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From Physicochemical Promise to Translational Readiness: An Evidence Map of Nano- and Targeted Drug Delivery Systems

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ABSTRACT

Nano- and targeted drug-delivery systems are frequently evaluated through favorable physicochemical attributes, mechanistic plausibility, or localized preclinical performance, although these forms of evidence do not necessarily establish translational readiness. This evidence-mapping review examines how the literature connects material characterization, biological identity, barrier interactions, biodistribution, intracellular delivery, pharmacological efficacy, safety, manufacturing control, and clinical or regulatory translation. A systematic evidence-mapping approach was used to identify eligible peer-reviewed literature, classify delivery-system technologies, chart development stages and validation contexts, and distinguish evidence presence from evidence quality, connectedness, or readiness. The mapped landscape indicates comparatively concentrated evidence around nanoparticle characterization, cancer-oriented delivery, lipid-based carriers, tumor transport, and microfluidic formulation. Evidence becomes less continuous when studies must connect bulk tissue accumulation with target-cell access, cellular uptake with functional intracellular release, preclinical efficacy with clinically relevant safety, or laboratory formulation with reproducible large-scale manufacture. Protein-corona prediction, biohybrid carriers, stimuli-responsive systems, endosomal escape, extrahepatic targeting, and patient-selection biomarkers represent important but variably validated clusters. Across technologies, translational maturity is limited less by the absence of promising mechanisms than by discontinuities between analytical, biological, pharmacological, manufacturing, and human-relevant evidence. The review therefore proposes a structured evidence landscape in which favorable findings remain bounded by the model, product, route, disease context, and validation level examined. The principal implication is that translational readiness should be interpreted as an evidence-linked, product-specific condition rather than as an automatic consequence of nanoscale design, targeting functionality, publication activity, or isolated preclinical success.

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

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INTRODUCTION

Nano- and targeted drug-delivery systems aim to control where, when, and how therapeutic payloads interact with biological tissues. Potential advantages include drug protection, pharmacokinetic modulation, preferential tissue exposure, intracellular transport, controlled release, and reduced non-target exposure. These possibilities have generated lipid, polymeric, inorganic, ligand-functionalized, stimuli-responsive, and biologically derived carriers. However, engineering advantages remain conditional on rigorous preclinical design, biological context, and

clinically meaningful development pathways [1–3]. A formulation may therefore be scientifically sophisticated yet insufficiently characterized for translation.

Precision nanoparticle engineering extends beyond carrier composition. Particle dimensions, morphology, surface chemistry, payload association, colloidal behavior, administration route, release kinetics, and interactions with biological fluids jointly determine delivery performance [4]. These variables are interdependent: a surface modification intended to improve receptor recognition may also affect protein adsorption, clearance, tissue penetration, intracellular trafficking, or manufacturability. Likewise, formulations optimized for encapsulation or in-vitro release may behave differently after storage, dilution, administration, or physiological exposure. Physicochemical promise should therefore be treated as an initial evidence domain rather than a surrogate for pharmaceutical utility.

The literature is commonly organized by carrier type, disease indication, or mechanistic advantage. Although useful for describing innovation, this structure can obscure whether evidence extends across the domains required for translation. A platform may demonstrate extensive physicochemical characterization but limited biodistribution evidence, strong tissue accumulation without target-cell delivery, or preclinical efficacy without scalable manufacturing. Progress should consequently be assessed through connected but non-substitutable evidence domains rather than as a single trajectory from invention to clinical use [5].

This systematic evidence-mapping review organizes the literature by delivery-system class, evidence domain, development stage, validation context, and translational boundary. It does not estimate pooled treatment effects, rank platforms, or predict approval. Instead, it maps where evidence is connected or fragmented and identifies uncertainties that prevent favorable material or biological findings from being interpreted as translational readiness.

Evidence-mapping questions and conceptual boundaries

The review examines how evidence is distributed across technologies and applications, which development stages and validation levels dominate, where evidence is concentrated or sparse, which systems progress across multiple translational domains, which methodological weaknesses limit interpretation, and which research priorities follow from identified gaps. Evidence presence is treated descriptively and does not imply effectiveness, safety, maturity, or proximity to implementation.

