

The mononuclear phagocyte system is one of the most consequential competing sinks for many intravenously administered nanocarriers, but its activity cannot be represented adequately by a fixed clearance constant independent of carrier state. Once exposed to biological fluids, nanoparticles acquire adsorbed proteins that modify recognition by monocytes and macrophages. Experimental comparisons of distinct coronas demonstrate that enrichment of opsonins and other surface-associated proteins can substantially alter interactions with THP-1 monocytes and macrophage-like cells [9]. The manufactured particle and the circulating biological particle are therefore not necessarily the same targeting entity.

This state dependence is also relevant to biomimetic strategies. Membrane wrapping or other biologically derived coatings may reduce particular recognition processes, but such surfaces remain capable of acquiring protein coronas that influence both uptake by intended cell populations and macrophage-mediated clearance [10]. Consequently, "stealth" should not be treated as an intrinsic binary property. A more defensible description is conditional: a carrier may exhibit reduced interaction with selected clearance pathways under defined biological conditions while remaining susceptible to other corona-, dose-, or compartment-dependent processes.

Within the proposed competing-sinks model, the mononuclear phagocyte system therefore has at least three analytically separate roles. First, it removes circulating carrier and reduces subsequent target availability. Second, it can alter the carrier through cellular processing or retention. Third, macrophage populations located within or adjacent to target tissue may redistribute carrier rather than simply eliminate it. These roles should not be merged into one generic "MPS uptake" variable when the intended pharmacological interpretation depends on whether material is irreversibly lost, transiently retained, or repositioned.

Capacity also matters. Phagocytic uptake is not necessarily linear across dose, and evidence discussed later shows that sufficiently high nanoparticle burdens can alter Kupffer-cell-mediated clearance in preclinical systems. This creates an important systems consequence: changing dose can change the apparent targeting mechanism itself. A formulation that performs differently at higher dose may not have acquired greater intrinsic affinity; instead, a competing clearance sink may have become less efficient. Dose-independent comparisons can therefore be misleading when sink capacities differ among formulations or biological states.

Liver and spleen sequestration

Liver and spleen are frequently categorized together as undesirable reticuloendothelial sinks, but this simplification can obscure both mechanism and therapeutic intent. The spleen can be deliberately targeted for immunological, hematological, or other therapeutic purposes, and splenic localization depends on factors including particle size, surface charge, ligand presentation, protein corona, and interactions with resident immune-cell populations [11]. The same measured splenic accumulation can therefore represent successful targeting in one application and competing sequestration in another.

Formulation chemistry can alter the balance between liver and spleen even when the nominal carrier class is unchanged. In lipid nanoparticles, helper-lipid structure has been shown to modify protein adsorption, including ApoE-associated interactions, together with subsequent liver-versus-spleen delivery [12]. This supports a broader principle used in the present framework: an apparently small formulation change can modify a carrier's biological identity and thereby redistribute exposure among competing organs. The relevant design variable is not simply the pre-injection formulation composition but the interaction between composition and the biological environment encountered after administration.

Selective organ targeting illustrates this redistribution experimentally. Incorporation of supplemental lipid components into LNPs can redirect functional mRNA delivery toward different organs in mice, including shifts among liver, spleen, and lung [13]. Such findings show that dominant organ sinks are design-responsive, but they do not establish fixed human organ-selection rules. Organ tropism remains dependent on formulation family, physicochemical state, cargo, route, species, and the biological proteins recruited to the carrier.

Even within apparently similar LNP systems, the identity of the ionizable lipid and the administration route can produce different pharmacokinetic and biodistribution profiles [14]. These differences argue against treating "LNP biodistribution" as one reusable constant. The liver and spleen should instead be represented as dynamic sinks whose uptake reflects carrier composition, acquired protein state, blood exposure, route, cell phenotype, and time. For systems design, the key question becomes not whether liver or spleen accumulation has been reduced absolutely, but where that exposure has been redirected and whether the newly favored compartment supports the intended pharmacological objective.

Renal and pulmonary sinks

Kidney and lung illustrate why an organ can function simultaneously as a clearance pathway, an unintended sink, or a deliberately selected target. Pulmonary targeting provides a particularly clear example of kinetic competition. Antibody-directed nanoparticles exploiting endothelial caveolae have been shown in rats to undergo very rapid lung extraction, allowing the pulmonary vascular target to capture particles before slower systemic scavenging pathways dominate [15]. The importance of this observation is not that caveolar targeting constitutes a general pulmonary solution. Rather, it demonstrates that the *rate* of target access relative to competing sink rates can determine delivery success.

