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The Biological Identity Ledger for Tracing Protein Corona Formation, Immune Recognition, Tissue Distribution, and Nanocarrier Fate

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ABSTRACT

Nanocarriers are commonly defined by properties measured before administration, yet their biologically operative identity changes as they encounter proteins, lipids, antibodies, cells, extracellular matrices, and intracellular environments. Fragmented reporting of manufactured attributes, acquired coronas, recognition events, tissue exposure, degradation, and clearance prevents these transformations from being traced as one evidence chain. This Original Evidence Architecture Article proposes the Biological Identity Ledger, a non-empirical scientific traceability architecture that links batch-resolved synthetic identity and manufacturing provenance to biological exposure events, acquired corona states, immune-recognition states, and fate states. Its central principle is that nanocarrier identity is neither a single static descriptor nor equivalent to efficacy: it is a versioned, compartment- and time-indexed record whose interpretation depends on measurement method, biological context, and uncertainty. The architecture introduces eight linked constructs: the Synthetic Identity Record, Manufacturing Provenance Record, Biological Exposure Event, Acquired Corona State, Recognition State, Fate State, Temporal-Compartment Key, and Evidence Provenance and Uncertainty Layer. Temporal updating is used to represent corona exchange, barrier transitions, intracellular remodeling, payload release, degradation, and clearance without presuming a universal causal sequence. Evidence provenance separates observation from inference and records analytical recovery limits, biological variability, and transferability constraints. Validation would require schema testing, longitudinal and multi-compartment experiments, batch-linked manufacturing studies, human-matrix and species-aware comparisons, interlaboratory reproducibility, and prospective assessment before decision use. The proposed ledger is an original conceptual synthesis for organizing testable relationships and reporting requirements; it is not a validated predictive model, clinical recommendation, regulatory standard, or deployment-ready system.

Key words: *Nocarrier, Nanomedicin, Targeted drug delivery, Biological barriers, Intracellular release, Biodistribution*

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INTRODUCTION

Current nanomedicine development faces a coupled design-barrier-reproducibility problem: material engineering is multivariate, tumor entry routes are not reducible to passive accumulation, and experimental transparency remains uneven [1-3]. Consequently, apparently similar carriers may encounter different transport constraints, cellular interfaces, or analytical interpretations, while a favorable physicochemical profile alone cannot establish in vivo targeting, intracellular delivery, or therapeutic performance.

The prevailing record of a nanocarrier is usually distributed across formulation files, batch characterization, corona analyses, cell studies, biodistribution measurements, and safety observations. Inconsistent disclosure of material, biological, and methodological conditions weakens traceability between these records [3]. What was manufactured, what biological identity was acquired, where that identity changed, and which fate followed are therefore seldom represented as a continuous evidentiary object.

This article addresses that gap by proposing the Biological Identity Ledger: a directed, versioned architecture that connects synthetic identity, manufacturing provenance, exposure context, acquired biological identity, recognition, and fate. The purpose is not to replace mechanistic experiments, pharmacokinetic analysis, toxicology, or quality systems, but to specify how their outputs may be linked without collapsing association into causation or analytical similarity into biological equivalence.

The contribution is an Original Evidence Architecture Article and therefore develops a proposed ontology, relationship structure, testable propositions, validation requirements, and decision boundaries rather than reporting a new dataset. It integrates nanomedicine, targeted drug delivery, protein-corona science, biological barriers, biodistribution, immune recognition, intracellular release, degradation, and clearance while retaining system-, host-, compartment-, and method-specific uncertainty.

Synthetic identity versus acquired biological identity

Synthetic identity is defined here as the pre-exposure description of a nanocarrier derived from composition, architecture, dimensions, morphology, surface chemistry, charge, payload state, and other measured attributes. Acquired biological identity begins when environmental biomolecules reorganize the interface presented to receptors; corona-mediated receptor binding demonstrates that receptor-facing identity can differ from the pristine surface specified during design [4].

