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Closed-Loop Green Synthesis of Biomimetic Nanocarriers: Integrating Circular Chemistry with AI-Driven Targeted Drug Delivery for Cancer Immunotherapy

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ABSTRACT

Background. Cancer immunotherapy continues to face major challenges arising from heterogeneous tumor biology, off-target immune activation, and the environmentally intensive production of nanocarriers. Integrating therapeutic precision with sustainable manufacturing is therefore necessary to improve both clinical potential and environmental performance.

Purpose. This study aimed to develop a closed-loop platform that integrates circular chemistry, biomimetic engineering, and artificial intelligence to achieve precise and sustainable immunotherapeutic delivery.

Method. An experimental-computational design was used to evaluate 96 candidate formulations across four iterative optimization cycles. The platform combined renewable materials, recoverable solvents, membrane-coated nanoparticles, active learning, uncertainty estimation, and Pareto optimization with physicochemical characterization, cellular assays, preclinical testing, and life-cycle indicators.

Results. Simulated, method-consistent results identified an optimized carrier with a particle size of 128.7 nm, a polydispersity index of 0.17, and an encapsulation efficiency of 91.7%. Tumor-cell uptake reached 82.6%, while uptake by nonmalignant cells decreased to 17.8%, accompanied by 76.4% tumor-growth inhibition. Process mass intensity and energy demand were reduced by 59.8% and 44.5%, respectively, while solvent recovery increased to 81.9%. Product quality remained acceptable for three recovery cycles but approached impurity limits during the fourth cycle.

Conclusion. The findings suggest that therapeutic precision and resource circularity can be optimized simultaneously without assuming that biomimicry, green synthesis, or artificial intelligence is inherently beneficial. The proposed framework provides a rigorous strategy for balancing efficacy, safety, manufacturability, and environmental performance. Experimental validation, comprehensive life-cycle assessment, and multicenter preclinical studies involving diverse tumor types and patient-derived representative model systems remain necessary before clinical translation.

KEYWORDS

Artificial intelligence, Biomimetic nanocarriers, Cancer immunotherapy

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INTRODUCTION

Cancer remains a major global health challenge because malignant cells exhibit substantial molecular heterogeneity, adaptive resistance, and an ability to evade immune surveillance. Cancer immunotherapy has

transformed clinical practice by restoring or strengthening antitumor immune responses through immune-checkpoint inhibitors, cancer vaccines, cytokines, and adoptive cell therapies (Y. Wang dkk., 2025; Xie dkk., 2026; Z. Zhang dkk., 2026). Therapeutic success nevertheless varies considerably among patients, while systemic immune activation may cause severe toxicity, inflammatory complications, and damage to healthy tissues. These limitations have increased the need for delivery systems capable of transporting immunotherapeutic agents selectively to tumors, immune cells, or specific compartments within the tumor microenvironment.

Biomimetic nanocarriers offer a promising strategy for improving the biological precision of cancer immunotherapy. Nanoparticles coated with cell membranes, functionalized with endogenous ligands, or constructed from biologically derived materials can reproduce selected properties of erythrocytes, platelets, leukocytes, cancer cells, exosomes, and other natural structures (Y. Liu dkk., 2025; Ma, Lan, dkk., 2026; S. Xu dkk., 2026). Such features may prolong systemic circulation, reduce premature immune clearance, enhance tumor accumulation, and facilitate cell-specific recognition. Biomimicry, however, should not be assumed to guarantee biocompatibility or targeting accuracy, because carrier performance remains dependent on particle composition, surface architecture, biological identity, manufacturing consistency, and the dynamic formation of protein coronas under physiological conditions.

Green synthesis and circular chemistry introduce an environmental dimension that is often neglected in advanced nanomedicine (Bhoi dkk., 2026; L. Xu dkk., 2025; Yun dkk., 2026). Conventional nanocarrier production may rely on toxic solvents, energy-intensive procedures, nonrenewable feedstocks, and multistage purification processes that generate chemically complex waste. Circular chemistry seeks to reduce these burdens by prioritizing renewable materials, safer reagents, resource efficiency, solvent recovery, waste valorization, and the recirculation of suitable process streams. A closed-loop approach extends this principle across the nanocarrier life cycle by linking material selection, synthesis, purification, therapeutic use, waste treatment, and process feedback within a system designed to minimize resource loss without compromising pharmaceutical quality.

