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Protein Corona Evolution Can Reverse the Intended Targeting Logic of Nanomedicines

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ABSTRACT

Active targeting is commonly designed as though the molecular identity presented by a nanomedicine at administration remains the identity that governs subsequent biological recognition. Protein-corona formation challenges that assumption. Adsorption, exchange, conformational rearrangement, compartment-specific replacement, and intracellular remodeling can alter both access to engineered ligands and exposure of newly acquired protein motifs. The resulting carrier may therefore retain, attenuate, lose, or functionally replace its intended recognition route. This Perspective argues that targeting failure and targeting reversal should not be treated as equivalent. We propose reserving functional reversal for situations in which the designed recognition pathway becomes subordinate while a corona-mediated pathway becomes the operative determinant of uptake, sequestration, transport, or clearance. Evidence from serum-dependent targeting, cerebrospinal-fluid masking, mucosal transport, complement activation, leukocyte sequestration, receptor mapping, and deliberately engineered coronas supports the individual transitions required for such a model, but not a universal reversal mechanism. A spatiotemporal interpretation is therefore needed in which corona state, ligand accessibility, receptor competence, compartment, and carrier fate are evaluated at the same biological decision point. This framing shifts nanomedicine design away from static ligand decoration toward validation of the biological identity actually presented during transport.

Keywords: Protein corona, Active targeting, Nanomedicine, Receptor recognition, Opsonization, Cellular uptake

INTRODUCTION

Nanomedicine targeting is often described from the perspective of the manufactured particle: a ligand is conjugated, a receptor is selected, and biological performance is interpreted according to the intended ligand–receptor interaction. Once the carrier encounters biological fluids, however, that description becomes incomplete. The adsorbed protein layer can evolve with material composition, biological environment, and time, creating a biological identity that differs from the nominal surface engineered during formulation [1]. Chemical and biophysical evidence further indicates that corona formation is jointly conditioned by nanoparticle properties and the surrounding bioenvironment rather than by one surface descriptor alone [2].

This distinction matters because the corona can affect whether an engineered targeting strategy is expressed, muted, or replaced in practice. Across nanodrug systems, protein adsorption has been reported to impair some targeting processes while enabling others, making “corona formation” an insufficiently specific explanation of

delivery behavior [3]. Host physiology can also alter that process: experimentally increased cholesterol changed corona composition, receptor-related interactions, and physiological responses in a defined nanoparticle model [4]. Thus, the relevant pharmaceutical question is not simply whether a corona forms, but which biological identity is presented at the location and time when a targeting decision is made.

This Perspective develops that problem through a distinction between targeting attenuation and functional targeting reversal. Attenuation denotes reduced access to, or reduced contribution from, the intended targeting route. By contrast, functional reversal is proposed here as a stricter state in which the intended route becomes subordinate and an acquired corona-dependent recognition or clearance route becomes the dominant determinant of carrier fate. This is a conceptual synthesis rather than a validated universal mechanism. Its purpose is to organize evidence that is otherwise interpreted separately as ligand masking, opsonization, altered uptake, altered biodistribution, or corona-mediated targeting.

Nanoparticles acquire dynamic biological identities

The biological identity of a nanocarrier begins with its manufactured surface but is not reducible to it. Surface chemistry strongly conditions initial adsorption. In gold nanoparticles bearing different surface coatings, PEG- and zwitterion-containing surfaces produced lower protein adsorption than more strongly interacting ligands under the tested conditions [5]. Yet adsorption is not merely a scalar quantity. In a functionalized gold-nanoparticle library, the surface chemistry determined the assemblage of associated proteins, and that acquired protein layer subsequently altered interaction with model membranes [6]. The important pharmaceutical transition is therefore from surface composition to surface-exposed biological function.