Nanomedicine and targeted delivery overlap but are not identical. Nanomedicine broadly concerns nanoscale materials used for diagnosis, treatment, delivery, or biological modulation, whereas targeted delivery seeks to modify the spatial, cellular, subcellular, temporal, or stimulus-dependent distribution of an intervention [1]. Targeting may arise from carrier dimensions, administration route, ligand–receptor interactions, cellular hitchhiking, environmental responsiveness, or intracellular trafficking. Conversely, a nanocarrier may improve solubility or stability without producing selective delivery. Carrier class is therefore coded separately from targeting mechanism.

The review also distinguishes physicochemical promise from translational readiness. Physicochemical promise includes controlled dimensions, payload association, stability, surface functionality, and responsive release. Translational readiness requires a broader chain connecting product identity with biological mechanism, pharmacological effect, safety, manufacturability, quality control, human relevance, and clinical-development context [4]. Strength in one domain cannot compensate automatically for absent evidence in another.

Interpretive boundaries are maintained throughout the synthesis. Tissue accumulation is distinguished from target-cell access; cellular association from internalization; internalization from endosomal escape or functional delivery; pharmacological activity from comparative clinical benefit; and analytical similarity from clinical equivalence. Computational predictions indicate model performance within defined datasets rather than pharmaceutical utility. The proposed categories organize heterogeneous evidence but do not constitute a validated readiness score, regulatory classification, clinical recommendation, or universal development pathway [2].

Search strategy, eligibility criteria, and source selection

A systematic evidence-mapping workflow was used to identify literature addressing delivery-system performance and translational progression. MEDLINE/PubMed, Scopus, Web of Science Core Collection, and Embase were searched using database-adapted terms related to nanomedicine, targeted delivery, carrier classes, physicochemical characterization, biological barriers, biodistribution, intracellular delivery, safety, manufacturing, scale-up, quality attributes, clinical development, and regulatory translation. Validation-related terms were included to capture reproducibility, external validation, comparability, patient stratification, and

implementation constraints. Publisher records, Crossref, and bibliographic databases supported metadata and DOI verification.

Eligible sources were peer-reviewed articles from relevant Q1 journals that contributed extractable mechanistic, methodological, validation, pharmacological, safety, manufacturing, clinical, regulatory, or translational evidence. Reviews were retained for definitions, field-level framing, methodological synthesis, and cross-domain interpretation. Primary studies were prioritized for claims concerning specific mechanisms, process relationships, biodistribution, predictive models, or translational validation. Records were excluded when they lacked a verifiable DOI, addressed only adjacent topics, contained unsupported promotional claims, or could not be assigned to a prespecified evidence domain.

Duplicates were removed through DOI and bibliographic matching. Titles and abstracts were screened for relevance, followed by full-record assessment of technology class, evidence contribution, development stage, validation context, and claim fit. Metadata and screening decisions underwent a separate verification pass. Data were charted without numerical readiness scoring or assumptions that publication frequency represented effectiveness. The synthesis emphasized evidence distribution and connectedness, including conflicting interpretations, methodological limitations, and missing transitions between analytical, biological, manufacturing, and clinical domains.

Data-charting framework and delivery-system taxonomy

The data-charting framework crosses delivery-system class with translational evidence domain. Platform classes include lipid nanoparticles and liposomes, polymeric carriers, ligand-targeted nanocarriers, inorganic or hybrid systems, stimuli-responsive formulations, biohybrid or cell-derived carriers, multidrug nanosystems, and organ-selective non-viral vectors. These classes are mapped against material identity, stability and release, acquired biological identity, barrier transport, biodistribution, intracellular delivery, efficacy and safety, manufacturing quality, and clinical or regulatory translation. The taxonomy is informed by established descriptions of smart and precision nanomedicine while its integrated evidence-map structure is an original synthesis [3]. **Figure 1** presents the original conceptual synthesis for evidence map across nanomedicine classes and translational domains, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

