RESEARCH PAPER

RECENT ADVANCES IN CHITOSAN NANOPARTICLES FOR CANCER THERAPY: TARGETED DELIVERY, MECHANISMS, AND CLINICAL PERSPECTIVES

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ABSTRACT

Background: Chitosan is an adaptable cationic polysaccharide used to construct nanoparticles for small-molecule, nucleic-acid, phototherapeutic, and immunomodulatory cancer interventions. Its apparent simplicity is misleading, because molecular weight, deacetylation, substitution, purity, assembly conditions, and biological medium can change delivery and safety. Objective: This review critically examines recent chitosan nanoparticle advances through a design–mechanism–translation framework, with emphasis on the validity of targeting claims, causal mechanisms, and clinical readiness. Methods: A structured critical review was conducted using PubMed/MEDLINE, Crossref-verified publisher records, Google Scholar citation chasing, and ClinicalTrials.gov for literature available from 1 January 2020 to 20 June 2026; foundational studies were retained where necessary. Evidence was mapped by material identity, formulation, cargo, route, targeting mechanism, biological model, pharmacology, safety, and development stage. Reporting was appraised using SANRA and MIRIBEL principles. Results: Four conclusions emerged. First, "chitosan nanoparticle" is not an adequate product identity; polymer attributes and process variables must be treated as critical quality attributes. Second, passive access, ligand recognition, stimulus-responsive release, and local retention solve different transport barriers and require different validation experiments. Third, contemporary systems extend beyond chemotherapy to RNA interference, CRISPR-associated delivery, photoimmunotherapy, radiosensitization, and tumor-immune modulation, but mechanistic claims frequently rely on downstream cytotoxicity rather than exposure, release, and target-engagement evidence. Fourth, clinical translation remains limited. PRV111 provides early peer-reviewed proof of local cisplatin delivery in oral cancer, whereas later PRV211 observations remain preliminary and non-peer-reviewed. Conclusion: Chitosan nanomedicines are most credible when a defined material and route address a specific clinical barrier, targeting is causally validated, pharmacokinetics and immunotoxicity are quantified, and manufacture is scalable. Added multifunctionality should be justified by measurable, nonredundant benefit rather than formulation novelty alone.

Keywords: Chitosan, Nanoparticles, Cancer therapy, Targeted delivery, Tumor microenvironment, Gene delivery, Clinical translation

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ABBREVIATIONS

CMC, chemistry, manufacturing, and controls; CRISPR, clustered regularly interspaced short palindromic repeats; DLS, dynamic light scattering; EPR, enhanced permeability and retention; ICG, indocyanine green; MIRIBEL, Minimum Information Reporting in Bio–Nano Experimental Literature; NSCLC, non-small-cell lung cancer; PDI, polydispersity index; PK, pharmacokinetics; ROS, reactive oxygen species; SANRA, Scale for the Assessment of Narrative Review Articles; siRNA, small interfering RNA; TAM, tumor-associated macrophage; TME, tumor microenvironment; TNBC, triple-negative breast cancer; Treg, regulatory T cell.

1. INTRODUCTION

Cancer remains a major global cause of morbidity and mortality. In 2022, almost 20 million new cases and 9.7 million deaths were estimated worldwide, and population ageing and growth are projected to increase annual incidence substantially by 2050 [1]. Therapeutic innovation has expanded the use of molecularly targeted agents, immune checkpoint inhibitors, antibody–drug conjugates, radiopharmaceuticals, and precision radiotherapy. Nevertheless, many anticancer interventions remain constrained by the same pharmacological problem: insufficient separation between exposure at malignant tissue and exposure in healthy organs. Heterogeneous perfusion, dense extracellular matrix, abnormal interstitial pressure, treatment-induced selection, and metastatic heterogeneity further narrow the therapeutic window.

Nanocarriers were developed to alter the spatial and temporal presentation of drugs rather than simply to increase payload mass [2,3]. Their proposed advantages include protection of unstable cargo, altered clearance, co-delivery, controlled release, and cell-selective uptake. Clinical experience, however, has tempered early assumptions about universal tumor accumulation. Quantitative analyses indicate that only a small fraction of an injected nanoparticle dose typically reaches solid tumors, while endothelial transport, tumor perfusion, macrophage sequestration, and stromal architecture vary markedly across models and patients [4,5]. A cancer nanomedicine should therefore be evaluated as an integrated product whose material attributes, transport behavior, pharmacology, safety, and manufacture support the same clinical hypothesis.

Chitosan is a linear polysaccharide generated by partial deacetylation of chitin. Its glucosamine-rich backbone contains protonatable amines that enable ionic gelation, polyelectrolyte complexation, mucoadhesion, and chemical conjugation [6,7].

These features make chitosan useful for encapsulating small molecules, condensing nucleic acids, coating lipid or inorganic cores, and constructing local delivery systems. Yet chitosan is not a chemically uniform excipient. Biological behavior depends on source, molecular-weight distribution, degree and pattern of deacetylation, residual protein and endotoxin, crystallinity, viscosity, and derivative-specific substitution [8]. The same versatility that enables design flexibility can therefore undermine reproducibility when material identity is incompletely reported.

Chitosan nanoparticles are commonly prepared by ionic gelation, polyelectrolyte complexation, emulsion-based crosslinking, nanoprecipitation, or self-assembly of amphiphilic derivatives [9,10]. Recent reviews have catalogued their use in chemotherapy, gene delivery, phototherapy, immunotherapy, and stimulus-responsive treatment [11-13]. Cataloguing applications is no longer sufficient. The more consequential question is which design decisions produce a robust therapeutic advantage and which merely increase formulation complexity. In particular, increased fluorescence or cytotoxicity in a receptor-positive cell line is often labelled active targeting without receptor blockade or whole-animal exposure data; apoptosis-marker changes are presented as mechanism without demonstrating altered intracellular delivery; and preclinical efficacy is rarely connected to sterility, storage stability, batch reproducibility, or clinically relevant safety.

This review addresses those deficiencies through a design–mechanism–translation framework. It has four objectives: (i) to identify the material and formulation variables that govern chitosan nanoparticle behavior; (ii) to distinguish passive tumor access, ligand-mediated recognition, stimulus-responsive release, and local or externally assisted delivery; (iii) to relate nanoparticle disposition and cargo release to causal anticancer mechanisms; and (iv) to evaluate the strength of clinical evidence and the development requirements that determine translational plausibility. The intended contribution is not an exhaustive catalogue of formulations but a critical account of how claims should be matched to evidence.

2. MATERIALS AND METHODS

2.1 Review design and analytical question

This work was conducted as a structured critical narrative review. The primary analytical question was: how do chitosan identity, nanoparticle architecture, targeting strategy, therapeutic cargo, and administration route influence biological mechanism, therapeutic performance, safety, and clinical translatability? Reporting and intellectual appraisal were guided by the Scale for the Assessment of Narrative Review Articles (SANRA), particularly its requirements for a justified question, transparent literature search, scientific reasoning, and appropriate referencing [14]. The article was not represented as a systematic review because no prospectively registered protocol, exhaustive database-denominator accounting, dual independent screening, or formal study-level risk-of-bias adjudication was undertaken. Consequently, no PRISMA flow diagram or pooled treatment estimate is presented.