That transition is sensitive to the protein environment. Folic-acid-modified chitosan nanoparticles developed different coronas in fetal bovine serum, healthy-human serum, and breast-cancer serum, with corresponding differences in cellular targeting behavior [7]. This finding places a strict boundary around routine extrapolation from a convenient culture supplement to a clinically relevant protein environment. It does not establish a universal disease-specific corona, but it demonstrates that the same nominal targeting architecture can be biologically rewritten by the source of the surrounding proteins.

Formulation variables remain important after adsorption begins. Changing phospholipid composition in lipid nanodiscs altered corona characteristics, including associations with complement-related proteins and apolipoproteins, with corresponding changes in in vivo behavior [8]. These findings argue against treating the corona as a nuisance layer added after formulation optimization. Rather, formulation and biological environment jointly specify an acquired carrier state.

A useful distinction is therefore between synthetic identity, which includes core material, lipid or polymer composition, charge, ligand presentation, and surface chemistry, and acquired identity, which includes the proteins and protein conformations that are accessible to biological receptors at a particular time. The latter cannot be inferred solely from the former. Nor should acquired identity be assumed to be stable: the same carrier can successively experience different protein pools, competition regimes, and tissue environments. This temporal problem becomes central when early corona observations are used to explain later targeting outcomes.

Early and late corona states

The conventional hard-corona/soft-corona distinction captures differences in binding persistence, but it can become misleading when treated as two immutable biological layers. Current mechanistic synthesis emphasizes exchange, competition, residence time, and context dependence rather than a universal binary structure [9]. A systematic analysis of corona layering and reversibility likewise showed that conclusions concerning adsorption and exchange depend on physicochemical conditions and experimental design, including how corona material is isolated and challenged [10]. “Early” and “late” states should therefore be interpreted operationally, not as fixed temporal stages with universal compositions.

Weakly associated proteins are particularly vulnerable to methodological erasure. In situ capture of soft-corona proteins demonstrated that dynamically associated proteins can influence cellular association even when they would be lost during conventional washing or isolation [11]. Conversely, more persistent binding does not make a corona functionally invariant. Comparative in vivo tracking of hard- and soft-corona states on PLGA nanoparticles showed different exchange behavior and biodistribution in a healthy animal model [12]. These observations support a state-based interpretation in which persistence and exchangeability are continuous properties relevant to fate, while cautioning against transferring one material-specific distinction to all carrier systems.

Kinetic heterogeneity also occurs within ostensibly identical particle populations. Real-time optical tracking at the single-particle level revealed heterogeneous adsorption behavior in serum and showed strong effects of surface chemistry within the tested nanoparticle panel [13]. Ensemble proteomics can therefore conceal subpopulations that present different biological surfaces at the same nominal sampling time.

For this Perspective, four proposed analytical states are useful. A nascent competitive state is dominated by rapidly changing adsorption immediately after environmental contact. An exchange-active state retains substantial replacement potential and may be especially sensitive to compartment changes. A persistence-enriched state contains more slowly exchanging interactions but should not be assumed irreversible. A functionally rewritten state is reached only when the biological surface presented at a relevant decision point differs sufficiently from the initial state to alter ligand accessibility, receptor engagement, or competing-sink capture. These states are not claimed as discrete physicochemical classes. They are reasoning categories for separating what is observed from what must still be demonstrated.

Because a measured corona state does not by itself establish which targeting mechanism is operating, the distinction needed for pharmaceutical interpretation is summarized in **Table 1**.

Table 1. Discriminating early and late corona states when judging whether targeting logic has been rewritten