Renal disposition is comparably multistage. Physiological analyses of renal nanomedicine emphasize that kidney targeting depends on vascular delivery, glomerular filtration where relevant, tubular exposure, cellular uptake, secretion, and extrusion, with size, charge, disease state, and nanoparticle composition modifying these processes [16]. A simple "small particles are renally cleared" rule is therefore insufficient for many systems. Experimental mapping of ultrasmall gold nanoparticles further shows that charge-dependent interactions within peritubular capillaries and proximal tubular regions can regulate renal elimination after glomerular passage, indicating that renal charge barriers are not confined to the filtration interface [17].

Pulmonary tropism likewise need not depend on an externally added affinity ligand. Biodegradable poly(beta-amino ester) nanoparticles have been engineered to deliver mRNA preferentially to lung tissue after systemic administration in mice through formulation-dependent chemistry rather than a conventional targeting ligand [18]. This reinforces the article's distinction between **access** and affinity. A carrier can exhibit useful tissue selectivity because of its interactions with biological transport and retention mechanisms even when no classical ligand-receptor targeting moiety is present.

Yet redistribution toward an organ is not necessarily beneficial. Physicochemical LNP strategies that favor lung localization have also been associated with serious clotting responses in preclinical systems, with positive charge and inflammatory state contributing to thrombogenic mechanisms [19]. Thus, a design that successfully weakens one competing sink may strengthen a different, clinically unacceptable interaction with blood components, endothelium, or coagulation pathways. This is a central constraint of the competing-sinks interpretation: increasing the share of exposure allocated to the intended organ cannot by itself establish an improved delivery system.

The renal and pulmonary examples therefore create a two-dimensional design problem. One axis concerns how rapidly and strongly the carrier enters or is retained by the intended compartment. The other concerns which competing pathways are strengthened or weakened as a consequence. This access-versus-affinity landscape is summarized in **Figure 1**, where successful redirection is conditional on preserving clearance, safety, and downstream functional-delivery boundaries rather than merely increasing organ accumulation.