Acquired identity should not be reduced to an inventory of tightly retained proteins. Lipids and other non-protein constituents can contribute to the biological response of nanocarriers, making the broader term biomolecular corona more appropriate when evidence extends beyond proteins [5]. The ledger therefore separates measured molecular composition from inferred interfacial function and avoids assigning universal importance to any constituent class.

Host context is an identity-forming variable rather than background noise. A human proof-of-concept study showed that PEGylated liposomes acquire an in vivo biomolecule corona, supporting direct recording of the host, administration context, sampling compartment, and recovery method [6]. This evidence establishes the feasibility of observing a human in vivo state, not population-wide generalizability or predictive clinical validity.

The proposed distinction is consequently relational: synthetic identity describes the administered material state, whereas acquired biological identity describes a measured or inferred interface after a specified exposure. Neither is synonymous with targeting success, safety, efficacy, or fate. Their value lies in enabling discrepancies between intended design and observed biological presentation to be documented, compared, and tested.

Components of the biological identity ledger

A biological identity architecture must distinguish soft-corona composition, barrier-specific corona evolution, and intracellular corona remodeling [7-9]. Treating these observations as one undifferentiated “protein corona” would erase differences in recoverability, compartment, time, and cellular processing. The ledger therefore represents them as related but non-interchangeable states rather than as repeated measurements of a single stable identity.

Eight proposed constructs form the architecture. The Synthetic Identity Record stores the measured pre-exposure carrier; the Manufacturing Provenance Record stores batch materials, unit operations, storage, and analytical lineage; the Biological Exposure Event specifies the encountered environment; and the Acquired Corona State records composition, conformation, and method-dependent soft components [7]. The Recognition State and Fate State record subsequent biological interactions and disposition observations.

The Temporal-Compartment Key links every observation to time, anatomical or intracellular location, biological matrix, and transition history, because corona composition can change across a biological barrier [8]. The Evidence Provenance and Uncertainty Layer records whether an entry is directly observed, analytically derived, mechanistically interpreted, or proposed, together with method limits, variability, missingness, and transferability conditions.

“Ledger” denotes scientific traceability, not blockchain, immutability, or automatic causal inference. Records may be revised when improved measurements become available, and directed links identify hypotheses or evidence-supported dependencies rather than guaranteed pathways. The constructs are an original conceptual synthesis

requiring computational, experimental, manufacturing, and implementation validation before they could support predictive or decision-oriented use.

Material attributes and manufacturing provenance

Material identity begins upstream of final characterization. Raw-material specifications, formulation sequence, mixing regime, microfluidic conditions, purification, sterilization, filling, storage, and scale can shape critical quality attributes; Quality by Design approaches consequently connect process understanding with nanomedicine manufacture [10]. The Manufacturing Provenance Record is proposed to preserve these controllable inputs alongside the resulting batch measurements.

Traceability also depends on sufficient reporting. Minimum-information frameworks for bio-nano experiments show why material descriptors, biological conditions, protocols, and analytical details must accompany reported outcomes [11]. Within the ledger, completeness is treated as an evidentiary property: an entry lacking essential context can remain visible but should carry an explicit limitation rather than be silently treated as comparable.

Characterization must span levels relevant to the claim, because physicochemical measurements alone do not resolve biological identity, and biological assays cannot retrospectively specify an inadequately documented material state. Translation-oriented interpretation therefore requires connected characterization of the carrier, payload, interface, exposure medium, and biological response [12]. Analytical provenance must additionally identify instruments, preparation steps, normalization choices, and detection limitations.

The proposed provenance architecture distinguishes critical material attributes, critical process parameters, batch provenance, analytical provenance, and biological exposure. It does not assume that a particular process parameter guarantees a corona, distribution, release, degradation, or clearance outcome. Instead, it creates a batch-resolved basis for testing whether reproducible manufacturing differences are associated with subsequent identity transitions and fate states.