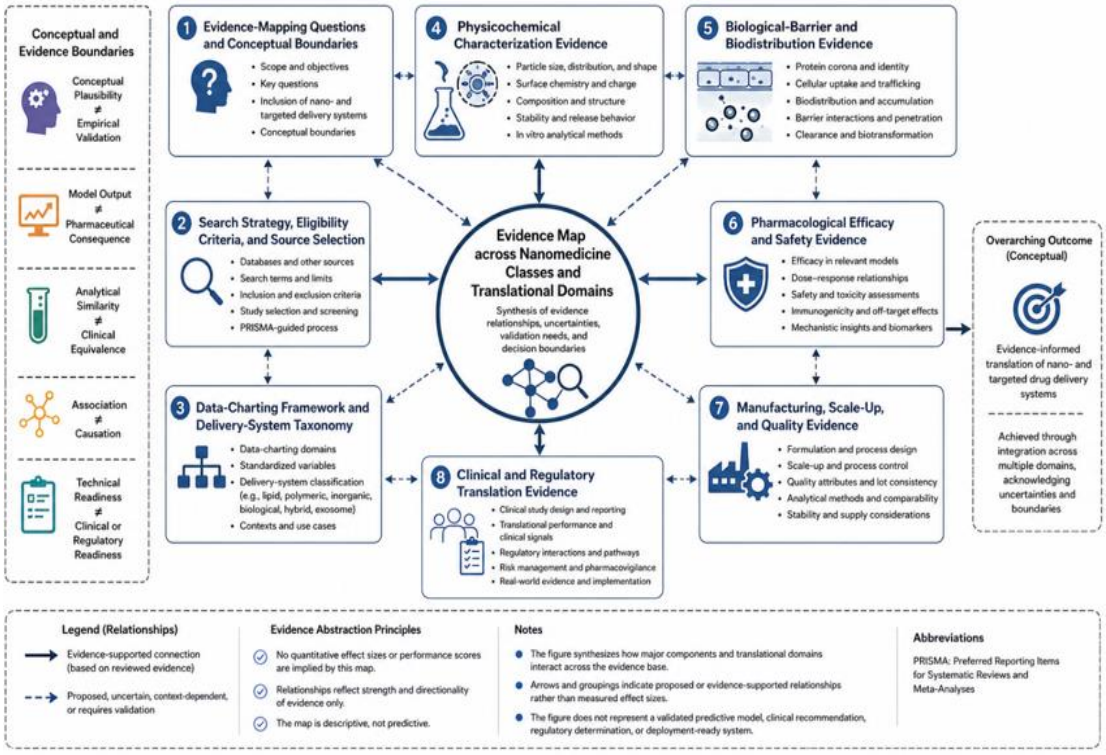

Figure 1. Evidence Map across Nanomedicine Classes and Translational Domains

The figure is an original conceptual synthesis developed for "From Physicochemical Promise to Translational Readiness: An Evidence Map of Nano- and Targeted Drug Delivery Systems." 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.

Articles were assigned only to evidence domains directly supported by their reported methods and results. Physicochemical characterization, biodistribution, intracellular delivery, and functional payload release were coded separately; discussion of several domains within one article did not establish continuity between them.

Development stage was charted independently of platform type and included analytical, cell-based, animal, process-development, human-tissue, clinical, and regulatory contexts. These categories indicate where evidence was generated rather than a universal maturity sequence.

Validation was classified according to what was actually tested, including orthogonal confirmation, replication, independent datasets, cross-model evaluation, human-relevant materials, process comparability, or clinical assessment. Internal model validation or repeated laboratory production was not treated as evidence of external validity or manufacturing robustness.

The final map records the delivery system, targeting mechanism, payload, route, biological context, model, endpoint, development stage, validation form, manufacturing relevance, and principal limitation. Evidence is also distinguished as directly demonstrated, inferred, computationally predicted, critically synthesized, or proposed. Map inclusion indicates evidence presence only, not superiority, clinical benefit, regulatory acceptability, or implementation readiness [4].

Physicochemical characterization evidence

Physicochemical characterization establishes the material identity underlying later biological and pharmacological claims. Reliable interpretation requires adequate reporting of composition, preparation, storage, analytical conditions, and complementary measurements of size, morphology, surface properties, aggregation, payload association, and chemical composition [6–8].

Particle size and polydispersity may influence stability, circulation, tissue transport, cellular interaction, loading, and release, but their significance is formulation- and context-dependent. Favorable mean values may conceal aggregates, multimodal populations, or instability after storage, dilution, administration, or exposure to biological fluids [9].