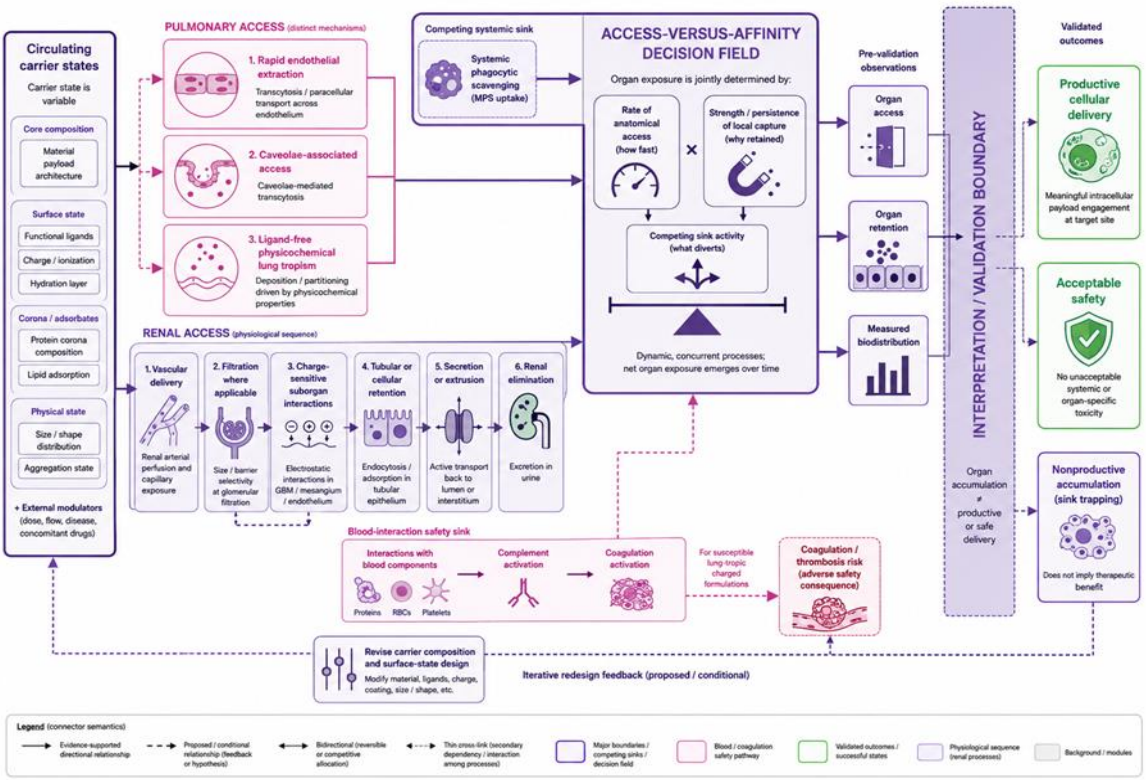


Figure 1. Kinetic access and affinity can redirect renal or pulmonary exposure while creating new competing sinks

Protein and cellular binding sinks

Before a carrier reaches a tissue receptor, it encounters a dense extracellular environment capable of changing its identity and availability. The protein corona is one of the most consequential examples. Reviews of nanoparticle

corona biology and direct experiments with mesenchymal-stem-cell-derived extracellular vesicles show that adsorbed proteins can alter cellular recognition, uptake, and in vivo distribution [20, 21]. Although synthetic nanoparticles and extracellular vesicles are not interchangeable platforms, both demonstrate the same systems-level boundary: the surface presented to cells in biological fluid can differ substantially from the surface defined during manufacture.

This biological identity is compartment-specific. Lipid nanoparticles exposed to plasma and cerebrospinal fluid acquire different protein coronas, and these differences can alter cellular association and functional transfection [22]. Importantly, greater cellular uptake did not necessarily translate into greater cargo delivery. This observation supports a distinction that is frequently blurred in targeted-delivery studies: cellular binding, internalization, intracellular trafficking, payload release, and functional response are separate states. A carrier can leave the circulating pool and therefore become a "sink loss" without generating productive pharmacological exposure.

Corona formation is heterogeneous, but it is not necessarily devoid of structure. A large meta-analysis and machine-learning analysis across nanoparticle systems found that material properties, size, surface characteristics, incubation conditions, and biological medium were associated with predictable patterns of protein-corona composition [23]. These models should not be interpreted as proving causal adsorption pathways or clinical fate. They nevertheless indicate that corona state can be treated as a probabilistic, design-relevant variable rather than as unstructured experimental noise.

Engineering can sometimes preserve targeting function despite corona formation. Pre-adsorption of antibodies onto nanocarriers has been shown to maintain target recognition more effectively than conventional covalent targeting under particular corona-forming conditions [24]. The implication is not that one attachment strategy solves the protein-corona problem universally. Instead, surface architecture can alter the sequence by which the carrier moves from manufactured state to biofluid-conditioned state, then to cellular engagement or nonproductive capture.

For the competing-sinks model, the key analytical unit is therefore a **state transition**, not simply an organ. Protein binding may expose or mask epitopes, promote phagocytic recognition, alter receptor access, or modify cellular uptake. Cellular binding may then lead to productive intracellular delivery, sequestration, recycling, degradation, or redistribution. **Table 1** organizes these transitions without assigning unsupported scores or assuming that any particular state is intrinsically favorable.

Table 1. Biological-identity transitions that determine whether protein and cellular capture remain productive or become competing sinks

State and entry conditions	Evidence through time	Transition and reassessment	
Precursor carrier state	**transition / Transition trigger / Observable readout**	**Downstream consequence / Condition that interrupts or reverses the sequence**	**Competing-sinks test**
Manufactured surface state	**Manuscript-derived transition:** Proposed transition: biological re-identification **Transition trigger:** Exposure to compartment-specific biofluid **Observable readout:** Acquired protein pattern and altered accessible surface	**Downstream consequence:** New recognition profile before tissue contact **Condition that interrupts or reverses the sequence:** Surface architecture that preserves intended recognition despite adsorption	Does the post-exposure carrier still engage the intended biological route?
Biofluid-conditioned carrier	**Manuscript-derived transition:** Proposed transition: phagocytic diversion **Transition trigger:** Opsonin-rich or macrophage-favoring surface composition **Observable readout:** Increased monocyte or macrophage association	**Downstream consequence:** Reduced freely circulating carrier; possible intracellular retention or processing **Condition that interrupts or reverses the sequence:** Reduced recognition, altered protein recruitment, or rapid target access	Is target gain accompanied by an equivalent or larger increase in phagocytic removal?