Protein corona evolution across biological environments

The corona encountered in vivo cannot be assumed from pre-injection characterization or a single static incubation. Circulating leukocyte-like carriers acquired an in vivo protein corona, showing that even biohybrid surfaces remain subject to host-derived interfacial remodeling [13]. The ledger therefore records each corona observation as an exposure-specific state linked to the carrier batch, biological matrix, recovery method, and sampling point.

Corona evolution can alter pharmaceutical function rather than merely conceal the manufactured surface. In temperature-sensitive liposomes, in vivo corona formation affected drug release, supporting separate records for carrier identity, acquired interface, triggering conditions, and payload behavior [14]. The proposed architecture does not presume the direction or magnitude of this effect for other materials, release mechanisms, or biological environments.

Immune history can redirect corona composition and downstream fate. Anti-polyethylene-glycol antibodies changed the corona deposited on nanoparticles and altered physiological pathways governing their in vivo disposition [15]. Accordingly, the Biological Exposure Event includes prior exposure, antibody status where relevant, co-medications, disease state, and donor or species context rather than treating plasma as a universally interchangeable medium.

Protein-corona evolution is therefore represented as a sequence of measured states, not as a universal hard-corona endpoint. Composition, conformation, exchange kinetics, and particle-level heterogeneity may change independently. These studies justify recording context-dependent transitions, but they do not establish a single corona signature that predicts intracellular release, biodistribution, therapeutic effect, or safety across platforms.

Complement, innate immunity, and cellular recognition

Complement belongs in a distinct Recognition State because adsorption, opsonization, activation, and clinical reaction are not equivalent outcomes. Complement activation has been identified as a safety-relevant concern for PEG-coated nanomedicines [16]. The ledger records the complement pathway, assay conditions, biological matrix, activation products, and interpretation separately rather than converting them into one universal immune-risk value.

Species context is a major transferability boundary. Complement opsonization of nanoparticles differs between humans and preclinical species, so an animal result cannot automatically validate a human recognition state [17].

Comparative entries must preserve species, donor, anticoagulant, disease context, assay format, and nanoparticle state, with uncertainty attached to any cross-species inference.

Cellular recognition is jointly conditioned by the acquired corona and immune-cell environment. Corona–immune-cell interplay has been shown to influence liposome blood residency [18]. The proposed ledger consequently separates soluble recognition, cellular association, uptake, and residence from downstream distribution or safety because a longer or shorter circulation time does not by itself establish efficacy, tolerability, or target engagement.

Recognition States are interpreted as context-bound evidence nodes connecting synthetic and acquired identity to later fate observations. Alternative explanations include assay artifacts, selective particle recovery, host heterogeneity, and correlations between corona features and unmeasured material variables. No universal complement threshold, immune-risk score, or clinical recommendation is proposed.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in the biological identity ledger for tracing protein corona formation, immune..

Table 1. Definitions, components, relationships, and intended uses in The Biological Identity Ledger for Tracing Protein Corona Formation, Immune**.**

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Synthetic Identity Record	Ambiguous starting material	Composition, dimensions, surface, payload	Defines the pre-exposure state [10].	Batch comparison	Orthogonal characterization	Hidden heterogeneity	Not a biological-performance claim
Manufacturing Provenance Record	Untraceable batch variation	Materials, process, scale, storage	Links controllable history to synthetic identity [11].	Source attribution	Batch-resolved records	Missing process variables	Completeness is not causality
Biological Exposure Event	Non-equivalent environments	Host, matrix, dose, time, flow	Conditions acquisition of biological identity [6].	Context preservation	Defined exposure metadata	Donor and sampling bias	No universal plasma surrogate
Acquired Corona State	Static protein-list framing	Proteins, lipids, antibodies, kinetics	Records the measured interfacial state [7].	Corona-state comparison	Recovery-aware assays	Soft-corona loss	Composition is not function
Recognition State	Conflated immune outcomes	Receptors, complement, immune cells	Connects the current interface to recognition [18].	Mechanistic traceability	Matched interaction assays	Species and assay dependence	Recognition is not clinical risk
Fate State	Accumulation treated as delivery	Location, integrity, release, degradation	Records downstream disposition [14].	Carrier–payload tracing	Integrity and localization assays	Label dissociation	Distribution is not efficacy
Temporal-Compartment Key	Static identity labels	Time, compartment, prior state	Versions identity across transitions [8].	Longitudinal linkage	Linked sampling	Missing transitions	Sequence does not prove causation
Evidence Provenance and Uncertainty Layer	Unsupported comparability	Method, replication, variance, transferability	Qualifies every field and relationship [11].	Evidence-bounded interpretation	Auditable metadata	False precision	Not calibrated decision risk