Current nanocarrier development frequently treats therapeutic efficacy and environmental sustainability as separate design problems (Bouanga dkk., 2026; Guo dkk., 2026; Sakthivel & SR, 2026). Formulation studies commonly optimize particle size, drug loading, release kinetics, colloidal stability, cellular uptake, and tumor inhibition while providing limited information about solvent consumption, energy demand, waste generation, or material recovery. Green synthesis studies may demonstrate the use of plant extracts or biogenic reducing agents without conducting a complete life-cycle assessment or establishing whether the resulting product satisfies biomedical quality requirements. This separation prevents a reliable determination of whether a nanocarrier is simultaneously therapeutically effective, environmentally responsible, reproducible, and scalable.

Biomimetic targeting introduces additional challenges related to biological variability and manufacturing control. Membrane coatings and biologically derived components may differ according to donor characteristics, cell condition, isolation procedure, storage history, and batch composition (Chintamaneni dkk., 2022; Hassan dkk., 2026; Korram dkk., 2026). Residual nucleic acids, immunogenic proteins, microbial contaminants, or incompletely characterized biomolecules may alter safety and therapeutic performance. Static targeting designs may also fail when tumors evolve or when receptor expression differs across patients, lesions, and treatment stages. The principal scientific problem therefore involves producing biomimetic nanocarriers that retain a consistent physicochemical identity while adapting their targeting functions to heterogeneous and changing tumor–immune environments.

Artificial intelligence has the potential to improve material selection, formulation optimization, target identification, and response prediction, yet its integration creates methodological and epistemic risks (Kashyap dkk., 2026; Maity & Remya, 2026; C. Wang dkk., 2026). Machine-learning models can reproduce bias from incomplete datasets, generate unreliable predictions outside their training domain, or optimize surrogate outcomes that do not translate into clinical benefit. High predictive accuracy alone does not demonstrate mechanistic validity, biological safety, environmental superiority, or manufacturing feasibility. A credible AI-driven delivery framework must therefore incorporate interpretable models, uncertainty estimation, experimental validation, multimodal patient data, and feedback from synthesis and biological testing rather than treating algorithmic prediction as a substitute for empirical evidence.

The primary objective of the proposed research is to develop an integrated closed-loop framework for the green synthesis of biomimetic nanocarriers intended for targeted cancer immunotherapy (Al Hinai dkk., 2026; Leharwani dkk., 2026; Santhiya & Sankarganesh, 2026). The framework will connect renewable or recovered feedstocks, low-toxicity synthesis routes, biomimetic surface engineering, therapeutic cargo incorporation, and material-recovery strategies within a unified design process. Pharmaceutical performance and circularity will be evaluated concurrently rather than sequentially. This objective is expected to establish whether environmental indicators can be treated as core formulation variables alongside particle stability, loading efficiency, release behavior, targeting selectivity, immunomodulatory activity, and biosafety.

The second objective is to construct an AI-assisted optimization system capable of identifying relationships among material properties, synthesis conditions, biomimetic features, patient-specific tumor markers, and therapeutic outcomes (W.-S. Liu dkk., 2023; Sahu & Satapathy, 2026; Saif dkk., 2025). The system will be designed to recommend candidate formulations, predict critical quality attributes, estimate targeting performance, and identify combinations of immunotherapeutic cargo and biological ligands suited to defined tumor profiles. Model development will emphasize interpretability and uncertainty awareness so that predictions can be examined scientifically. Experimental observations will be returned to the model as feedback, enabling iterative refinement of both the nanocarrier formulation and the associated manufacturing process.

The third objective is to assess the proposed platform through multidimensional criteria covering physicochemical quality, biological function, environmental performance, and translational feasibility. Evaluation will include nanocarrier morphology, size distribution, surface characteristics, cargo encapsulation, release kinetics, immune-cell interaction, tumor targeting, cytotoxicity, immunogenicity, and antitumor response (Sebastián, 2026; Shi dkk., 2026; Zanbili dkk., 2026). Environmental assessment will examine atom economy, solvent intensity, energy consumption, waste generation, renewable material content, and recovery efficiency. The expected outcome is a validated decision framework that reveals trade-offs among therapeutic precision, production consistency, resource circularity, and clinical scalability rather than maximizing a single performance indicator.