Corona-bearing ligand carrier	**Manuscript-derived transition:** Proposed transition: target-binding preservation **Transition trigger:** Retention of functional targeting moiety after adsorption **Observable readout:** Measurable target binding under biological-fluid conditions	**Downstream consequence:** Continued receptor-directed engagement **Condition that interrupts or reverses the sequence:** Ligand masking, steric occlusion, conformational loss	Is measured binding performed on the biological rather than only pristine carrier state?
Cell-associated carrier	**Manuscript-derived transition:** Proposed transition: nonproductive cellular capture **Transition trigger:** Membrane binding or internalization without effective payload processing **Observable readout:** High uptake with weak functional cargo output	**Downstream consequence:** Cellular sink formation despite apparent delivery **Condition that interrupts or reverses the sequence:** Escape, trafficking, or release mechanism that restores payload availability	Does uptake predict functional delivery in the relevant cell and biofluid context?
Internalized carrier	**Manuscript-derived transition:** Proposed transition: productive intracellular flux **Transition trigger:** Correct trafficking, release, and payload availability **Observable readout:** Functional molecular or pharmacological response	**Downstream consequence:** Carrier capture becomes useful exposure rather than loss **Condition that interrupts or reverses the sequence:** Endosomal retention, degradation, recycling, or payload inactivation	Is functional output demonstrated separately from association or internalization?
Cell-retained carrier	**Manuscript-derived transition:** Proposed transition: secondary redistribution **Transition trigger:** Cell migration, processing, release, or intercellular transfer **Observable readout:** Movement of carrier or payload away from initial binding cell	**Downstream consequence:** Redistribution to a new cellular or tissue compartment **Condition that interrupts or reverses the sequence:** Irreversible degradation or stable intracellular sequestration	Is cellular capture terminal, temporary, or transport-enabling in the intended system?

Table note. The transition classes are proposed article-level synthesis. They are intended to distinguish biological states and necessary measurements, not to rank targeting technologies. "Productive" refers only to preservation of the intended downstream delivery objective and does not imply clinical efficacy.

Target-receptor capacity

Affinity-based targeting introduces another sink whose limitation is easy to overlook: the intended receptor population itself is finite and biologically regulated. Increasing ligand density can increase multivalent binding only while accessible receptors remain available and functional. In antibody-functionalized LNPs targeting CD8, delivery exhibited a non-monotonic relationship with ligand density, with excessive avidity contributing to receptor loss and reduced mRNA delivery; work with DNA-scaffolded nanoparticles targeting prostate-specific membrane antigen likewise showed that ligand presentation must be matched to receptor context rather than maximized indiscriminately [25, 26]. These findings undermine the assumption that increasing the number of targeting ligands necessarily increases productive target capture.

The systems consequence is important. Receptor binding consumes both carrier and accessible receptor capacity. If carrier arrives faster than receptors recycle or if multivalent interactions promote receptor internalization, degradation, or steric crowding, the effective target sink can become self-limiting. This capacity is distinct from anatomical access. A tumor or organ may receive abundant carrier while only a fraction encounters a receptor population capable of further productive uptake. Conversely, high receptor expression measured in untreated tissue does not establish equivalent capacity throughout exposure if receptor state changes dynamically.

Ligand density may also redistribute exposure beyond the intended target. In renal-clearable folate-functionalized nanoparticles, increasing targeting-ligand density improved kidney targeting but simultaneously reduced renal

clearance and increased extrarenal accumulation [27]. The example demonstrates why target-receptor optimization cannot be separated from whole-body disposition: strengthening one interaction may increase residence, change elimination, and amplify another off-target sink. The relevant design objective is therefore not maximal binding but a balance among receptor engagement, productive processing, clearance, and off-target exposure.

Accurate measurement becomes critical. Single-molecule analysis of ligand-functionalized nanoparticles has shown that functional ligand number on the carrier and receptor density on the cell jointly influence targeting selectivity [28]. Nominal ligand feed ratio, bulk conjugation efficiency, or receptor-expression category therefore cannot always substitute for the number of interaction-competent molecules actually available at the nano-bio interface.

The proposed competing-sinks perspective treats effective receptor capacity as a conditional state determined by accessible receptor abundance, functional ligand presentation, avidity, internalization or recycling, and the carrier arrival rate. **Table 2** separates what can be observed directly from the mechanistic interpretations that require additional discrimination.