2.2 Information sources and search strategy

The literature search covered records available from 1 January 2020 through 20 June 2026. PubMed/MEDLINE was the principal bibliographic source. Crossref-linked publisher records were used to verify publication metadata and digital object identifiers, Google Scholar was used for backward and forward citation chasing rather than denominator-based retrieval, and ClinicalTrials.gov was searched for clinical-stage chitosan systems. Foundational publications before 2020 were retained when they established polymer chemistry, nanoparticle preparation, transport principles, reporting standards, or regulatory context. The core PubMed logic combined: (chitosan OR glycol chitosan OR carboxymethyl chitosan OR trimethyl chitosan) AND (nanoparticle* OR nanocarrier* OR nanocomplex* OR nanoformulation*) AND (cancer* OR tumor* OR tumour* OR neoplasm* OR carcinoma*) AND (therap* OR drug delivery OR gene delivery OR siRNA OR CRISPR OR photothermal OR photodynamic OR immunotherap*). Trial-registry searches used "chitosan cancer," "PRV111," and "PRV211." Reference lists of high-relevance primary studies and recent reviews were screened to identify additional eligible evidence.

2.3 Eligibility and evidence prioritization

Eligible primary evidence comprised in-vitro, ex-vivo, animal, and human studies in which chitosan or a defined chitosan derivative was an essential nanoparticle core, matrix, shell, coating, or nucleic-acid-condensing component used for cancer therapy. Studies were considered when they reported at least one relevant domain: physicochemical characterization, tumor or cell targeting, intracellular trafficking, release, target engagement, efficacy, pharmacokinetics, biodistribution, safety, or clinical outcome. Diagnostic-only reports, non-cancer applications, bulk chitosan films or hydrogels without a nanoparticle component, conference abstracts lacking adequate methods, retracted articles, and studies in which the contribution of chitosan could not be distinguished were excluded from the central analysis. English-language peer-reviewed evidence was prioritized; registry and news sources were used only to describe current clinical status and were explicitly separated from peer-reviewed efficacy evidence.

2.4 Data mapping and study selection for comparative tables

For high-relevance studies, information was mapped by chitosan source or derivative, molecular characteristics when reported, preparation method, particle size and polydispersity, zeta potential, cargo, ligand or stimulus, route, cancer model, comparator, mechanistic assay, pharmacokinetics, biodistribution, safety, and evidence stage. Dynamic light-scattering and zeta-potential measurements were interpreted as medium- and method-dependent descriptors rather than immutable particle properties [15]. The representative study table was purposively constructed to capture diversity of cargo, targeting mechanism, cancer model, route, and development stage. It was not used to estimate publication frequency or pooled efficacy, and inclusion in that table should not be interpreted as a quality ranking.

2.5 Critical appraisal

Reporting completeness was assessed against the Minimum Information Reporting in Bio–Nano Experimental Literature (MIRIBEL) framework, which emphasizes material identity, biological characterization, and experimental-protocol detail [16]. Greater interpretive weight was assigned when studies reported: defined polymer characteristics; orthogonal particle characterization in biologically relevant media; blank-particle, free-cargo, and matched non-targeted controls; receptor blockade or target-low validation for active targeting; orthotopic, metastatic, or immunocompetent models where appropriate; quantitative pharmacokinetics and organ biodistribution; normal-tissue and immunological safety; and manufacturing or stability information. No composite quality score was calculated because the included experimental designs were heterogeneous and no validated cross-domain weighting scheme exists.

2.6 Synthesis

Evidence was synthesized thematically across four linked domains: material and formulation identity; delivery strategy; mechanism and therapeutic modality; and translational readiness. Meta-analysis was not undertaken because cargos, routes, doses, models, comparators, and outcome definitions were not sufficiently homogeneous. Apparent efficacy was interpreted in relation to exposure, comparator quality, model relevance, and reporting completeness rather than ranked by nominal effect size alone.

2.7 Ethics

The review used published literature and publicly accessible trial-registry information. It generated no new data from human participants or animals; institutional ethics approval and informed consent were therefore not applicable.

3. RESULTS OF THE CRITICAL EVIDENCE SYNTHESIS

3.1 Evidence architecture: chitosan is a design variable, not a fixed excipient

The evidence converged on a central principle: the phrase "chitosan nanoparticle" is an incomplete product identity. Molecular weight influences viscosity, mixing, chain entanglement, nucleic-acid condensation, degradation, and release. Degree and pattern of deacetylation determine protonatable amine density, solubility, ionic crosslinking, and interaction with proteins and membranes. Increasing cationic character may improve mucoadhesion or cellular association, but it can also increase aggregation, hemolysis, complement activation, and phagocytic clearance [8,11].

Chemical modification addresses route-specific limitations. Trimethylation preserves cationic character closer to neutral pH; carboxymethylation increases aqueous solubility and introduces amphoteric behavior; glycol chitosan supports amphiphilic self-assembly; thiolation can strengthen mucoadhesion and support redox-sensitive linkages; and hydrophobic grafts improve loading of poorly soluble drugs. These derivatives cannot be treated as interchangeable. Degree of substitution, linkage chemistry, residual reagents, and degradation products are mechanistically and regulatorily relevant.

The proposed design–mechanism–translation framework is shown in Figure 1. It emphasizes that material identity and assembly determine delivery function, which in turn conditions biological mechanism and clinical feasibility. The critical material and formulation variables and their translational consequences are summarized in Table 1.

Table 1. Critical material and nanoparticle design variables that influence cancer-therapy performance.

Design variable	Effect on nanoparticle behavior	Therapeutic opportunity	Principal translational risk
Source and purity	Residual proteins, ash, metals, bioburden, and endotoxin alter safety and reproducibility.	Renewable feedstock and adaptable supply.	Lot variability, immunogenic contaminants, and incomplete traceability.
Molecular weight and distribution	Controls viscosity, chain entanglement, condensation, degradation, and release.	Tune stability, mucoadhesion, and nucleic-acid complexation.	Scale-dependent mixing and poor comparability when only nominal grade is reported.
Degree and pattern of deacetylation	Determines protonatable amine density, solubility, charge, and enzyme sensitivity.	Tune membrane interaction and ionic crosslinking.	Excess cationic character may increase protein adsorption, blood-cell interaction, and clearance.
Derivative and degree of substitution	Changes solubility, hydrophobicity, ligand presentation, and stimulus response.	Trimethyl, carboxymethyl, glycol, thiolated, and amphiphilic derivatives broaden route and cargo options.	New impurities, degradation products, and product-specific CMC requirements.
Crosslinker and assembly process	Determines network density, size distribution, cargo retention, and burst release.	Mild aqueous assembly can protect labile cargo.	Sensitivity to pH, ionic strength, mixing order, scale, and residual reagents.
Size distribution and morphology	Influences filtration, transport, uptake, clearance, and release.	Route-specific optimization for local, mucosal, or systemic delivery.	Mean size can mask aggregates; measurements vary by medium and technique.
Surface charge and shielding	Balances mucoadhesion/cell interaction against serum stability and immune recognition.	Tune regional retention or systemic circulation.	Aggregation, complement activation, rapid phagocytic uptake, or reduced uptake after over-shielding.
Cargo association and integrity	Determines loading, protection, release, and pharmacological activity.	Co-delivery of drugs, genes, and photosensitizers.	Burst release, chemical degradation, altered nucleic-acid integrity, and difficult release testing.
Sterility and storage	Sterilization and storage can change chain length, aggregation, charge, and release.	Lyophilized or local dosage forms may improve shelf life.	Sterilization damage, endotoxin, reconstitution failure, and weak stability-indicating assays.