Manuscript-derived corona state	Directly observable carrier feature	Interpretation that cannot yet be assumed	Discriminating experiment	Carrier-level consequence if confirmed	Relevance to the proposed reversal test
Nascent competitive state — proposed	Rapidly changing protein association after first biofluid contact	The most abundant early proteins will determine later targeting	Time-resolved adsorption paired with ligand-accessibility measurement	Initial ligand exposure may remain intact, fluctuate, or become transiently shielded	Too early to classify reversal unless a competing functional route is already demonstrated
Exchange-active state — proposed	Substantial turnover or weakly retained proteins remain detectable	Weakly bound proteins are biologically unimportant	In situ or minimally perturbing capture combined with receptor or uptake perturbation	Transient proteins may influence recognition despite low persistence	Supports possible route substitution only when a functional interaction is shown
Persistence-enriched state — proposed	More slowly exchanging protein associations persist during challenge	Persistent binding necessarily fixes biological fate	Competitive-exchange testing followed by functional targeting assessment	A stable-looking corona may preserve, mask, or expose recognition determinants	Reversal remains unproven without comparison against the intended targeting pathway
Functionally rewritten state — proposed	Corona composition or accessibility pattern differs after a biological transition	Composition change alone equals targeting reversal	Paired pre-transition and post-transition measurements of ligand access, acquired receptor engagement, and fate	Carrier recognition becomes conditional on the later biological state	Candidate reversal state only if the acquired route becomes operative while the intended route is subordinated

Exchange kinetics across biological compartments

A nanomedicine does not encounter one protein environment. Blood, extracellular matrices, mucus, cerebrospinal fluid, intracellular vesicles, and disease-associated fluids provide distinct competitive adsorption conditions. Consequently, a corona measured at one location should not automatically be used to explain a biological decision occurring later in another compartment.

This problem is illustrated by nanovesicles engineered to undergo protein-corona changes between blood, liver, and tumor-associated environments. Their protein profiles changed across those locations, and the later corona contained proteins associated with altered cellular interaction in the studied tumor system [14]. The result supports compartment-specific rewriting but not a general tumor-homing rule. The relevant inference is narrower: a corona characterized in circulation can cease to represent the carrier surface that interacts with cells after tissue entry.

Cerebrospinal fluid provides a particularly clear targeting boundary. Transferrin-functionalized nanoparticles exposed to cerebrospinal-fluid proteins showed loss of transferrin-dependent targeting capacity in the studied system, while uptake could still proceed through other mechanisms [15]. Thus, persistence of cellular entry after

loss of ligand specificity cannot be interpreted as successful active targeting. The biological route responsible for entry must be distinguished from the route intended during formulation.

Mucosal transport adds another level of conditionality. For transferrin-functionalized nanoparticles, mucus-derived corona formation could mask transferrin-related recognition, whereas subsequent intracellular protein interactions were associated with a different influence on transcellular transport [16]. The same carrier can therefore encounter sequential biological identities whose functional effects are not directionally equivalent.

Corona evolution can also continue after internalization. Proteomic analysis of internalized gold nanoparticles in HepG2 cells identified intracellularly acquired proteins that changed with internalization time [17]. This observation places an important boundary around the common practice of ending corona analysis at plasma or cell-surface contact. If intracellular trafficking is part of the delivery mechanism, the relevant carrier state may continue to evolve after entry.

Taken together, these findings support a proposed checkpoint view of corona evolution: every transition into a new protein environment can create a new opportunity for ligand masking, receptor substitution, immune capture, or recovery of another transport pathway. A checkpoint need not produce a meaningful change; it becomes mechanistically important only when the altered state changes a functional interaction. This prevents mere compositional turnover from being overinterpreted as targeting reversal.

Ligand masking and target recognition

The most direct route from corona formation to targeting failure is steric or functional masking of an engineered ligand. Yet even this mechanism is architecture dependent. Antibody-bearing nanocarriers showed that biomolecular-corona formation can compromise accessibility, whereas pre-adsorbed antibody configurations preserved targeting more effectively than some covalently presented formats [18]. Corona masking is therefore not an inevitable property of active targeting; it depends on how the ligand is positioned relative to the evolving biological surface.

A similar conditionality was observed for Fn14-targeted nanoparticles. Serum exposure reduced total cellular uptake under some conditions but did not simply eliminate targeting specificity, and the magnitude of the corona effect differed between full antibodies and Fab-based targeting architectures [19]. Total uptake and targeting specificity are therefore distinct endpoints. A decrease in uptake does not demonstrate loss of receptor selectivity, just as retained uptake does not demonstrate preservation of the intended receptor route.