Morphology, surface charge, encapsulation efficiency, and release profiles are similarly dependent on measurement conditions. These attributes should therefore be interpreted together with the analytical environment and the pharmaceutical consequence they are intended to predict.

Characterization is treated as a necessary starting point, not proof of delivery performance. Favorable size, loading, release, or colloidal stability does not establish biological identity, tissue penetration, target-cell access, intracellular payload availability, safety, or clinical benefit. The map therefore records whether measurements are orthogonal, biologically relevant, and empirically connected to downstream outcomes. **Table 1** presents the evidence-map eligibility, classification, and data-charting framework from physicochemical promise to translational readiness.

Table 1. Evidence-map eligibility, classification, and data-charting framework for From Physicochemical Promise to Translational Readiness

Evidence domain or review construct	Review question	Eligible evidence type	Key extraction fields	Appraisal or relevance criterion	Synthesis role	Main limitation	Interpretation boundary
Material identity	Is the investigated delivery system defined sufficiently to attribute later observations to a reproducible product?	Compositional analysis, formulation records, morphology, size, surface, payload, and stability evidence	Carrier composition; payload; excipients; preparation method; route; storage; analytical environment	Reporting must permit identification of the tested formulation. Minimum-information principles guide this judgement [6].	Establishes the analytical object represented in the map	Nominal composition may not represent the administered or biologically transformed product	Material identity does not establish biological identity or therapeutic utility

Orthogonal physicochemical characterization	Are key properties supported by complementary methods?	Microscopy, scattering, separation, spectroscopy, thermal, chemical, and surface-analysis methods	Method; sample preparation; concentration; medium; replicate context; agreement across techniques	A second method should resolve a different aspect or known limitation of the first. Complementarity is method-dependent [7].	Distinguishes convergent characterization from single-method description	Techniques may measure different particle populations or conditions	Agreement among methods supports characterization, not in-vivo validity
Particle-size distribution	Does the evidence resolve central tendency, dispersion, and heterogeneous populations?	Orthogonal particle-sizing workflows and distribution analyses	Mean or mode; distribution; polydispersity; intensity, number, or mass basis; dilution; medium	Measurement complexity should match product heterogeneity. Orthogonal sizing is preferred [8].	Supports comparability and interpretation of transport-related claims	Reported averages can obscure aggregates or minor populations	A favorable size distribution does not predict biodistribution alone
Formulation performance	Are loading, stability, and release linked to relevant conditions?	Encapsulation, association, degradation, leakage, release, and storage evidence	Loading definition; free versus associated payload; time; medium; temperature; sink conditions	Conditions must be sufficiently described and relevant to the claimed application	Connects product identity with expected exposure behavior	In-vitro release may not reproduce in-vivo transport and clearance	Controlled release in a test system is not proof of site-specific release
Biological identity	Is transformation after contact with biological media examined?	Protein-corona, aggregation, opsonization, surface-transformation, and biofluid-stability studies	Biofluid; species; concentration; incubation; adsorbed proteins; functional consequence	Evidence must examine the transformed carrier rather than infer it from nominal surface design	Bridges physicochemical and barrier evidence	Corona composition and function vary by biological context	Biological identity in one medium cannot be generalized universally
Barrier interaction and biodistribution	Does the study distinguish tissue presence from transport mechanism and target-cell access?	Imaging, quantitative biodistribution, histology, transport studies, and cell-resolved analyses	Organ; tissue; cell type; route; time; label; intact carrier or payload; transport mechanism	Measurements must identify what is detected and at what spatial level	Maps localization and transport evidence	Labels may dissociate from carriers; bulk tissue signals can conceal cellular distribution	Accumulation is not equivalent to target-cell delivery
Intracellular delivery	Does the study distinguish association, internalization, trafficking, escape, release, and function?	Microscopy, fractionation, trafficking assays, cytosolic-delivery assays, and payload-function measures	Cell type; uptake route; compartment; escape method; functional endpoint	Functional intracellular availability should not be inferred solely from fluorescence uptake	Connects cellular transport with payload action	Many assays cannot distinguish membrane association from cytosolic delivery	Uptake does not establish endosomal escape or payload function
Pharmacological efficacy and safety	Are delivery findings connected to mechanism-relevant	Target engagement, pharmacodynamic, disease-model, toxicity,	Comparator; dose; exposure; endpoint; timing;	Outcomes must be interpreted within the tested model,	Connects delivery with pharmaceutical consequence	Surrogate or preclinical outcomes may not	Preclinical efficacy is not comparative clinical benefit