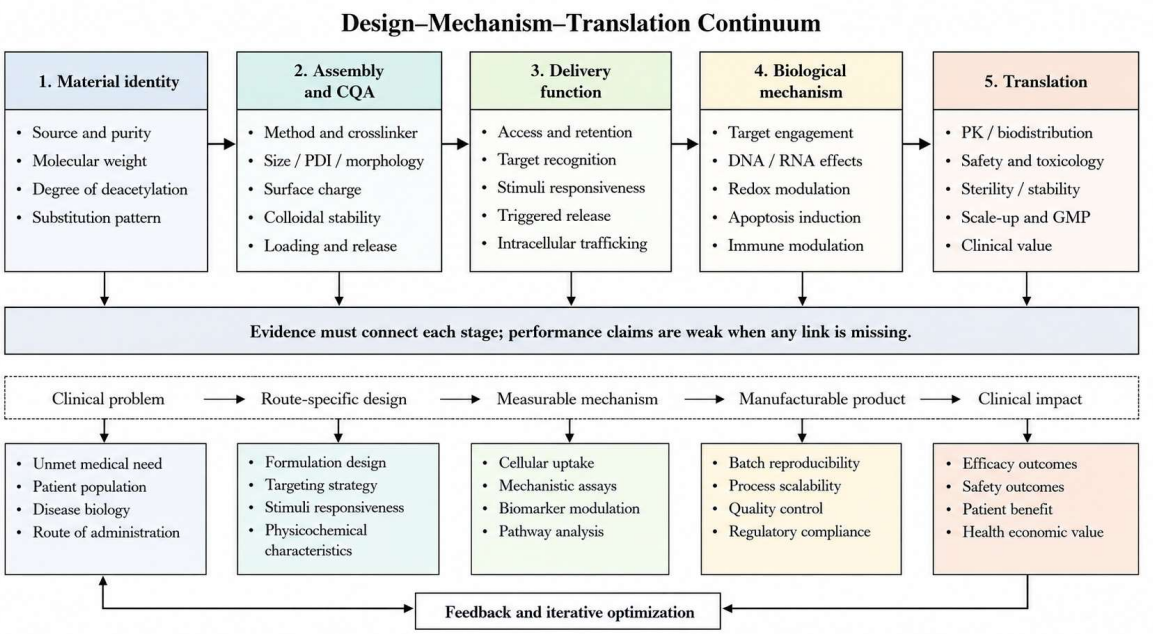

Figure 1. Design–mechanism–translation continuum for chitosan nanoparticles. Upstream material identity determines assembly, delivery function, biological mechanism, and clinical feasibility; "chitosan" alone is not an adequate formulation descriptor.

[[TABLE 1: table_01.csv]]

3.2 Preparation and characterization determine biological interpretation

Ionic gelation with multivalent anions such as tripolyphosphate remains common because it is aqueous, relatively mild, inexpensive, and compatible with labile cargo. Its apparent simplicity conceals sensitivity to polymer concentration, chitosan-to-crosslinker ratio, pH, ionic strength, mixing energy, addition rate, temperature, and purification. Polyelectrolyte complexation is particularly useful for DNA and RNA, whereas amphiphilic self-assembly can improve hydrophobic-drug loading. Emulsion and covalent-crosslinking methods may increase structural stability but introduce solvents or reactive reagents that require analytical control [9,10]. Hybrid designs that incorporate magnetic oxides, metals, lipids, carbon materials, or photosensitizers add function while multiplying interfaces, impurities, release mechanisms, and regulatory questions.

Characterization should begin with chemistry rather than particle diameter. A minimum dataset includes polymer molecular-weight distribution, degree of deacetylation and substitution, purity, residual crosslinker or solvent, cargo integrity, morphology, hydrodynamic size distribution, polydispersity, surface charge, loading, encapsulation efficiency, release under sink and biologically relevant conditions, stability after dilution into protein-containing media, and storage stability. Mean size alone can conceal aggregates, and a low polydispersity index in water does not establish stability in plasma, culture medium, or mucus [15,16]. For nucleic-acid formulations, gel retardation is insufficient without nuclease protection, unpacking, endosomal escape, and functional transfection data.

Surface charge illustrates the need for route-specific optimization. Positive charge can increase mucin binding and adsorptive endocytosis but may also accelerate protein adsorption, complement activation, blood-cell interaction, and mononuclear phagocyte uptake. Shielding with polyethylene glycol or zwitterionic groups can improve colloidal stability, yet excessive shielding may reduce cellular interaction and endosomal disruption. Strong mucoadhesion may therefore be advantageous for local oral delivery but undesirable for an intravenously administered product.

3.3 Targeted delivery: access, recognition, release, and retention are distinct

Recent primary studies illustrate the breadth of "targeting" strategies: folate-modified carboxymethyl chitosan for breast-cancer combination therapy [17]; AS1411 aptamer-decorated erlotinib nanoparticles for non-small-cell lung cancer [18]; alendronate–polyethylene glycol–chitosan constructs intended for mineralized metastatic niches [19]; M2-macrophage-directed peptide–chitosan particles [20]; stepwise responsive carboxymethyl chitosan [21]; magnetic indocyanine-green chitosan phototherapy [22]; iontophoresis-assisted buccal cisplatin delivery [23]; and the topical PRV111 cisplatin platform [24]. These systems do not solve the same barrier and should not be judged by the same endpoint.

The distinct routes by which chitosan systems can create tumor selectivity are illustrated in Figure 2. The validation requirements for each targeting strategy are summarized in Table 2.

Table 2. Targeting strategies for chitosan nanoparticles and the evidence required to support each claim.