Compartment-specific studies sharpen this distinction. In cerebrospinal fluid, transferrin targeting could be functionally masked while other entry mechanisms remained available [15]. In mucus-associated transport, transferrin accessibility could likewise be compromised even though later transport behavior remained dependent on subsequent biological interactions [16]. These cases show why the visible presence of a targeting ligand on the manufactured nanoparticle is an inadequate proxy for functional availability.

The proposed reversal concept consequently requires two tests. First, the intended ligand–receptor interaction must be shown to become reduced, inaccessible, or subordinate at the relevant biological decision point. Second, a competing corona-mediated interaction must be shown to account for the observed fate. Without the second condition, the appropriate interpretation is attenuation or masking, not reversal. This distinction prevents a mechanistic label from being assigned merely because a targeting ligand performs worse after protein exposure.

Opsonization and clearance reprogramming

Targeting can also be defeated before a carrier reaches its intended receptor. Corona-mediated recognition by complement components, immunoglobulins, coagulation proteins, and phagocytic cells can create competing biological sinks that dominate exposure and tissue access.

The amount of adsorbed protein is an especially poor surrogate for this process. In preclinical and clinical nanoparticle systems, corona-associated immunoglobulins could strongly influence complement C3 deposition, demonstrating that the identity and functional presentation of particular corona components can matter more than total protein mass [20]. This mechanism should not be generalized to all materials or patients, but it illustrates why an apparently modest corona feature can redirect immune recognition.

At the cellular scale, liposomal coronas altered interactions with peripheral blood mononuclear cells in whole blood, and manipulation of the preformed corona changed cellular sequestration behavior [21]. Such *ex vivo* capture is not equivalent to clinical clearance, yet it identifies a competing sink that may reduce the fraction of carrier remaining available for the intended target.

Surface chemistry can push the system further toward clearance-associated states. Polycatecholamine-coated drug nanocrystals developed fibrinogen-enriched coronas and showed rapid clearance and liver accumulation in the studied setting; PEG incorporation did not simply erase that behavior [22]. Importantly, this does not establish fibrinogen as a universal clearance determinant. It shows that a nominal stealth strategy can be overridden when the acquired surface recruits a functionally unfavorable protein environment.

Conversely, broad “opsonin” and “dysopsonin” categories can also overstate mechanistic certainty. Time-resolved studies of iron oxide nanoparticles found that different circulation behaviors were not adequately explained by aggregate membership in those conventional protein classes [23]. Protein abundance tables therefore cannot substitute for functional validation of exposed motifs, receptor engagement, and cellular capture.

Surface engineering can nevertheless shift the acquired state in a favorable direction. GlycopolymERIC nanoparticles were reported to develop less immunogenic coronas, show lower mononuclear-phagocyte interaction, and improve tumor-versus-liver delivery relative to PEGylated comparators in a defined mouse tumor model [24]. The result supports corona-aware design in that system but does not establish universal or clinical superiority.

The cross-scale problem is that a molecular signal observed in a corona must traverse several inference steps before it can explain altered targeting. **Table 2** separates those steps so that a clearance-associated carrier state is not mistaken for a clinically established delivery consequence.

Table 2. Cross-scale routes by which corona-dependent immune capture can pre-empt intended nanomedicine targeting