	effects and bounded safety observations?	immunological, and tolerability evidence	model; adverse observation	dose, and comparator		transfer to patients	
Manufacturing, scale-up, and quality	Are process variables linked to reproducible product attributes and function?	Process-development, microfluidic, scale-up, comparability, and critical-quality-attribute studies	Mixing; flow; concentration; unit operation; scale; batch; downstream processing; function	Scale or process change should be evaluated through relevant analytical and biological comparability	Maps developability and production evidence	Laboratory repeatability does not establish commercial robustness	Scale-up feasibility is not GMP or commercialization readiness
Clinical and regulatory translation	Is the platform evaluated in a product-, indication-, and decision-specific human context?	Human-tissue, clinical-development, comparability, regulatory-science, and commercialization literature	Product; indication; patient group; endpoint; comparator; regulatory question; development status	Evidence must be interpreted for the specific product and decision context	Maps human relevance and translational progression	Regulatory and clinical pathways vary by jurisdiction, indication, and product	Clinical or regulatory activity does not establish superiority or universal readiness
Evidence connectedness	Are adjacent evidence domains linked within or across studies?	Cross-domain experimental chains and evidence-supported synthesis	Domains linked; direct or indirect relationship; validation context; unresolved transition	Connections must be directly demonstrated or clearly identified as review-level interpretation	Proposed evidence-map construct	Qualitative connectedness is not a validated maturity score	Presence of connected evidence does not predict approval or success
Evidence gap	Which required relationship is absent, indirect, or insufficiently validated?	Missing-domain analysis, contradictory findings, and methodological limitations	Missing transition; affected system; model limitation; validation need	Gaps must be phrased as absence within the mapped evidence, not absence from all science	Directs future research questions	Search and eligibility boundaries can influence apparent gaps	A mapped gap does not demonstrate ineffectiveness or impossibility

Biological-barrier and biodistribution evidence

Delivery is often inferred from measurements that do not resolve the relevant spatial level. Ligand coating may improve receptor interaction, while bulk tumor accumulation may reflect vascular retention, extracellular material, uptake by stromal or immune cells, or detached labels. Total tumor-associated material must therefore be distinguished from delivery to malignant cells [10]. Evidence should specify whether an endpoint represents blood exposure, organ accumulation, tissue penetration, target-cell association, internalization, or functional payload availability.

The protein corona can transform a designed nanoparticle into a distinct biological entity by altering recognition, clearance, cellular interaction, and organ distribution. Its composition varies with the material, biological fluid, species, exposure time, and analytical method. Corona and material features may predict aspects of in-vivo fate, but dataset-level performance does not establish validity across formulations, laboratories, species, diseases, or patients [11].

Tumor access should not be attributed universally to passive leakage. Mechanistic studies indicate that endothelial transport can contribute substantially to nanoparticle entry into solid tumors [12]. Vascular phenotype, perfusion, extracellular matrix, tumor architecture, and immune composition may therefore influence accumulation as strongly as particle size or ligand density.

Cellular uptake is only one stage in a sequence involving endocytosis, trafficking, degradation, recycling, endosomal escape, release, and access to the relevant intracellular compartment. Fluorescence or cell-associated

labels may overestimate delivery when material remains membrane-bound, vesicle-trapped, degraded, or separated from its payload. Uptake, internalization, trafficking, and functional delivery must therefore be evaluated separately [13].

Pharmacological efficacy and safety evidence

Targeting is meaningful only when altered distribution produces therapeutic benefit without disproportionate harm. Ligand-mediated binding may not translate into consistent delivery because performance depends on receptor accessibility, disease heterogeneity, carrier stability, circulation, and competing uptake by non-target tissues [14]. Target expression and ligand binding should therefore be distinguished from exposure, target engagement, efficacy, and safety.

Nanomedicines may modify immune exposure, enabling antigen delivery, immune-cell targeting, or adjuvant activity, while also causing innate activation, complement responses, cytokine release, or inflammation. Outcomes depend on carrier chemistry, payload, route, dose, disease state, and immune mechanism [15]. Context-specific responses and short-term tolerability cannot establish general or long-term safety.