Targeting strategy	Primary mechanism	Representative application	Minimum validation	Frequent overclaim
Passive tumor access	Perfusion, endothelial transport, retention, and stromal penetration.	Systemic particles intended for prolonged exposure.	Plasma PK, absolute tumor concentration, tumor-to-organ ratios, and spatial distribution.	Assuming a nominal nanoscale diameter proves EPR-mediated targeting.
Receptor ligand	Binding and endocytosis after tumor access.	Folate-modified breast-cancer systems [17].	Receptor quantification, blockade, target-low control, and matched non-targeted particle.	Equating greater cell uptake with greater whole-tumor delivery.
AS1411 aptamer	Nucleolin recognition and internalization.	Erlotinib-loaded chitosan particles for NSCLC [18].	Aptamer specificity, competition, serum stability, and in-vivo target engagement.	Attributing uptake entirely to aptamer despite charge or corona effects.
Bone-seeking ligand	Affinity for hydroxyapatite/mineralized niches.	Alendronate–PEG–chitosan for siRNA/curcumin [19].	Bone and lesion biodistribution, metastatic exposure, and off-target skeletal retention.	Inferring metastatic targeting from ligand chemistry and in-vitro assays.
Immune-cell peptide	Recognition of a tumor-associated immune-cell phenotype.	M2pep–chitosan–curcumin with anti-PD-L1 [20].	Phenotype-specific binding, competition, immune-cell biodistribution, and syngeneic efficacy.	Calling macrophage repolarization tumor targeting without cell-specific exposure.
Stimulus-responsive	pH-, redox-, enzyme-, ROS-, heat-, magnetic-, or light-triggered release/function.	Stepwise responsive carboxymethyl chitosan [21].	Physiologic trigger range, plasma stability, matched nonresponsive control, and in-vivo benefit.	Using extreme buffer conditions as proof of tumor-selective release.
Externally assisted	Magnetic field, light, or iontophoresis localizes or activates therapy.	ICG magnetic phototherapy [22] and buccal iontophoresis [23].	Field/light dosimetry, penetration, component controls, and tissue-safety mapping.	Attributing combined physical effects solely to nanoparticle targeting.
Local/mucoadhesive	Anatomical placement, retention, and regional penetration.	PRV111 topical cisplatin system [24].	Local exposure, systemic leakage, mucosal toxicity, retention, and device performance.	Conflating anatomical targeting with receptor-specific targeting.

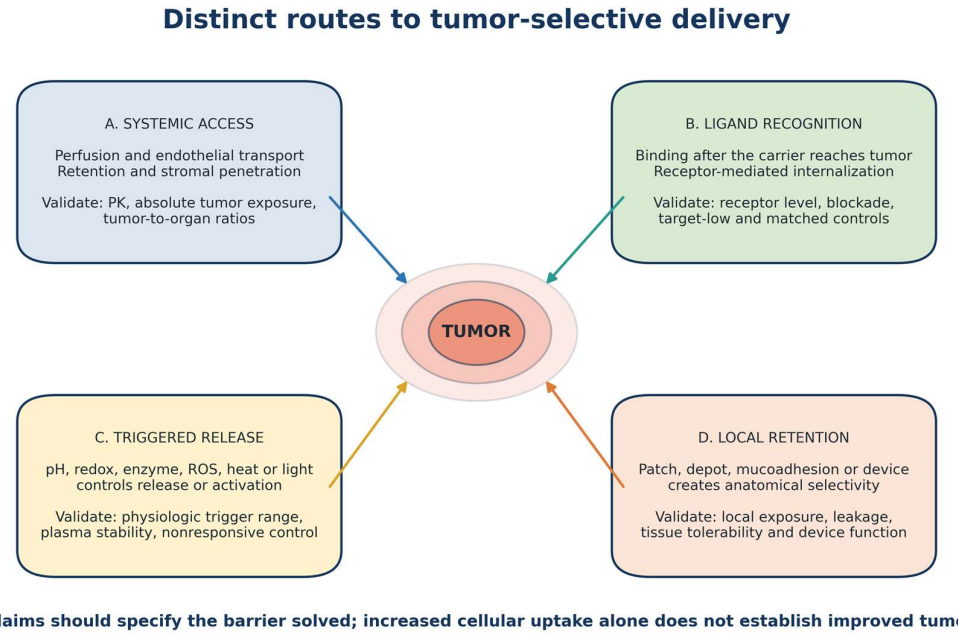

Figure 2. Distinct routes to tumor-selective delivery. Systemic access, ligand recognition, triggered release, and local retention solve different transport barriers and therefore require different validation experiments.

[[TABLE 2: table_02.csv]]

Passive tumor access is governed by circulation, perfusion, endothelial transport, retention, stromal penetration, and clearance. It cannot be inferred from a particle diameter between 50 and 200 nm. Nanoparticle delivery to solid tumors is generally low and heterogeneous, and active transendothelial transport may contribute alongside vascular discontinuity [4,5,25]. Appropriate evidence includes plasma pharmacokinetics, absolute tumor concentration, tumor-to-blood and tumor-to-organ ratios, and spatial distribution within viable tumor regions.

Ligand-mediated targeting usually acts after the carrier has reached the tumor. A ligand may increase cell binding and internalization without increasing total tumor accumulation. Receptor expression, receptor-low or receptor-negative controls, competitive inhibition or blockade, and a non-targeted particle matched for size, charge, cargo, and dose are therefore essential. Without these controls, higher uptake may arise from charge,

aggregation, or protein-corona differences rather than ligand specificity.

Stimulus-responsive designs add temporal control through pH, redox state, enzymes, reactive oxygen species, heat, magnetic fields, or light. Reviews describe extensive smart chitosan systems [12,26], but release is often tested under extreme buffer conditions that do not represent plasma or the intended intracellular compartment. A defensible claim requires stability before reaching the target, a physiologically justified trigger range, a matched nonresponsive control, and evidence that responsiveness improves in-vivo therapeutic index.

Local and regional delivery may be especially compatible with chitosan. Mucoadhesive patches, intratumoral depots, inhaled systems, and device-assisted buccal administration can bypass the low probability of systemic tumor deposition. Their selectivity arises principally from anatomy, residence time, and controlled regional penetration rather than receptor recognition. This distinction is not semantic: it clarifies the mechanism of advantage and the safety endpoints that must be measured.

3.4 Therapeutic cargos and multifunctional combinations

Small-molecule chemotherapy remains the largest application category. Chitosan nanoparticles have been used to improve solubility, stability, local concentration, and release of doxorubicin, cisplatin, 5-fluorouracil, erlotinib, curcumin, auranofin, and related agents. A raloxifene-functionalized system combined doxorubicin loading with a breast-cancer targeting concept [27]. More recent examples include nicotinic-acid-modified chitosan particles carrying resveratrol [28] and ionic-gelation nanoparticles containing 5-fluorouracil [29]. These in-vitro studies show formulation feasibility but do not establish site-specific delivery. Sustained release or higher cytotoxicity should be separated from targeting unless a spatial determinant and in-vivo distribution evidence are present.

Nucleic-acid delivery exploits electrostatic condensation by protonated chitosan. Modern strategies include plasmid DNA, siRNA, microRNA, and CRISPR-associated constructs [30]. A folate- and pH-responsive trimethyl-chitosan platform co-delivered doxorubicin with survivin-directed CRISPR/Cas9 or RNA-interference plasmids [31], while a miR-340 chitosan formulation was evaluated in 4T1 breast-cancer cells [32]. The major bottlenecks are serum stability, nuclease protection, endosomal escape, controlled unpacking, transfection efficiency, off-target gene effects, and the combined CMC burden of carrier plus genetic payload.