Row-defining competing-sink case	Immediate failure mode	Design lever suggested by the evidence	Dose dependence that must be established	Transferability boundary	Discriminating experiment	Resulting carrier state	Endpoint in the proposed reversal logic
Corona immunoglobulin enables complement recognition	Complement-mediated opsonization becomes favored over target access	Control surface features that govern functional immunoglobulin presentation	Cannot be assumed from corona composition; must be measured under relevant concentration conditions	Plasma composition, complement status, material class, species	Deplete or perturb the implicated corona component and quantify complement deposition	Immune-recognition-dominant	Candidate pre-target reversal only if complement-dependent removal measurably subordinates intended target engagement
Leukocyte sequestration in blood	Circulating carrier is captured by immune cells before target encounter	Modify corona formation or preconditioning that changes cell association	Blood cell-to-particle exposure conditions must be tested rather than inferred	Ex vivo capture does not establish clinical pharmacokinetics	Compare cellular sequestration with matched free-carrier availability and downstream target access	Cellular-sink-dominant	Supports competing-sink diversion, not target reversal unless intended exposure is demonstrably displaced
Coagulation-protein-enriched surface	Rapid clearance and liver-directed disposition can dominate	Reconsider coating chemistry rather than assuming nominal stealth	Formulation dose and protein availability require direct testing	Specific coating, carrier, and animal context	Perturb the implicated surface-protein interaction and track circulation plus organ fate	Clearance-prone	Compatible with reversal of delivery logic when clearance rather than target recognition becomes fate determining
Similar aggregate opsonin/dysopsonin profiles	Protein-class labels fail to discriminate fate	Use multivariate and functional	Dose effects remain unresolved without	Protein abundance may not report	Compare matched carriers using	Mechanistically indeterminate	Reversal classification withheld

with different circulation	corona characterization	explicit experiments	orientation, conformation, or receptor competence	functional receptor or cell-capture assays		
Less-immunogenic glycopolymer corona	Phagocyte capture is reduced relative to a comparator coating	Engineer the acquired corona rather than minimize protein adsorption alone	Must be established for each material and administration regime	Preclinical tumor model and defined polymer chemistry	Compare corona function, phagocyte uptake, circulation, and target exposure in the same system	Lower competing-sink pressure Preserves target opportunity; does not itself prove active-targeting success

To make the competition among these routes visually recoverable, **Figure 1** places molecular opsonization, blood-cell sequestration, organ-level clearance, and surviving target-directed transport in parallel rather than treating them as one linear pathway.

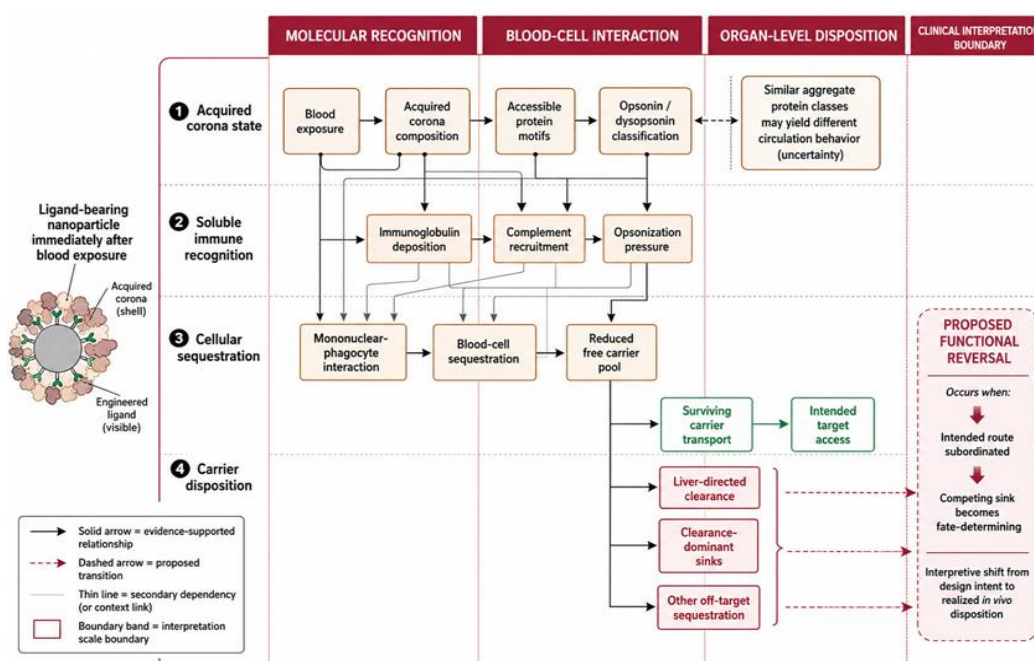


Figure 1. Blood-corona decision fields that can divert a targeted carrier before receptor encounter