Messenger RNA lipid nanoparticles demonstrate that formulation science, intracellular delivery, scalable manufacturing, and human use can form a connected translational chain. However, this success is specific to particular chemistries, payloads, routes, and indications. Limitations remain in organ selectivity, repeat dosing, inflammation, storage, and delivery beyond established tissues [16].

Multidrug nanomedicines require evidence beyond co-encapsulation. Performance depends on drug interactions, release sequence, exposure ratios, co-localization, pharmacokinetic compatibility, dose selection, and combined toxicity [17]. Co-loading should therefore be distinguished from synchronized delivery, pharmacological synergy, and clinically meaningful benefit. **Table 2** maps evidence across delivery domains, systems, populations, outcomes, uncertainties, and boundary conditions.

Table 2. Distribution of evidence across article-specific domains, systems, populations, and outcomes

Method, platform, or evidence category	Representative application	Reported strength	Validation context	Generalization concern	Contradictory evidence	Evidence gap	Review interpretation
Lipid nanoparticles	Nucleic-acid delivery	Comparatively connected evidence from formulation to human use for selected products [16]	Analytical, preclinical, manufacturing, and clinical contexts	Product-specific success may not transfer across payloads, routes, organs, or lipid compositions	High translational progression coexists with unresolved repeat-dosing and extrahepatic-delivery constraints	Organ-specific delivery, long-term tolerability, and cross-product comparability	Represents translational progression for defined systems, not universal platform readiness
Lipidic nanocarriers characterized by size and PDI	Solubility enhancement and payload delivery	Strong descriptive physicochemical literature linking size and dispersion to pharmaceutical behavior [9]	Formulation and preclinical evidence	Associations vary with composition, method, route, and biological context	Similar size metrics can accompany different biological identities or outcomes	Empirical linkage between specific attributes and clinically relevant consequences	Size and PDI are necessary descriptors but insufficient predictors
Ligand-targeted nanoparticles	Receptor-directed cancer delivery	Mechanistically plausible targeting with cell-level quantitative evidence [10]	In-vitro and animal tumor models	Target expression and accessibility vary across cells, tumors, and patients	Increased tumor presence does not necessarily produce increased malignant-cell delivery	Human-relevant target-cell delivery and comparative therapeutic benefit	Targeting should be mapped at tissue, cell, and functional levels separately

Protein-corona-informed prediction	Prediction of in-vivo nanomaterial fate	Demonstrates that corona and material features can support predictive modelling [11]	Experimental proteomics, machine learning, and animal outcomes	Dataset shift across biofluids, species, laboratories, and materials	Nominal surface design may not predict the acquired biological identity	Independent external validation and decision-relevant prospective testing	Predictive association is promising but not equivalent to pharmaceutical utility
Tumor endothelial transport	Nanoparticle entry into solid tumors	Mechanistic evidence supports active endothelial contribution [12]	Cell-resolved and in-vivo tumor studies	Tumor vascular phenotypes are heterogeneous	Passive-leakage-only explanations do not fully account for observed transport	Cross-platform, cross-tumor, and human-tissue validation	Tumor entry should be interpreted as a biological transport process rather than a universal material property
Intracellular trafficking and escape	Cytosolic delivery of nucleic acids or intracellular drugs	Strong conceptual and methodological basis for separating uptake from functional delivery [13]	Cellular imaging, trafficking, fractionation, and functional assays	Assay signals may arise from surface association, vesicular trapping, or label dissociation	High cellular fluorescence can coexist with low payload function	Direct, quantitative, and standardized escape measurements	Uptake is an intermediate observation, not an intracellular-delivery endpoint
Nanomedicine-enabled immunotherapy	Antigen, adjuvant, or immune-modulator delivery	Mechanistically rich evidence for spatial and temporal control of immune exposure [15]	Preclinical and selected clinical contexts	Immune state, route, carrier, and payload alter outcomes	Immune activation may improve efficacy or produce inflammatory toxicity	Longitudinal safety, patient heterogeneity, and mechanism-specific validation	Immune effects require context-specific benefit–risk interpretation
Multidrug nanomedicine	Coordinated cancer combination therapy	Offers a rationale for co-delivery and exposure control [17]	Primarily analytical and preclinical combination evidence	Drug interactions, release sequence, and dose ratios are product-specific	Co-encapsulation does not guarantee pharmacological synergy	Clinical comparators, interaction validation, and combined safety	Component efficacy cannot establish system-level combination benefit
Biohybrid and cell-derived carriers	Immune evasion or organ-directed delivery	Biologically inspired functions with compelling preclinical mechanisms	Predominantly mechanistic and animal evidence	Source-cell variability and biological identity can affect consistency	Biological coatings may introduce functionality and new quality risks	Batch control, long-term safety, process comparability, and human validation	Promising class with fragmented translation evidence
Stimuli-responsive systems	Triggered release in tumor microenvironments	Strong design rationale for spatial or temporal release control	Predominantly laboratory and preclinical models	Trigger intensity and distribution may differ between models and patients	Responsiveness in simplified systems may not persist in heterogeneous tissues	In-vivo trigger verification and linkage to clinical benefit	Responsiveness is a mechanism claim requiring direct contextual validation