Energy-activated and hybrid systems broaden the mechanism spectrum. Indocyanine-green-loaded chitosan–polysaccharide nanoparticles produced photothermal tumor control and immune activation in a syngeneic CT26 model [33]. Chitosan–bimetallic constructs have been used to deliver 5-fluorouracil [34], and metformin-loaded chitosan nanoparticles were combined with silver nanoparticles and radiation in breast-cancer cells and spheroids [35]. Multifunctionality can be valuable, but component-specific controls and formal interaction analyses are required to distinguish synergy from additive toxicity caused by light, radiation, metal ions, or the free cargo.

Immunomodulatory work represents a substantive recent shift. Chitosan nanoparticles carrying siRNAs against BATF and PRDM1 were investigated for regulatory T-cell modulation in prostate cancer [36]. Chitosan-coated poly(lactic acid)/poloxamer nanoparticles were designed to promote immunogenic cancer-cell death and combined chemo-immunotherapeutic activity [37]. A DEC-205-binding peptide–chitosan oral vaccine promoted Peyer's-patch uptake, dendritic-cell maturation, cross-presentation, and antitumor activity in a B16-OVA model [38]. These studies require immunocompetent models, longitudinal immune phenotyping, cytokine and organ-safety assessment, and controls that separate cargo-specific effects from intrinsic chitosan immunostimulation.

Other mechanistic directions include redox-active drug repurposing and tumor-surface recognition. Auranofin-loaded chitosan nanoparticles showed potency in triple-negative breast-cancer models [39], while core–shell chitosan particles targeting membrane-bound heat-shock protein 70 illustrate coupling of particle architecture to tumor-surface biology [40]. Their translational significance depends on whether the carrier improves target exposure at an equivalent systemic dose, not simply whether the final formulation is more cytotoxic.

3.5 Mechanisms of anticancer action

The anticancer mechanism of a chitosan nanoparticle is a sequence rather than a single downstream marker. It begins with exposure in blood, mucus, or a local tissue compartment; proceeds through transport, retention, cell interaction, uptake, and intracellular trafficking; and culminates in cargo release, target engagement, and cell or immune responses. The mechanistic sequence linking nanoparticle exposure to anticancer response is illustrated in Figure 3.

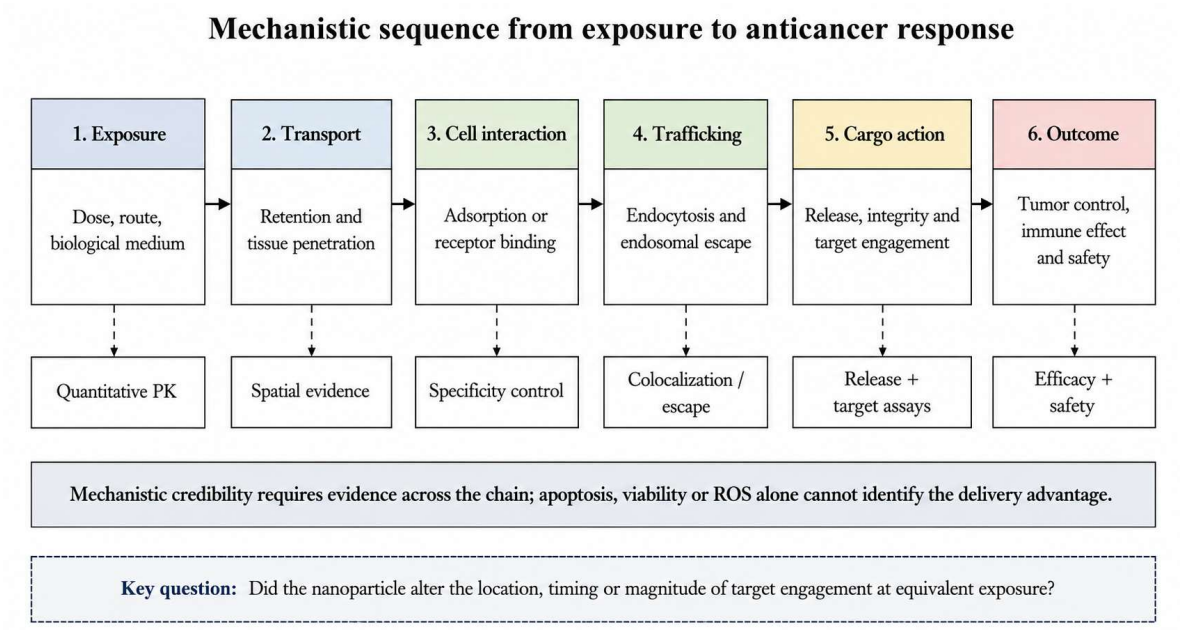

Figure 3. Mechanistic sequence from nanoparticle exposure to anticancer response. Mechanistic credibility requires linked evidence for transport, cell interaction, intracellular trafficking, cargo action, target engagement, efficacy, and safety.

Cationic chitosan can increase adsorptive membrane interaction, whereas ligands can bias internalization toward receptor-mediated routes. Nucleic-acid delivery additionally requires endosomal escape and controlled unpacking. Chitosan's buffering behavior is pH-dependent and generally weaker than that of highly protonatable synthetic polycations; chemical modification, membrane-active components, or stimulus-responsive destabilization may therefore be needed. Cytosolic fluorescence alone is not proof of intact cargo delivery unless degradation products and endosomal colocalization are excluded.

Downstream effects are cargo-specific. Doxorubicin and cisplatin cause DNA damage; erlotinib inhibits epidermal-growth-factor-receptor signaling; auranofin disrupts thioredoxin-reductase-dependent redox control; photosensitizers generate heat or reactive oxygen species; and RNA cargos alter gene expression. Viability loss, apoptosis, or increased reactive oxygen species are outcomes, not complete mechanisms. Strong causal evidence includes release-location measurements, target engagement, pathway inhibition or rescue, receptor blockade, and efficacy at exposure-matched doses.

Photothermal and photodynamic systems can cause local cytotoxicity and immune effects. Translation requires calibrated light dose, tissue penetration, thermal or reactive-oxygen-species mapping, and controls for light, free photosensitizer, blank carrier, and individual components.

3.6 Representative recent evidence and cross-study patterns

Representative studies and the principal limitations that constrain their interpretation are summarized in Table 3. The table is deliberately analytical: it places the reported advance beside the missing evidence needed to support a stronger therapeutic or translational claim.

Table 3. Representative chitosan nanoparticle studies in cancer therapy (2020–2026) and their principal interpretive limitations.