Barrier-specific corona evolution demonstrates why identity must be traced across compartment transitions rather than inferred from a single exposure [8]. **Figure 1** presents the original conceptual synthesis for evolution of nanocarrier identity across biological compartments, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

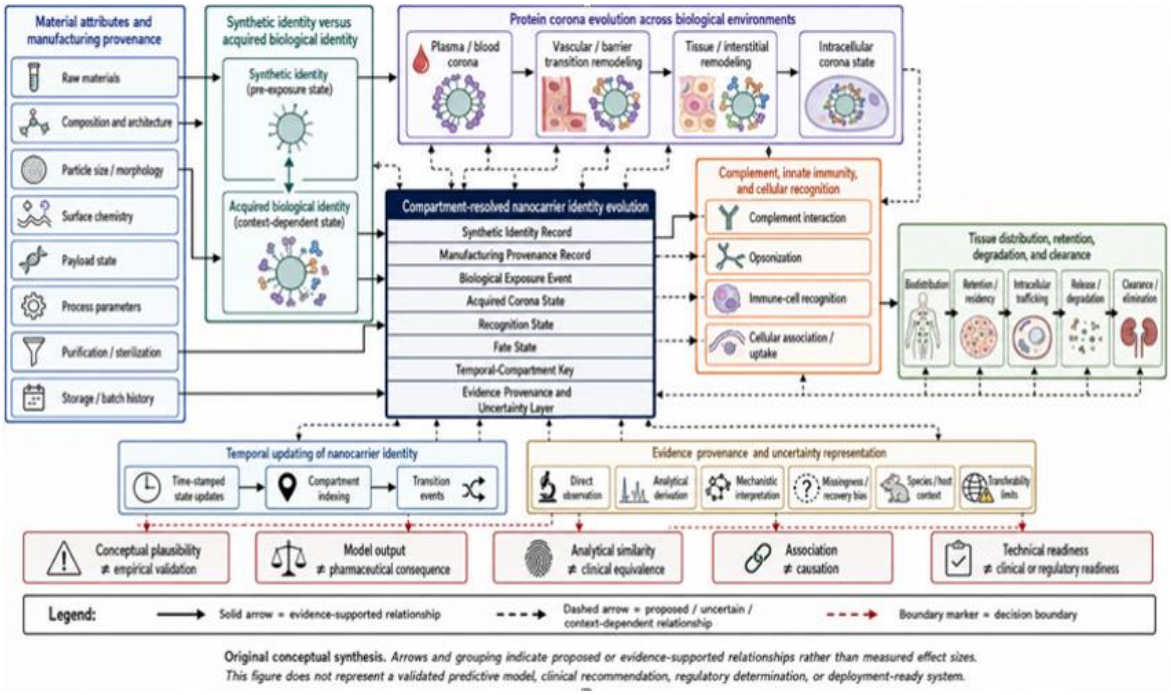

Figure 1. Evolution of Nanocarrier Identity across Biological Compartments

The figure is an original conceptual synthesis developed for "The Biological Identity Ledger for Tracing Protein Corona Formation, Immune Recognition, Tissue Distribution, and Nanocarrier Fate." 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.