Manufacturing, scale-up, and quality evidence

Manufacturing conditions can alter nanoformulation structure and performance. In lipid nanoparticles, mixing geometry, flow, concentration, solvent ratio, and addition order affect self-assembly, encapsulation, and particle

properties [18, 19]. Process development must therefore establish relationships between manufacturing variables and critical product attributes.

Microfluidics can improve mixing control, reproducibility, and formulation screening, but laboratory success does not demonstrate scalable production [20]. Throughput, clogging, downstream processing, sterilization, raw-material variability, and equipment changes remain important. Parallelized production may preserve selected attributes across tested conditions, yet it does not establish commercial robustness or GMP readiness [21]. The map therefore separates formulation feasibility, process understanding, scale-up comparability, and regulated manufacture.

Clinical and regulatory translation evidence

Clinical translation requires more than scientific novelty. A product must address a defined medical need and demonstrate meaningful value relative to available treatments while remaining safe, manufacturable, practical, and commercially feasible [22].

Regulatory assessment is product-specific because composition, structure, manufacturing history, and biological behavior may be interdependent. Analytical similarity alone may not establish equivalent biodistribution, release, immunological effects, or clinical performance [23].

Translation therefore requires early coordination of material design, biological validation, manufacturing, indication, comparator, dosing, and product profile [24]. Clinical testing indicates sufficient evidence to justify investigation, not therapeutic superiority, broad safety, regulatory endorsement, or commercial success [25].

Evidence-Density and Readiness Map

Evidence density reflects how well findings connect across material, biological, pharmacological, and translational domains, not publication count or effectiveness. Readiness weakens when studies lack reproducibility, clinical relevance, or links between quality attributes and performance [26–29].

Evidence is comparatively connected for physicochemical characterization, lipid nanoparticles, selected nucleic-acid applications, tumor biodistribution, and microfluidic manufacturing. Major gaps remain between protein-corona findings and validated delivery predictions, tissue accumulation and target-cell access, cellular uptake and functional payload release, and preclinical efficacy and scalable manufacture or long-term safety.

Readiness is therefore product-specific and depends on continuity across domains rather than progress in any single area. The map highlights these discontinuities without assigning numerical scores.

Understudied systems and validation gaps

Biohybrid carriers introduce uncertainties in biological-source variability, composition, orientation, sterilization, storage, and batch comparability that conventional size and charge measurements cannot resolve [30].

Red-blood-cell hitchhiking can redirect carriers toward selected organs, but requires validation across routes, species, disease states, payloads, safety outcomes, and clinically relevant conditions [31].

Stimuli-responsive systems must demonstrate effective transport, trigger exposure, selective response, payload release, and pharmacological action within heterogeneous tissues rather than simplified media [32].

Endosomal escape also remains poorly quantified. Downstream activity or microscopy may not establish how much intact payload reaches the cytosol, while stronger membrane disruption may increase toxicity [33].

Limitations

This map reflects only the selected databases, journals, eligibility criteria, and recent peer-reviewed literature; relevant earlier, industrial, regulatory, or unpublished evidence may be absent. Substantial variation in formulations, models, methods, doses, and outcomes also limits comparison, particularly when reporting is incomplete [6].