Table 2. Mechanistic discrimination of finite receptor capacity in affinity-targeted delivery

Scientific configuration		**Observable support**	**Mechanistic test and consequence**
receptor scenario / Mechanistic interpretation uncertain	**Relevant carrier state / Unresolved article-level question**	**What can be observed directly**	**Discriminating measurement or experiment / Consequence for the competing-sinks model**
Manuscript-derived receptor scenario: Low effective receptor availability Mechanistic interpretation that remains uncertain: Insufficient receptor number, inaccessible receptor, masked ligand, or poor carrier proximity	**Relevant carrier state:** Biological-fluid-conditioned carrier at target interface **Unresolved article-level question:** Is delivery limited upstream by access or locally by interaction-competent receptor abundance?	Weak binding or uptake despite measurable anatomical exposure	**Discriminating measurement or experiment:** Quantify functional receptor availability together with carrier-associated functional ligand **Consequence for the competing-sinks model:** Target tissue is accessible but receptor sink capacity is small
Manuscript-derived receptor scenario: Matched ligand presentation and receptor capacity Mechanistic interpretation that remains uncertain: Contribution of avidity versus improved encounter probability	**Relevant carrier state:** Target-engaging carrier **Unresolved article-level question:** Does the observed gain persist when receptor state changes during exposure?	Increased selective uptake and productive payload response	**Discriminating measurement or experiment:** Controlled ligand-density series with receptor quantification and functional payload readout **Consequence for the competing-sinks model:** Larger fraction of target-arriving carrier enters productive pathway
Manuscript-derived receptor scenario: Excessive ligand density or avidity Mechanistic interpretation that remains uncertain: Receptor depletion, steric crowding, altered internalization, degradation, or nonproductive binding	**Relevant carrier state:** High-avidity carrier **Unresolved article-level question:** At what point does additional affinity cease to increase productive flux?	Plateau or fall in functional delivery despite stronger nominal targeting	**Discriminating measurement or experiment:** Time-resolved receptor abundance, recycling, internalization, and payload-response measurements **Consequence for the competing-sinks model:** Target sink becomes capacity-limited or self-inhibiting
Manuscript-derived receptor scenario: Improved target capture with impaired elimination	**Relevant carrier state:** High-ligand-density carrier **Unresolved article-level question:** Does increased	Higher target-organ retention accompanied by slower clearance	**Discriminating measurement or experiment:** Simultaneous target, excretion, blood, and off-target tissue measurements

Mechanistic interpretation that remains uncertain: Strong binding may extend residence while shifting exposure to secondary organs	target residence justify the additional systemic burden?		**Consequence for the competing-sinks model:** Target gain is coupled to redistribution of other sink terms
Manuscript-derived receptor scenario: High nominal receptor expression but weak delivery **Mechanistic interpretation that remains uncertain: Receptor may be inaccessible, nonfunctional, spatially segregated, or mismatched to ligand geometry**	**Relevant carrier state:** Target-facing carrier **Unresolved article-level question:** Which receptor measurement best predicts interaction-competent capacity?	Receptor detected by bulk assay; limited nanoparticle uptake or response	**Discriminating measurement or experiment:** Single-molecule or spatially resolved receptor measurement under delivery-relevant conditions **Consequence for the competing-sinks model:** Nominal receptor expression overestimates effective sink capacity
Manuscript-derived receptor scenario: Strong cellular uptake without proportional function **Mechanistic interpretation that remains uncertain: Receptor capture is successful but intracellular processing becomes the dominant downstream sink**	**Relevant carrier state:** Internalized targeted carrier **Unresolved article-level question:** Should receptor capacity be optimized against uptake or against functional payload flux?	High internalization with weak pharmacological or molecular output	**Discriminating measurement or experiment:** Pair receptor engagement with trafficking, payload-release, and functional-response assays **Consequence for the competing-sinks model:** Receptor sink feeds a nonproductive intracellular compartment

Table note. The scenarios and competing-sinks interpretations are proposed synthesis derived from the completed manuscript section. They do not define universal receptor-density, ligand-density, or affinity thresholds and are intended to guide mechanism discrimination rather than technology ranking.