Tissue distribution, retention, degradation, and clearance

Nanocarrier elimination is not one endpoint but a sequence involving cellular processing, organ distribution, degradation, and excretion pathways [19]. The Fate State therefore records anatomical compartment, cell type, carrier integrity, degradation products, sampling route, and terminal or censored status. Tissue accumulation is treated as an observation, not proof of productive delivery or target engagement.

Long-term fate can depend on surface chemistry and the associated corona. In vivo biodegradation of iron oxide nanoparticles varied with these interfacial conditions [20]. This platform-specific evidence supports linking Synthetic Identity Records and Acquired Corona States to degradation observations while precluding the assumption that the same relation applies to all inorganic, polymeric, lipid, or biohybrid carriers.

Carrier and payload trajectories must remain separable because corona formation can modify release behavior [14]. Dual labels, integrity assays, colocalization, and metabolite-sensitive measurements are therefore preferable where feasible. A tissue signal from a label cannot establish the presence of intact carrier, active payload, or released degradation products unless label stability and molecular identity have been demonstrated.

The proposed Fate State integrates distribution, retention, intracellular trafficking, release, degradation, and clearance without collapsing them into a readiness score. Its principal value is traceability across linked states. It does not supply dosing recommendations, universal clearance classifications, clinical safety judgments, or an assumption that greater target-tissue exposure is necessarily beneficial.

Temporal updating of nanocarrier identity

Ensemble averages can conceal coexisting particle states. Super-resolution microscopy has revealed dynamic heterogeneity in nanoparticle protein coronas [21]. A valid ledger must therefore allow distributions,

subpopulations, and state uncertainty rather than assigning every particle in a batch one uniform identity at each nominal time point.

In situ analysis of the soft corona further supports time-stamped observation of dynamic exchange while reducing disruption introduced by isolation [22]. Such methods strengthen longitudinal inference but do not establish one mandatory analytical platform or sampling cadence. Measurement choice must remain appropriate to carrier chemistry, biological matrix, compartment, and the distinction being tested.

The proposed Temporal-Compartment Key binds each record to absolute or relative time, anatomical or intracellular location, prior state, transition event, sampling route, and missingness. Barrier-dependent corona evolution provides evidence for the need to version identity across compartments [8]. The key is an original organizing mechanism; it does not establish that an observed sequence is causal.

Update rules should be event-triggered when a carrier crosses a barrier, enters a cell, releases payload, degrades, or encounters a materially different biological environment. Scheduled observations may complement event-triggered records, but no universal interval is proposed. Sampling cadence and state granularity require platform-specific validation.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for the biological identity ledger for tracing protein corona formation, immune.

Table 2. Testable propositions, evidence requirements, and validation criteria for The Biological Identity Ledger for Tracing Protein Corona Formation, Immune.

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
Time-compartment indexing	Version identity	State plus time and location	Links all ledger records	Reproducible transition-linked differences [22].	Perturbative sampling	Predefine cadence and censoring	No universal interval
Manufacturing-to-identity link	Trace controllable variation	Process to synthetic attributes	MPR to SIR	Designed batch comparison [10].	Unmeasured lot effects	Control process and storage	Association is platform-specific
Exposure-to-corona link	Record acquisition context	SIR plus matrix to ACS	BEE conditions ACS	Matched exposure experiments [13].	Selective recovery	Preserve host and method metadata	No universal corona
Corona-to-recognition link	Test interfacial function	ACS features to RS	Receptors, complement, cells	Orthogonal confirmation [4].	Collinearity or leakage	Include negative controls	Prediction is not utility
Recognition-to-fate link	Trace downstream disposition	RS to localization and residence	RS connects to FS	Linked immune and fate measurements [18].	Unmeasured host factors	Separate association and causation	No clinical-risk inference
Carrier–payload linkage	Distinguish material trajectories	Carrier, payload, fragments	Multiple FS records	Validated integrity and label stability [14].	Label dissociation	Use orthogonal tracking	Distribution is not efficacy
Provenance and uncertainty	Qualify evidence	Method and variance metadata	Cross-cuts all layers	Reproducible metadata capture [11].	False precision	Audit missingness and transferability	Completeness is not correctness
Decision-use gate	Prevent premature application	Validated evidence to intended use	Follows all prior layers	Independent, use-specific assessment [12].	Dataset or workflow shift	Predeclare acceptance criteria	Not deployment-ready