Corona-dependent cellular entry

A corona can redirect cellular entry only if its components are functionally presented to the cell. Detection of a protein by mass spectrometry is insufficient because adsorption may bury receptor-binding domains, alter protein conformation, or place the protein in a crowded layer that prevents productive interaction. Direct receptor-oriented experiments are therefore essential.

Evidence that corona proteins can become functional ligands comes from mapping exposed motifs on nanoparticle-bound proteins. Adsorbed LDL- and immunoglobulin-associated motifs were shown to retain receptor-recognition capacity in defined experimental systems, demonstrating that the corona can present biologically active binding information rather than merely passivate the surface [25]. This establishes feasibility of acquired receptor recognition, not its universal dominance.

Genome-scale receptor interrogation provides a stronger route to mechanism. In serum-coated gold nanoparticles interacting with U-87 MG cells, genetic screening identified LDL receptor involvement, with corona-associated proteins contributing to receptor-dependent uptake in that system [26]. Such evidence meets an important requirement for the proposed reversal concept because it links an acquired biological surface to a specific cellular

entry pathway. Nevertheless, receptor dominance in one cell line and nanoparticle formulation cannot be generalized to other tumors, tissues, species, or protein environments.

Protein identity is also not equivalent to protein function. Albumin-corona conformation influenced stability, cellular behavior, and renal targeting of a defined nanoparticle system, indicating that structural state can matter even when the nominal protein identity is unchanged [27]. A corona description based only on protein names or abundance therefore risks missing functionally important conformational information.

Conversely, not every change in cellular uptake after surface engineering is corona mediated. Heparosan-modified nanoparticles showed reduced serum-protein adsorption while retaining or increasing uptake in some cell types, and the observed uptake behavior could not simply be attributed to the reduced protein corona [28]. This is a critical counterexample to any model in which corona abundance is assumed to determine cellular entry monotonically.

The resulting mechanistic boundary is represented in **Figure 2**: engineered-ligand recognition, corona-mediated receptor recognition, nonspecific or polymer-mediated interaction, and intracellular processing must remain separable until perturbation evidence identifies which route is operative.