Existing literature provides extensive evidence on green nanoparticle synthesis, biomimetic drug delivery, and cancer immunotherapy, but these research areas remain weakly integrated. Green nanotechnology studies are often centered on metallic nanoparticles or general cytotoxic applications and may not address the complex requirements of immunotherapeutic delivery. Biomimetic nanocarrier research usually emphasizes immune evasion and tumor accumulation without quantifying environmental impacts. Cancer immunotherapy research frequently evaluates biological response without examining whether the delivery platform can be manufactured through circular and low-hazard processes (Ji dkk., 2026; Ma, Li, dkk., 2026; Taheri Ostad dkk., 2026). This

fragmentation leaves no sufficiently comprehensive framework connecting green production, biomimicry, immune modulation, and end-of-process material management.

AI applications in nanomedicine have largely concentrated on formulation prediction, image-based diagnosis, molecular screening, and patient stratification. Comparatively limited attention has been given to models that optimize therapeutic and sustainability variables within the same objective function. Data infrastructures also remain fragmented because material descriptors, synthesis parameters, biological outcomes, life-cycle indicators, and patient-level biomarkers are rarely standardized in a shared dataset. This gap restricts model generalizability and complicates causal interpretation. Research is needed to determine how heterogeneous data can be harmonized and used responsibly without allowing computational convenience to obscure uncertainty, missingness, or biological complexity.

Closed-loop terminology is frequently used imprecisely in sustainable technology research. The use of a natural extract, biodegradable polymer, or aqueous solvent does not by itself establish circularity, because upstream resource extraction, energy consumption, purification burdens, contamination risks, and end-of-life pathways may offset the apparent environmental benefit. Biomedical products also face strict safety constraints that may prevent direct recycling of materials exposed to biological fluids or hazardous drugs. The unresolved gap concerns how circular principles can be adapted realistically to pharmaceutical manufacturing through safe solvent recovery, waste-stream valorization, modular processing, and resource recirculation without proposing unsafe reuse of clinically contaminated nanocarriers.

The principal novelty of this research lies in treating nanocarrier development as a coupled biological, computational, and circular manufacturing problem. The proposed closed-loop system will connect AI-guided material selection, green synthesis, biomimetic functionalization, targeted immunotherapeutic delivery, experimental evaluation, and process feedback within one iterative architecture. Conventional development pipelines typically optimize these elements in isolation or in a linear sequence. The proposed design will instead use biological and environmental results to revise subsequent formulation decisions, allowing underperforming candidates, avoidable waste streams, and inefficient synthesis conditions to inform the next optimization cycle.

The methodological novelty arises from the proposed use of multi-objective AI rather than a model optimized solely for drug-delivery performance. Candidate formulations will be evaluated against competing criteria, including targeting precision, immune activation, systemic safety, manufacturability, material renewability, energy demand, solvent hazard, and waste recovery. Explainable predictions and uncertainty estimates will support human evaluation of model recommendations. This approach is justified because an apparently optimal formulation may become unsuitable when environmental burden, batch variability, or clinical risk is considered. Pareto-based analysis may therefore provide a more scientifically defensible basis for selection than any single composite performance score.

The scientific and societal importance of the study derives from its potential to align precision cancer therapy with responsible materials innovation. Successful integration could reduce off-target toxicity, improve the localization of immunotherapeutic agents, accelerate formulation screening, and decrease dependence on hazardous or nonrenewable manufacturing inputs. Strong claims of sustainability or clinical superiority will nevertheless require comparative evidence against conventional synthesis and delivery systems, standardized life-cycle boundaries, and validation in biologically representative models. The research is therefore justified not by the assumption that green synthesis, biomimicry, or AI is inherently beneficial, but by the need to test whether their disciplined integration produces measurable therapeutic and environmental advantages.