Evidence provenance and uncertainty representation

Corona composition, molecular conformation, exchange kinetics, and biological function are distinct signatures and should not be treated as interchangeable measurements [23]. The Evidence Provenance and Uncertainty Layer therefore tags what was measured, how it was measured, and which inference was drawn, preventing compositional abundance from being presented automatically as receptor activity, immune consequence, or fate prediction.

The protein-corona literature is uneven in its coverage and characterization of relevant variables [24]. Ledger completeness must consequently be reported field by field rather than implied by the existence of a record. Missing host context, recovery conditions, material details, or analytical calibration should remain visible as limitations that restrict comparison and transferability.

Analytical procedures can preferentially retain stable constituents while losing dynamic soft-corona components [7]. Recovery uncertainty, detection limits, normalization, batch effects, particle loss, and contamination therefore belong beside each observation. These entries should distinguish known absence from non-detection, unmeasured variables, censored transitions, and method-dependent missingness.

The proposed evidence classes are direct observation, analytically derived result, mechanistic interpretation, model-based inference, and original proposed relationship. Uncertainty is separated into analytical uncertainty, biological variability, model uncertainty, bias, missingness, and transferability. These qualitative classes organize evidence limitations but must not be converted into calibrated probabilities or decision-risk estimates without use-specific validation.

Experimental validation and reporting requirements

Validation requires both analytical reproducibility across proteomics workflows and standardized reporting of biocorona experiments [25, 26]. Initial schema validation should test field definitions, interoperability, version control, and auditability. Analytical validation should then examine recovery, sensitivity, selectivity, calibration, stability, and interfacility reproducibility using shared materials and prespecified metadata.

Experimental validation should use batch-linked, longitudinal, and compartment-resolved designs. Human and preclinical studies must preserve species context because complement opsonization is not automatically transferable [17]. Longitudinal methods should minimize sampling-induced remodeling where feasible, while in situ approaches may help characterize dynamic soft-corona states [22]. No single method is mandated for every platform.

Manufacturing validation should establish whether controlled process variation changes the Synthetic Identity Record and whether any resulting Acquired Corona or Fate State difference is reproducible. Quality-by-Design principles provide a basis for connecting process understanding with nanomedicine attributes [10]. Mechanistic validation additionally requires perturbations, negative controls, transition verification, and alternative explanations rather than retrospective correlation alone.

Computational validation should compare ledger-informed models with simpler baselines, prevent batch or donor leakage, and use independent data. Prospective validation is required before development or clinical decision use. Interfacility heterogeneity in corona proteomics makes blinded replication and variance decomposition essential [25]. Reporting completeness, retrospective fit, or conceptual coherence alone cannot establish predictive validity, clinical utility, regulatory acceptance, or implementation readiness.

Limitations and implementation priorities

The architecture faces the same development constraints that affect nanomedicine more broadly, including scalable manufacture, sufficiently discriminating characterization, relevant biological models, and stage-appropriate development decisions [27]. A comprehensive ledger may increase documentation burden, and some states will remain inaccessible because sampling alters the interface or cannot be performed repeatedly in vivo.

Claims for smart or targeted nanomedicine remain conditional on biological context, delivery route, disease environment, payload, and intended utility [28]. The ledger cannot make an unsuitable carrier effective, infer causality from incomplete observations, resolve all label or recovery artifacts, or guarantee that a measured corona feature remains relevant across hosts, species, compartments, or time.

Implementation priorities are shared reference materials, longitudinal multi-compartment studies, human-matrix comparisons, batch-linked manufacturing experiments, interlaboratory exercises, machine-readable schemas, and prospective tests of intended decisions. Multisite evidence shows why analytical variance must be identified rather than absorbed into a nominal corona state [25]. Governance should preserve revision history, access control, provenance, and explicit responsibility for interpretations.