Saturation and dose dependence

Competing biological sinks are not necessarily linear. Their apparent importance can change with administered dose because cellular uptake, receptor availability, blood interactions, intracellular processing, and clearance pathways have finite capacities. This is particularly important for the mononuclear phagocyte system. In mouse tumor models, nanoparticle tumor delivery increased after nanoparticle dose exceeded a system-specific regime associated with saturation of Kupffer-cell uptake, prolonged circulation, and greater availability for tumor delivery [29]. The finding establishes dose-dependent nonlinearity in the studied systems; it does not establish a universal nanoparticle threshold or a directly transferable human dose.

This distinction changes the interpretation of apparent targeting improvements. If two formulations are compared at doses that engage competing sinks differently, a higher target-tissue exposure can result from partial saturation of clearance rather than superior target affinity. Conversely, a formulation evaluated below the capacity of a dominant clearance pathway may appear inefficient even though its intrinsic target-access properties are favorable. Dose is therefore not merely an independent experimental variable. It can alter the relative strengths of the sink network itself.

Receptor-mediated targeting introduces another form of capacity dependence. As developed above, increasing ligand density may eventually fail to increase productive delivery because accessible receptors become limiting, receptor processing changes, or high avidity promotes nonproductive retention. These processes should remain analytically separate from phagocytic saturation. Both produce nonlinear exposure relationships, but they operate through different biological mechanisms and therefore require different measurements.

The proposed competing-sinks interpretation consequently represents dose as a modifier of individual sink capacities and transfer rates rather than as a simple multiplier of every compartment. This formulation allows several qualitatively distinct dose responses: proportional increases when all important pathways remain unsaturated; redistribution when one sink approaches capacity; declining marginal target gain when target-receptor capacity becomes limiting; and emergent toxicity when increased circulating or organ exposure activates pathways that were negligible at lower doses. None of these states can be inferred from administered dose alone.

They require time-resolved measurement of where carrier, payload, and functional activity are actually redistributed.

A competing-sinks mass-balance model

Quantitative analyses of nanoparticle biodistribution demonstrate that administered material is distributed highly unequally among organs and that this distribution varies with nanoparticle characteristics and experimental context [30]. Such evidence argues against representing all off-target exposure as a single residual compartment. Liver uptake, splenic sequestration, renal elimination, pulmonary extraction, protein binding, circulating-cell association, target access, target exit, and receptor-limited cellular uptake can differ both mechanistically and quantitatively.

The central contribution of this Systems Perspective is therefore a proposed competing-sinks mass-balance model. It is not a fitted pharmacokinetic model and does not assign universal coefficients. Instead, it provides a conceptual accounting rule: at any relevant time, administered carrier and available payload are partitioned among circulating material, intended target compartments, competing tissue sinks, biological binding states, elimination pathways, and material that has re-entered circulation or undergone irreversible processing. The interpretation of target delivery depends on how those terms change together.

In its simplest conceptual form, target exposure increases when the rate of productive target entry exceeds the combined effects of competing capture, target exit, nonproductive binding, and elimination. Yet each term is state dependent. A protein corona can change tissue or cellular affinity; dose can reduce the marginal capacity of a phagocytic sink; organ-specific uptake can redirect the remaining circulating fraction; receptor internalization can reduce effective target capacity; and intracellular sequestration can convert apparently successful uptake into functional loss. The model therefore uses *carrier state* as well as anatomical location as an accounting dimension.

A useful consequence of this representation is that a targeting intervention can be classified according to what it actually changes. Some interventions increase access to the intended tissue. Others reduce an upstream competing sink. Others alter the carrier's acquired biological identity, increase residence after tissue entry, change receptor engagement, accelerate productive intracellular release, or reduce target-tissue exit. These are not pharmacologically equivalent mechanisms even if they produce similar terminal biodistribution measurements.

Computational methods may help parameterize portions of this system. PBPK and data-driven analyses have related nanoparticle physicochemical descriptors to organ-level biodistribution and kinetic parameters, with good performance for some outputs but poorer prediction of particular concentration-time profiles [31]. Such results support model-informed hypothesis generation while simultaneously illustrating the need for external validation. A descriptor-to-biodistribution relationship cannot by itself establish the underlying mechanism, and a model trained on healthy-mouse datasets cannot be assumed to predict altered disease physiology or human distribution.

Accordingly, the proposed mass-balance model separates measurement, mechanistic interpretation, and prediction. Direct biodistribution measurements populate exposure terms. Mechanistic studies explain why selected terms change. Computational models estimate relationships within their validated domain. None of these layers should automatically substitute for the others.