Study	Formulation and model	Principal advance	Evidence stage	Critical limitation
Mohammadi et al., 2020 [27]	Raloxifene-functionalized doxorubicin chitosan nanoparticles; breast-cancer cell models.	Combined carrier-mediated and raloxifene-associated targeting concept.	In vitro	Requires receptor-specific controls, in-vivo exposure, and safety comparison.
Saravanakumar et al., 2020 [18]	AS1411-decorated pH-responsive erlotinib chitosan nanoparticles; A549/NSCLC models.	Nucleolin-directed uptake with stimulus-responsive release.	Predominantly in vitro	Systemic biodistribution and rigorous target blockade remain necessary.
Li et al., 2022 [31]	Folate/pH-responsive trimethyl chitosan co-delivering doxorubicin and survivin CRISPR/RNAi plasmid; cell and tumor models.	Combined chemotherapy and gene suppression.	In vitro and in vivo	Editing specificity, durability, immunogenicity, and complex CMC remain unresolved.
Peng et al., 2022 [21]	Stepwise responsive carboxymethyl chitosan; drug-resistant breast-cancer models.	Designed to improve uptake/release and suppress resistant disease.	Preclinical	Trigger specificity, PK, and heterogeneous clinical resistance require broader validation.
Goldberg et al., 2022 [24]	PRV111 topical cisplatin-loaded chitosan particle patch; animals and resectable oral cancer.	High local retention, low systemic exposure, and short-term clinical response.	Phase I/II, single arm	Ten enrolled/eight evaluable; no comparator and only six-month follow-up.
Lv et al., 2024 [17]	Folate-modified carboxymethyl chitosan combination system; breast-cancer models.	Combination therapy linked to mitochondrial calcium regulation.	Preclinical	Complex causal mechanism needs exposure-matched controls and independent validation.
Mushtaq et al., 2024 [19]	Alendronate–PEG–chitosan carrying cell-death siRNA or curcumin; MCF-7 and hydroxyapatite assays.	Bone-affinity concept with therapeutic cargo.	In vitro	No lesion-level biodistribution or in-vivo bone-metastasis efficacy.
Afrifa et al., 2024 [39]	Auranofin-loaded chitosan nanoparticles; triple-negative breast-cancer models.	Delivery of a redox-active repurposed drug.	Preclinical	Comparative PK, long-term toxicity, and exposure-matched benefit are needed.
Ryu et al., 2024 [33]	ICG-loaded Codium polysaccharide/chitosan nanoparticles; CT26 syngeneic tumors and rechallenge.	Photothermal control with dendritic-cell and cytotoxic-T-cell activation.	Immunocompetent in vivo	Light penetration, thermal dosimetry, and scale-up constrain generalization.
Chen et al., 2024 [23]	Iontophoretic buccal cisplatin-loaded chitosan nanoparticles; mouse oral cancer.	Device-enhanced local delivery and efficacy.	In vivo	Device parameters, mucosal safety, and standard-treatment comparison need extension.
Dong et al., 2025 [20]	M2pep–chitosan–curcumin nanoparticles plus anti-PD-L1; 4T1 TNBC.	TAM repolarization and improved checkpoint response.	In vitro and syngeneic in vivo	Immune-cell PK, independent replication, and chitosan-specific immune contribution are unresolved.
Zhao et al., 2025 [36]	Chitosan nanoparticles carrying si-BATF/PRDM1; prostate-cancer immune models.	Regulatory T-cell modulation by dual gene silencing.	Preclinical	Cell-specific delivery, systemic immune effects, and off-target silencing require deeper study.
Lee et al., 2025 [37]	Chitosan-coated PLA/poloxamer chemo-immunotherapy nanoparticles; cell and tumor models.	Immunogenic cell death and combined chemo-immunotherapeutic activity.	Preclinical	Component-specific causality, quantitative PK, and reproducible immune safety require definition.
Wang et al., 2026 [38]	DEC-205-binding peptide–chitosan oral vaccine; Peyer's-patch/DC studies and B16-OVA.	Mucosal uptake, cross-presentation, STING-associated activation, and tumor prevention.	Immunocompetent in vivo	Model-antigen and prophylactic design limit inference to established human tumors.
Şentürk et al., 2026 [28]	Nicotinic-acid-modified chitosan carrying resveratrol; HeLa cells.	Improved delivery and anticancer activity with low blank-particle toxicity.	In vitro	No in-vivo exposure, target validation, or comparative safety.
Ekpo et al., 2026 [29]	Ionic-gelation chitosan nanoparticles carrying 5-fluorouracil; MCF-7 cells.	Sustained release and time-dependent cytotoxicity.	In vitro	No targeting ligand, normal-cell testing, PK, or in-vivo validation; low encapsulation efficiency.

[[TABLE 3: table_03.csv]]

Four cross-study patterns are evident. First, breast-cancer models dominate, particularly MCF-7, MDA-MB-231, and 4T1 systems. This concentration facilitates methodological familiarity but limits disease generalizability. Second, many ligand-bearing systems remain at the in-vitro stage; chemical plausibility is commonly stronger than evidence of whole-animal target engagement. Third, immunotherapy and photoimmunotherapy gain biological relevance when evaluated in syngeneic models, yet they also become more sensitive to the intrinsic immunological effects of chitosan. Fourth, local oral-cancer delivery has progressed further clinically than systemic chitosan nanomedicine, suggesting that anatomical retention may be a more tractable translational advantage than increasingly complex systemic targeting.

The strongest preclinical studies use controls that reflect the stated mechanism. Combination gene–drug platforms should compare each single component, the combination, blank particles, and a matched non-targeted carrier. Stimulus-responsive systems require a nonresponsive analogue. Receptor-directed systems require blockade and target-low models. Immune platforms require syngeneic disease, cell-specific

exposure, and evaluation of systemic immune perturbation. Without these controls, an apparent formulation advantage cannot be assigned confidently to the proposed mechanism.

3.7 Clinical perspectives

Clinical translation of chitosan nanoparticles remains limited compared with the volume of preclinical literature. This is consistent with the broader nanomedicine field, in which clinically established products more often use manufacturing platforms with mature analytical and pharmacokinetic precedents [41,42]. Chitosan introduces additional variation in source, molecular-weight distribution, deacetylation, protein and endotoxin contamination, pH-dependent solubility, and sterilization response. Each derivative and hybrid interface may require product-specific safety and CMC justification.

The most developed peer-reviewed human evidence identified is PRV111, a topical transmucosal cisplatin system for accessible oral tumors. In the published phase I/II open-label, single-arm study (NCT03502148), 10 participants were enrolled and eight were evaluable. The report described high local retention, low systemic platinum exposure, a mean tumor-volume reduction of approximately 69% over about seven days, and no dose-limiting toxicity; however, the cohort was small, nonrandomized, and followed for only six months [24,43]. These findings establish feasibility and local pharmacological proof of concept, not comparative effectiveness or durable survival benefit.

A later open-label program evaluating PRV111 and the intraoperative PRV211 system is registered as NCT05893888 [44]. A February 2026 oncology report based on sponsor-provided information described no treatment-related serious adverse events, systemic toxicities, dose-limiting toxicities, or wound-healing complications among the first eight PRV211 recipients, with negligible systemic platinum exposure [45]. Because those observations were not peer-reviewed and recurrence follow-up was immature, they should be interpreted as preliminary safety and pharmacokinetic signals rather than efficacy evidence.

The clinical lesson is route-specific. A topical neoadjuvant product must deliver a reproducible dose across irregular tumor surfaces without compromising subsequent surgery. An intraoperative product must be compatible with hemostasis and wound healing and must demonstrate a clinically meaningful reduction in locoregional recurrence. A systemic formulation must additionally justify circulation, organ exposure, immune effects, and comparative benefit over established therapies. Clinical endpoints should therefore progress from local pharmacology to pathological response, function, quality of life, recurrence, event-free survival, and overall survival according to the product's intended role.