Manufacturing provenance is the upstream anchor needed to test whether controllable process history contributes to later biological differences [10]. **Figure 2** presents the original conceptual synthesis for biological identity ledger linking material provenance to in vivo fate, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected

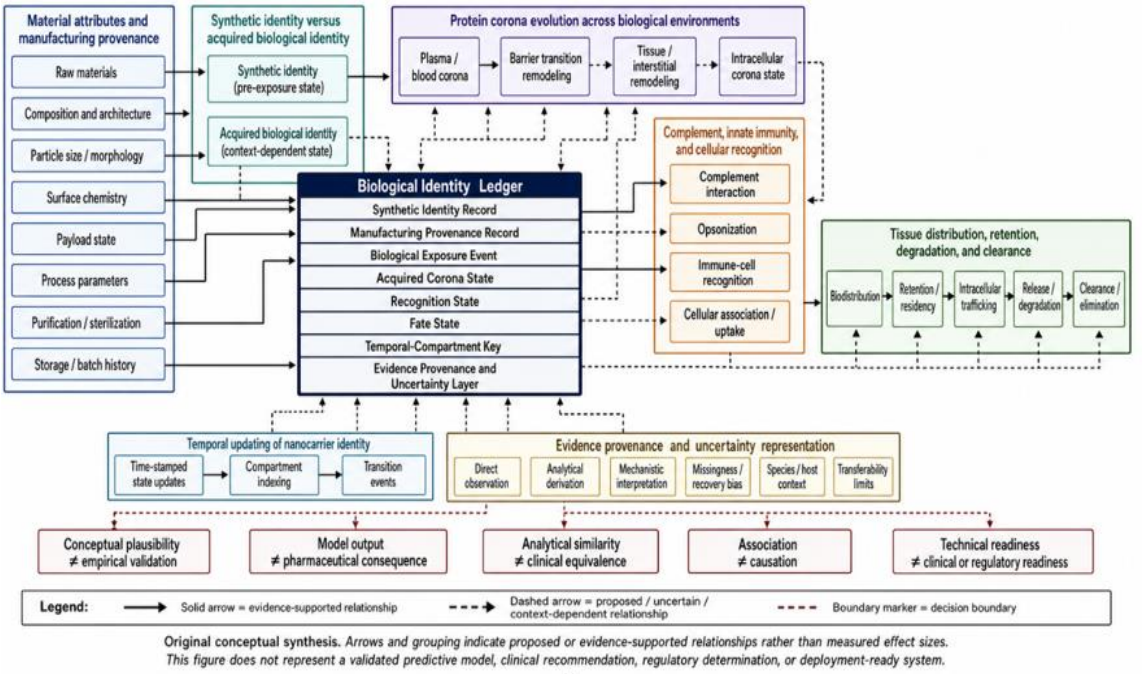

Figure 2. Biological Identity Ledger Linking Material Provenance to In Vivo Fate

The figure is an original conceptual synthesis developed for "The Biological Identity Ledger for Tracing Protein Corona Formation, Immune Recognition, Tissue Distribution, and Nanocarrier Fate." 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.

CONCLUSION

The Biological Identity Ledger is proposed as an evidence architecture for tracing how a manufactured nanocarrier becomes a succession of context-dependent biological states. By linking synthetic identity and manufacturing provenance to exposure events, biomolecular coronas, recognition, distribution, intracellular processing, release, degradation, and clearance, it makes assumptions, missing transitions, and uncertainty visible. Its original contribution is not a new prediction of nanocarrier performance but a structured basis for formulating and falsifying claims across batches, compartments, hosts, and time. The architecture remains non-empirical and requires schema, analytical, mechanistic, manufacturing, translational, prospective, and implementation validation. It does not equate corona composition with function, accumulation with delivery, biodistribution with efficacy, reporting completeness with validity, or technical feasibility with clinical or regulatory readiness.

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