Figure 2 compresses this architecture by nesting tissue-level allocation with cellular and receptor-level states while placing explicit validation gates between measured exposure, mechanistic interpretation, and translational prediction.

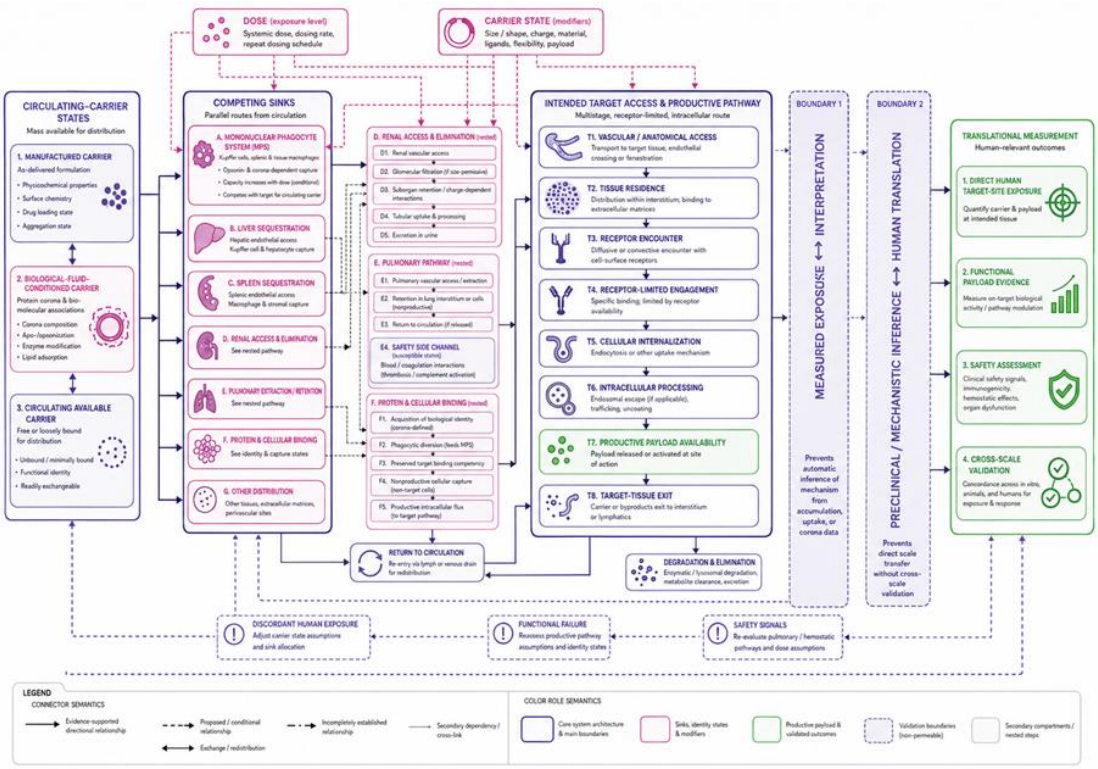


Figure 2. Cross-scale exposure accounting reveals where apparent targeting gains are redistributed or lost

Design strategies for redirecting exposure

Once delivery is viewed as competition among sinks, formulation design can be reframed from "increase targeting" to "redistribute exposure deliberately." The distinction is consequential because the same target gain may arise through several mechanisms. An intervention may increase target-access rate, reduce macrophage capture, change organ sequestration, recruit endogenous proteins, preserve ligand accessibility after corona formation, increase receptor-compatible avidity, facilitate intracellular release, or slow target-tissue exit.

Selective organ targeting LNPs provide a mechanistic example. Their organ preference is not explained only by a synthetic ligand directly recognizing the destination. SORT chemistry modifies the surface state of the particle after administration, influencing recruitment of endogenous proteins and subsequent engagement with tissue-associated receptors [32]. This mechanism demonstrates how formulation can redirect exposure indirectly by changing the biological identity through which competing organs recognize the carrier.

The implication extends beyond SORT. A rational redesign should identify the dominant limiting sink for the specific carrier and disease state before modifying the formulation. If rapid phagocytic capture limits availability, altering receptor affinity at the target may have little effect. If vascular entry is limiting, increasing intracellular-release efficiency cannot compensate for inadequate tissue access. If receptor capacity is limiting, increasing ligand density can be ineffective or counterproductive. If renal elimination is therapeutically desirable, stronger target binding must be evaluated against the possibility of prolonged systemic or off-target residence.