3.8 Translational readiness

The translational evidence gaps and minimum development requirements are summarized in Table 4. A stage-gated roadmap for clinical translation is presented in Figure 4.

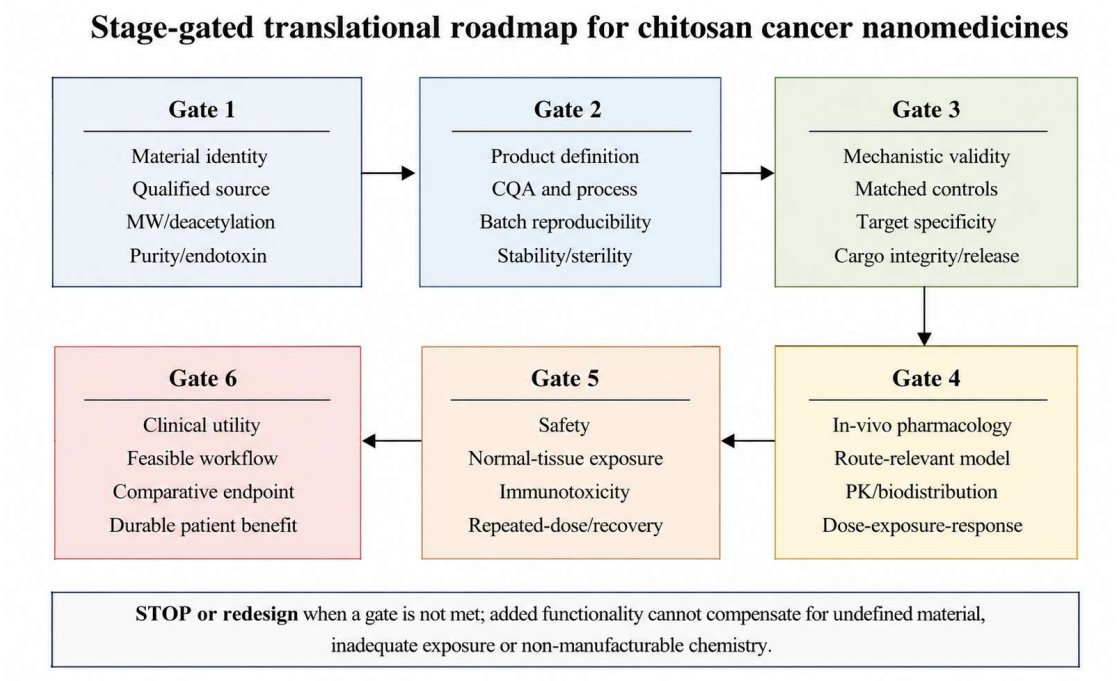

Figure 4. Stage-gated translational roadmap for chitosan-based cancer nanomedicines. Product development should stop or be redesigned when material identity, reproducible manufacture, mechanistic validity, pharmacology, safety, or clinical utility is not demonstrated.

Table 4. Translational evidence gaps and minimum development requirements for chitosan cancer nanomedicines.

Translational domain	Current pattern	Key gap	Minimum next-step requirement
Material identity	Commercial grade is often reported without full molecular-weight distribution, deacetylation, substitution, protein, metal, or endotoxin content.	Poor interlaboratory comparability.	Qualified raw-material specifications, orthogonal chemistry, and lot acceptance criteria.
Formulation and CMC	Laboratory ionic gelation and self-assembly are common; scale-up data are rare.	Mixing and purification can change size, loading, and release.	Critical process parameters, in-process controls, mass balance, batch reproducibility, and scalable purification.
Stability and sterility	Short-term colloidal stability is often measured in water or buffer.	Shelf life, reconstitution, sterile manufacture, and endotoxin control are weakly integrated.	Stability-indicating assays, container compatibility, sterility strategy, endotoxin limits, and shipping studies.
Targeting validity	Uptake differences in receptor-positive cells are commonly reported.	Blocking, target-low models, exposure-matched controls, and cell-specific in-vivo exposure are often absent.	Causal target validation and quantitative biodistribution.
PK and biodistribution	Strongest for selected local platforms; limited for many systemic constructs.	Fluorescence often substitutes for absolute drug and carrier measurement.	Blood, tumor, and organ concentrations; clearance; tumor-to-organ ratios; carrier–cargo concordance.
Safety and immunology	Body weight and terminal organ histology are frequent endpoints.	Complement, cytokines, hematology, coagulation, degradation products, and repeated-dose recovery are underexamined.	Route-appropriate toxicology, immunotoxicity, normal-tissue exposure, and recovery assessment.
Human evidence	PRV111 demonstrates early local pharmacology and feasibility [24].	Small nonrandomized cohort with short follow-up.	Controlled evidence with durable local control, function, quality of life, recurrence, and survival.
Ongoing development	NCT05893888 evaluates PRV111/PRV211; early PRV211 observations were reported outside peer review [44,45].	No mature peer-reviewed comparative efficacy or recurrence results.	Prospective publication of prespecified endpoints, mature safety, recurrence, quality of life, and effect estimates.

[[TABLE 4: table_04.csv]]

A credible development program must connect product attributes to biological performance. Smart nanomedicine concepts are valuable only when added features solve a defined barrier [46]. Industry experience shows that excessive complexity, weak comparators, scale-dependent processes, and uncertain differentiation from standard care frequently derail anticancer nanomedicines [47]. Chitosan systems also require deliberate immunological assessment because cationic and particulate materials can affect complement, cytokines, coagulation, and mononuclear-phagocyte uptake [48]. Lessons from the National Cancer Institute Nanotechnology Characterization Laboratory emphasize orthogonal physicochemical measurement, sterility and endotoxin control, and fit-for-purpose biological assays [49]. Regulatory guidance likewise expects product-specific characterization and a justified relationship between nanomaterial attributes, manufacture, and clinical performance [50].

These requirements favor a stage-gated strategy. Raw-material identity and critical quality attributes should be fixed before extensive efficacy optimization; formulation and purification should be scalable before additional ligands are added; mechanistic specificity should be demonstrated before broad animal testing; and pharmacokinetics, biodistribution, and safety should precede claims of clinical readiness. A formulation should be redesigned when it fails a gate rather than compensated with another functional component.

4. DISCUSSION

4.1 Principal interpretation

The contemporary chitosan literature demonstrates real scientific expansion, but not equivalent translational maturation. Modern platforms combine receptor ligands, environmental triggers, nucleic acids, photosensitizers, metals, immune-cell targeting, and checkpoint therapy. This breadth is enabled by chitosan chemistry and is scientifically important. The central synthesis, however, is that functional sophistication has advanced faster than evidence linking formulation design to exposure, mechanism, safety, and manufacture. The field's limiting problem is no longer the ability to construct a multifunctional carrier; it is the ability to prove that each feature produces a clinically relevant, reproducible advantage.