Publication bias may overrepresent successful targeting, efficacy, or scale-up while obscuring negative findings. Reproducibility concerns further mean that dense evidence does not necessarily indicate reliable transferability [27]. Evidence connectedness is an original qualitative construct, not a validated predictor of approval, commercialization, or patient benefit [25].

Translational research priorities

Future studies should distinguish tissue accumulation from vascular transport, carrier integrity, target-cell access, and functional delivery, while reporting negative and competing mechanisms [34].

Patient and tissue biomarkers require standardized, independent, and prospective validation and must predict meaningful exposure or response rather than bulk tissue signal alone [35].

Design, efficacy, safety, manufacturing, regulatory planning, and clinical need should be integrated early [36]. Validation must also remain specific to the organ, route, payload, cell type, and disease context rather than extrapolated from hepatic lipid nanoparticle success [37]. **Figure 2** presents the proposed readiness ladder from physicochemical characterization to clinical translation.

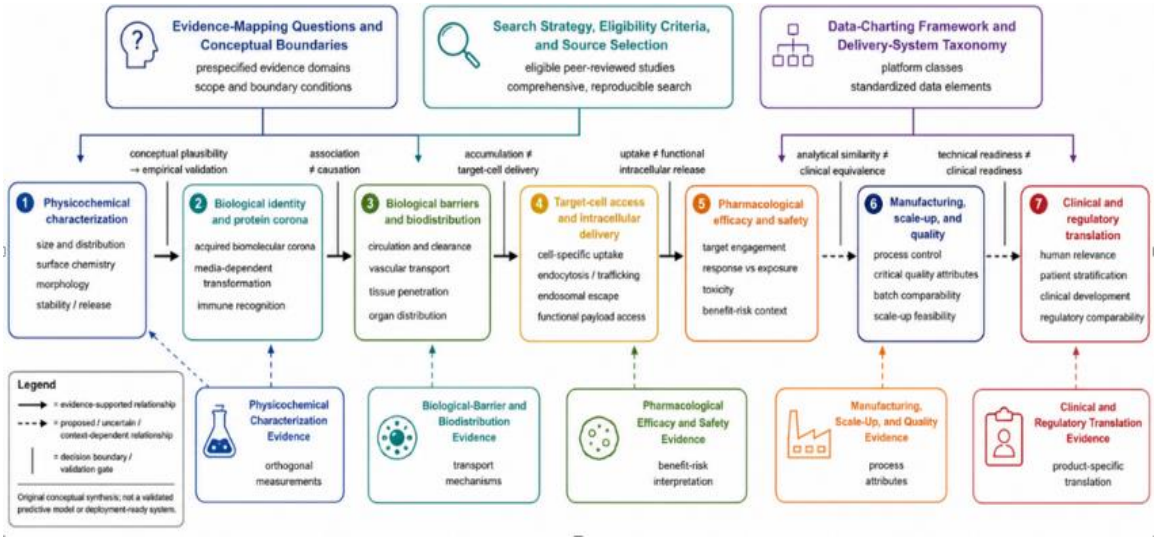

Figure 2. Readiness Ladder from Physicochemical Characterization to Clinical Translation

CONCLUSION

This evidence-mapping review shows that nano- and targeted drug-delivery systems are supported by a broad but unevenly connected evidence landscape. Physicochemical characterization, tumor-oriented transport research, lipid nanoparticle formulation, and selected manufacturing approaches form comparatively developed clusters, whereas protein-corona prediction, target-cell delivery, intracellular escape, biohybrid identity, multifunctional responsiveness, extrahepatic targeting, patient stratification, and long-term safety remain more fragmented. The central translational discontinuity does not arise simply from an absence of promising materials or mechanisms; it arises when analytical identity, biological transport, payload function, pharmacological consequence, safety, process control, human relevance, and clinical need are not linked for the same product and decision context. The proposed evidence map and readiness ladder make these discontinuities visible without treating publication presence as effectiveness or converting qualitative evidence into a validated score. Their appropriate use is to identify where uncertainty resides, what type of validation is missing, and which claims must remain bounded. Translational readiness should therefore be treated as a product-specific and evidence-linked condition rather than an inherent property of nanoscale size, targeting functionality, responsive design, preclinical efficacy, clinical activity, or regulatory interaction.

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