This perspective also discourages evaluating formulation changes using one terminal biodistribution endpoint. A successful redirection experiment should ask where the additional target exposure originated. Was liver capture reduced? Was circulation prolonged? Was renal elimination suppressed? Did pulmonary or splenic exposure increase? Did more material bind cells without releasing payload? Did the dose move a clearance pathway toward saturation? A target-organ increase without this accompanying accounting leaves the mechanism of improvement unresolved.

The same principle applies to safety. Redistribution may expose blood components or vulnerable organs to higher carrier concentrations even when the intended target receives more material. A pharmaceutical decision should therefore consider at least three linked consequences: target gain, redistribution among competing sinks, and emergence of new biological liabilities. The proposed competing-sinks framework treats these as inseparable components of the same design intervention.

Translational measurement

Translation requires measurements capable of determining whether the sink architecture observed in experimental models is preserved in humans. Conventional biodistribution studies often provide organ-level measurements at selected time points, whereas the relevant pharmaceutical question may concern temporal exposure, cellular localization, payload release, or pharmacological activity. The measurement strategy must therefore match the level of inference.

Direct human imaging provides one route to reducing this uncertainty. PET-CT imaging of radiolabelled polymeric nanoparticles has demonstrated that nanoparticle accumulation in tumors can be measured clinically and that accumulation can vary substantially among patients and lesions [33]. This study does not establish a universal predictor of therapeutic response or generalize automatically to other nanoparticle classes. It demonstrates something narrower but important: human target-site exposure can be measured directly rather than inferred solely from animal biodistribution.

For a competing-sinks analysis, target imaging alone is still insufficient. Translation should ideally quantify both the intended destination and major competing compartments, together with systemic pharmacokinetics. Where possible, tissue-level measurements should be connected to cellular localization and functional payload readouts. A carrier that reaches a tumor but remains extracellular, is captured predominantly by nonproductive macrophages, or fails to release its payload represents a different delivery state from one producing the intended intracellular pharmacology.

Measurement must also retain temporal information. Early target accumulation can coexist with rapid exit, redistribution, degradation, or later clearance. Conversely, an initially dominant liver or splenic sink can change as phagocytic capacity, carrier state, or circulating concentration changes. Sparse terminal measurements risk collapsing these states into a misleading average.

The proposed translational strategy therefore separates four questions: Where did the carrier go? Which cells or molecular interfaces captured it? Did the payload become functionally available? What safety consequences accompanied that allocation? These questions require different assays and should not be treated as interchangeable validation endpoints.

Cross-scale modelling can help connect them, but its role should remain calibrated. A model can organize measured mass balance, estimate unobserved states, and nominate experiments that distinguish competing mechanisms. Validation nevertheless requires observations external to the data used to construct or calibrate the model, ideally under disease, dose, formulation, and biological conditions relevant to the intended use.

The strongest translational test of targeted delivery is consequently not simply a higher target-to-background ratio. It is a coherent exposure account showing that target gain is reproducible, mechanistically interpretable, functionally productive, and not achieved by creating a clinically unacceptable competing sink elsewhere.

CONCLUSION

Targeted drug delivery is better represented as an allocation problem than as an isolated affinity problem. After administration, carriers compete simultaneously for vascular access, phagocytic capture, liver and spleen sequestration, renal and pulmonary pathways, proteins, cells, receptors, intracellular destinations, and elimination. These pathways differ in capacity, kinetics, reversibility, and biological consequence, and their relative importance can change with formulation composition, acquired biological identity, dose, tissue state, and time.

The proposed competing-sinks mass-balance perspective provides an organizing framework for interpreting these interactions without assuming universal quantitative coefficients. Its principal implication is that increased target accumulation cannot be judged independently of the exposure removed from, or redirected toward, other compartments. A useful targeting intervention should therefore be characterized by the mechanism producing target gain, the competing sinks that were weakened or strengthened, the capacity limits encountered, and whether measured cellular capture resulted in productive payload delivery.

This perspective also creates a stricter translational standard. Biodistribution, cellular uptake, mechanistic interpretation, computational prediction, functional activity, and safety occupy different evidentiary levels. None should substitute automatically for another. Designing around competing biological sinks therefore means accounting not only for where a carrier is intended to go, but for every biologically consequential destination capable of capturing, transforming, redistributing, or eliminating it along the way.

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