4.2 A barrier-specific definition of targeting

The term targeting should be decomposed into access to the tumor, penetration through tumor tissue, recognition of the intended cell population, internalization, and release at the relevant subcellular site. Passive access, ligand binding, trigger-responsive release, and anatomical retention are not interchangeable. This distinction resolves a recurrent interpretive error: higher uptake in a receptor-positive monolayer can demonstrate cell interaction, but it cannot establish increased whole-tumor delivery. Likewise, a locally applied patch may produce greater clinical selectivity than a ligand-decorated systemic particle even though it lacks molecular recognition. A Q1-level evidence standard should therefore require investigators to name the barrier being solved and select experiments that isolate that barrier [4,5,25].

4.3 Mechanistic causality and model relevance

Mechanistic claims should explain why the nanoparticle is superior to free cargo and to a physicochemically matched

carrier. Downstream apoptosis, oxidative stress, or tumor-volume reduction does not establish whether the advantage arose from altered uptake, release, target engagement, immune activation, or simply a higher effective dose. Causal studies should include rescue or inhibition where feasible and should quantify intact cargo at the relevant compartment. The model hierarchy should also reflect the intended clinical mechanism. Two-dimensional culture is appropriate for screening but omits protein corona, tissue transport, clearance, and immune effects. Spheroids, organoids, microfluidic models, orthotopic tumors, metastatic models, patient-derived systems, and syngeneic models each address specific uncertainties; no single model is universally superior. Model choice should be justified prospectively by route, barrier, and therapeutic mechanism.

4.4 Why local and regional delivery may translate first

The PRV111 experience suggests that chitosan may provide its clearest near-term value in accessible anatomical compartments. Mucoadhesion, local retention, and controlled release can be directly aligned with a clinical delivery problem and can reduce dependence on heterogeneous systemic tumor accumulation. This does not imply that systemic chitosan nanomedicine is unpromising. Rather, systemic programs must solve circulation stability, organ sequestration, carrier–cargo concordance, and repeat-dose immunology before receptor ligands or multiple triggers can be meaningfully evaluated. Development should begin with the clinical route and failure mode, not with the maximum number of functions that can be incorporated.

4.5 Manufacturing and regulatory implications

Chitosan source, molecular-weight distribution, degree of deacetylation, derivative substitution, purity, and endotoxin should be treated as critical quality attributes. Process parameters such as mixing order, shear, addition rate, pH, purification, and sterilization can alter size distribution, loading, and release. These relationships should be expressed through a quality target product profile and risk-based control strategy, not added retrospectively after efficacy studies. Hybrid formulations require separate control of each component, interface, degradation product, and release pathway. An efficacious laboratory batch is not a viable product if its material identity cannot be qualified or its manufacture cannot be scaled [47,49,50].

4.6 Clinical interpretation

PRV111 provides proof that local chitosan-based cisplatin delivery can achieve high regional exposure with limited systemic platinum in a small oral-cancer cohort [24]. It does not validate chitosan nanoparticles as a class, nor does it establish comparative efficacy. The subsequent PRV211 observations are encouraging for feasibility but remain vulnerable to selective reporting until prespecified peer-reviewed outcomes mature [44,45]. Future trials should incorporate clinically interpretable comparators, pathological and functional endpoints, patient-reported outcomes, wound-healing assessments where relevant, and sufficiently long follow-up for recurrence and survival. The correct translational claim at present is early clinical feasibility for a local platform, not broad clinical validation of chitosan nanotherapy.

4.7 Implications for research design

A rational development sequence is therefore clinical-problem first, material second, and added functionality third. Investigators should define the intended route, target compartment, dominant transport barrier, minimum clinically meaningful advantage, and product constraints before selecting a chitosan derivative. Each ligand, trigger, or combination component should have a prespecified contribution that can be isolated experimentally. This approach favors simpler formulations when they solve the same problem and directs complex systems toward indications in which their extra functionality is indispensable.

5. LIMITATIONS

This review has methodological and evidence-level limitations. The search was structured and updated to 20 June 2026 but was not a prospectively registered systematic review; omission and selection bias therefore remain possible. Google Scholar was used for citation chasing rather than reproducible denominator-based screening, and the representative study table was purposive rather than exhaustive. The included literature was too heterogeneous for quantitative pooling, and incomplete reporting of chitosan identity, colloidal behavior, pharmacokinetics, and normal-tissue safety restricted cross-study comparison. Publication bias probably favors positive efficacy and underrepresents failed scale-up, unstable formulations, and null targeting studies. Clinical-trial status and non-peer-reviewed interim reports may change after the search date and should be rechecked immediately before submission. Finally, the critical appraisal used reporting and translational domains rather than a validated single risk-of-bias tool applicable across cell, animal, material, and clinical studies.

6. FUTURE DIRECTIONS

Future work should establish reference materials and reporting standards for chitosan source, molecular-weight distribution, deacetylation, substitution, protein contamination, metals, endotoxin, and degradation products. Interlaboratory studies using shared formulations would help distinguish true structure–property relationships from batch and method effects.

Targeting research should progress from receptor expression and blockade to quantitative cell-specific biodistribution and exposure-matched efficacy. Spatial methods that distinguish carrier from released cargo, together with pharmacokinetic–pharmacodynamic modelling, are needed to identify where the therapeutic advantage is generated. For systemic formulations, absolute tissue concentrations should replace fluorescence intensity as the principal exposure metric whenever feasible.

Mechanistic programs should integrate route-relevant three-dimensional and animal models, cargo-integrity assays, endosomal-escape measurements, target engagement, and rescue experiments. Immunomodulatory systems require longitudinal immune phenotyping, immunocompetent disease models, and assessment of complement, cytokines, coagulation, and repeated-dose effects. Gene-editing systems require off-target analysis, duration of expression, germline-exposure assessment where applicable, and a manufacturing strategy that controls both vector and nucleic-acid quality.

Clinical translation should prioritize indications in which chitosan's properties solve a specific unmet delivery problem. Local mucosal, intratumoral, inhaled, and post-resection applications may offer clearer exposure control than broad systemic targeting. Early development should integrate scalable mixing and purification, sterilization, stability-indicating assays, container compatibility, and clinically feasible administration. Comparative trials should then test durable local control, function, quality of life, recurrence, and survival rather than relying exclusively on short-term tumor shrinkage.

7. CONCLUSION

Chitosan nanoparticles have evolved from simple drug carriers into platforms for receptor-directed uptake, stimulus-responsive release, nucleic-acid delivery, phototherapy, radiosensitization, and immune modulation. Their scientific value derives from chemical and route-specific adaptability; their principal translational risk is the same adaptability when polymer identity, mechanism, and manufacturing controls are undefined. The most credible systems are not necessarily the most complex. They are those that use a qualified chitosan material to solve a defined transport problem, validate targeting causally, demonstrate intact cargo delivery and target engagement, quantify pharmacokinetics and safety, and remain reproducible at scale. Human evidence is still limited. PRV111 supports early feasibility of localized chitosan-based cisplatin delivery in oral cancer, whereas durable comparative benefit and later PRV211 outcomes remain

unproven. Progress should therefore be judged by integrated design, exposure, mechanism, safety, and manufacturability rather than by multifunctionality alone.

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