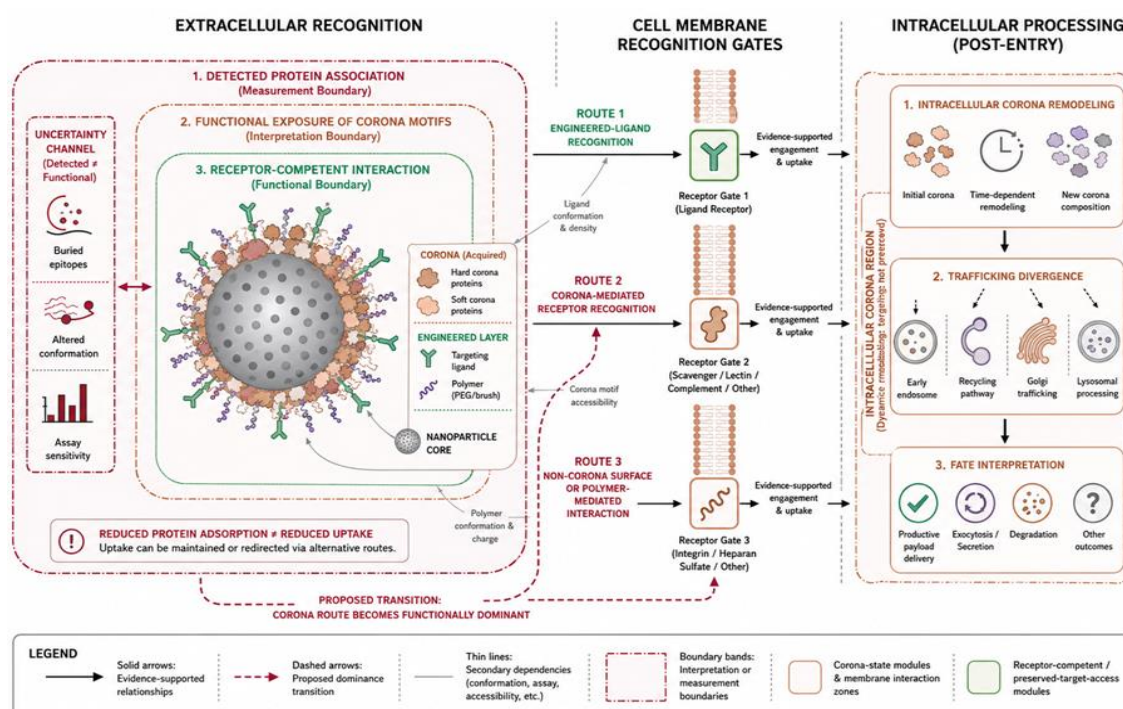


Figure 2. The cellular-recognition boundary where acquired corona ligands compete with engineered targeting cues

When targeting direction is functionally reversed

Loss of engineered-ligand activity should not automatically be described as reversal. A stricter interpretation requires evidence that another biological recognition route has become operative. Such a switch is experimentally plausible because coronas can themselves be deliberately recruited as targeting interfaces. Surface peptides designed to capture apolipoproteins generated corona-dependent brain-targeting behavior in preclinical carrier systems [29]. Likewise, an oriented artificial protein layer could shield nanoparticles from undesirable serum interactions while retaining HER2-directed recognition [30]. A temporary HDL-derived corona has also been engineered to support SR-BI-dependent targeting before being displaced later in the delivery process [31]. These examples establish that a corona can function as a targeting interface, but they do not show that uncontrolled endogenous corona evolution routinely produces beneficial redirection. This Perspective therefore proposes functional targeting reversal only when three conditions coincide: the intended recognition route becomes functionally subordinate; an acquired corona-dependent route is demonstrably active; and the alternative route materially governs the observed carrier fate. Reduced ligand accessibility alone remains attenuation. Altered biodistribution without pathway evidence remains redirection of uncertain mechanism.

A spatiotemporal corona-targeting model

A static corona description cannot represent a carrier that successively encounters plasma, tissue fluids, extracellular barriers, cell surfaces, and intracellular environments. The proposed spatiotemporal corona-targeting model instead treats targeting as a sequence of biological decision points. At each point, the relevant state is defined by the accessible engineered ligand, the functionally presented corona motifs, the available receptors or competing sinks, and the carrier fate that follows.

Time-resolved proteomic trajectories can contain information related to subsequent organ disposition within a controlled experimental system [32]. This supports treating corona history as informative, but not as universally predictive. In the proposed model, a transition is therefore assigned mechanistic meaning only when a changed corona state is linked to altered ligand accessibility, receptor dependence, immune capture, transport, or intracellular processing.

The model also separates composition change from functional state change. A protein may appear or disappear without altering targeting, whereas a modest compositional change can matter greatly if it exposes a receptor-binding motif or promotes a competing clearance route. Functional reversal is consequently positioned as one possible trajectory among preserved targeting, attenuated targeting, indeterminate rerouting, and acquired-route dominance.

Measurement and validation priorities

Validation must reproduce the biological conditions under which the targeting decision actually occurs. Temperature, plasma concentration, and surface modification can alter both corona composition and cellular uptake, demonstrating that apparently technical assay conditions can change biological interpretation [33]. Sampling at one convenient condition is therefore insufficient when the intended claim concerns another compartment, concentration regime, or exposure history.

Analytical reproducibility is an independent constraint. A multicenter study showed that harmonized data processing substantially improved agreement in corona proteomics across facilities [34]. Molecular resolution is another issue: top-down proteomics can reveal proteoforms that conventional protein-group identification does not distinguish [35]. Neither result means that every nanomedicine study requires identical analytical technology; rather, measurement depth should match the mechanistic claim being made.

The practical boundary conditions for claiming preservation, attenuation, or reversal of targeting are summarized in **Table 3**.

Table 3. Boundary conditions that determine whether corona-dependent targeting interpretations remain supportable

Governing validation condition	Interpretation supported when condition is met	Failure mode when condition is absent	Design or measurement lever	Dose and exposure dependence	Translation boundary	Consequence for the proposed reversal synthesis
Corona measured at the relevant biological decision point	Carrier state can be related to the observed interaction	Earlier or different-compartment corona is substituted for the operative state	Time- and compartment-matched sampling	Must be tested under relevant protein and particle exposure	In vitro state may not reproduce in vivo transition history	Reversal remains indeterminate
Engineered ligand accessibility measured directly	Loss or preservation of intended recognition can be distinguished	Ligand presence is mistaken for ligand function	Accessibility and receptor-competition assays	Surface occupancy may vary with exposure	Assay-specific accessibility may not equal tissue accessibility	Establishes whether attenuation has occurred
Corona-mediated receptor competence demonstrated	Acquired recognition route is mechanistically plausible	Detected protein is assumed to be a functional ligand	Receptor perturbation or blocking	Receptor and corona abundance require contextual testing	Cell-line dependence limits transfer	Necessary for route substitution

Competing clearance pathway tested	Pre-target diversion can be separated from failed receptor binding	Low target accumulation is attributed solely to masking	Complement, phagocyte, and disposition measurements	Dose may alter protein availability and immune capture	Preclinical clearance does not establish clinical PK	Can support pre-target functional reversal
Analytical workflow reproduced	Corona differences are less likely to arise from processing artifacts	Pipeline variation masquerades as biology	Harmonized acquisition and processing	Not inherently dose resolving	Cross-laboratory reproducibility remains distinct from clinical validity	Strengthens confidence in state assignment
Protein structure resolved when mechanistically necessary	Functional state can extend beyond protein identity	Abundance-only analysis misses conformation or proteoforms	Structural or proteoform-sensitive methods	Context dependent	Added molecular detail does not itself prove outcome relevance	Prevents overconfident route assignment

Design implications

The design objective should neither be “eliminate the corona” nor “exploit the corona” in the abstract. Antibody presentation can make targeting more resistant to masking [18], glycopolymer coatings can reduce immune capture in a defined preclinical setting [24], and low-fouling surfaces can still display substantial cell interaction independent of serum-protein adsorption [28]. The relevant objective is therefore to engineer and test the biological state required at each delivery decision point.

This Perspective consequently proposes a targeting-validation chain: characterize the operative corona state, verify engineered-ligand accessibility, test any acquired receptor route, measure competing clearance, and repeat these assessments after biologically important compartment transitions. Disease-relevant biofluids deserve particular attention because serum source can alter targeting behavior [7], and compartment changes can rewrite corona identity [14]. This sequence is a research strategy, not a regulatory requirement or validated predictor of clinical success.

CONCLUSION

Protein-corona evolution changes the meaning of “targeted” nanomedicine because the molecular surface engineered during formulation may not be the surface that ultimately encounters the decisive receptor, barrier, immune cell, or intracellular machinery. The important distinction is therefore not simply corona versus no corona, but whether biological evolution preserves, attenuates, replaces, or redirects the intended recognition logic.

Functional targeting reversal, as proposed here, should be reserved for cases in which the intended route becomes subordinate and an acquired corona-dependent route demonstrably governs carrier fate. This criterion prevents ordinary masking, nonspecific uptake, or altered biodistribution from being overinterpreted mechanistically. A spatiotemporal view of corona state, coupled to functional validation at the relevant biological decision point, offers a more defensible basis for nanomedicine design while preserving the substantial experimental and translational boundaries that remain.

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