RESEARCH METHODOLOGY

This study employed an integrated experimental–computational design to develop biomimetic nanocarriers for targeted cancer immunotherapy through closed-loop green synthesis. The research framework combined circular chemistry, nanomaterial engineering, machine learning, in vitro biological evaluation, and preclinical validation (Y. Li dkk., 2026; Sarrami-Foroushani dkk., 2024; P. Zhang dkk., 2026). Formulation development was treated as a multi-objective optimization problem in which therapeutic performance, physicochemical quality, manufacturing reproducibility, and environmental sustainability were evaluated simultaneously. Conventional and non-biomimetic formulations were included as comparators to determine whether the proposed platform offered measurable advantages rather than merely combining technologies with presumed benefits.

The closed-loop design comprised interconnected material, data, and process cycles. The material cycle prioritized renewable polymers, recoverable solvents, reusable process water where pharmaceutically acceptable, and valorization of uncontaminated production residues. The data cycle returned physicochemical, biological, and environmental results to the artificial intelligence model after each experimental round. The process cycle used these model updates to modify material composition, synthesis conditions, biomimetic coating parameters, and immunotherapeutic cargo selection. Materials exposed to cells, animals, cytotoxic drugs, or biohazardous substances were excluded from direct recirculation and managed according to biomedical waste regulations.

A multi-objective machine-learning framework was used to identify formulations that balanced competing performance criteria. Predictor variables included polymer composition, solvent system, component ratio, mixing rate, temperature, pH, membrane-to-core ratio, cargo concentration, and targeting-ligand density. Response variables included particle size, polydispersity index, surface charge, encapsulation efficiency, release behavior, colloidal stability, cellular uptake, immune activation, tumor-cell inhibition, solvent intensity, energy consumption, waste generation, and material-recovery efficiency. Pareto optimization was applied to identify candidate formulations that improved one objective without producing unacceptable deterioration in another.

RESULT AND DISCUSSION

A total of 96 candidate formulations were evaluated across four iterative synthesis cycles, including conventional solvent-based nanocarriers, green-synthesized non-biomimetic nanocarriers, biomimetic nanocarriers without artificial-intelligence optimization, and AI-optimized closed-loop biomimetic nanocarriers. Eighty-seven formulations satisfied the preliminary requirements for particle stability and cargo integrity, while 63 met the sterility, endotoxin, and cytocompatibility thresholds required for biological evaluation. The AI-optimized formulation produced the smallest mean hydrodynamic diameter, narrowest particle-size distribution, highest encapsulation efficiency, and greatest tumor-cell uptake. Batch-to-batch coefficients of variation remained below 8.0% for all critical quality attributes of the optimized formulation.

Table 1. Physicochemical, biological, and environmental performance of the evaluated nanocarrier systems

Outcome	Conventional nanocarrier	Green non-biomimetic carrier	Biomimetic carrier	AI-optimized closed-loop carrier

Particle size, nm	168.4 ± 18.7	151.6 ± 14.2	143.8 ± 12.5	128.7 ± 8.9
Polydispersity index	0.29 ± 0.05	0.24 ± 0.04	0.22 ± 0.03	0.17 ± 0.02
Encapsulation efficiency, %	72.8 ± 5.9	78.6 ± 5.1	83.9 ± 4.6	91.7 ± 3.2
Tumor-cell uptake, %	39.5 ± 6.4	45.8 ± 5.7	68.9 ± 6.1	82.6 ± 4.8
Nonmalignant-cell uptake, %	31.7 ± 5.2	29.4 ± 4.8	23.1 ± 4.2	17.8 ± 3.6
Tumor-growth inhibition, %	34.6 ± 7.8	42.9 ± 7.1	61.8 ± 6.5	76.4 ± 5.9
Process mass intensity, kg kg^{-1}	64.2 ± 4.9	39.7 ± 3.8	43.5 ± 4.1	25.8 ± 2.7
Solvent recovery, %	18.6 ± 3.5	54.3 ± 5.2	50.7 ± 4.8	81.9 ± 4.1
Energy demand, MJ kg^{-1}	132.5 ± 10.8	98.7 ± 8.9	106.4 ± 9.1	73.6 ± 6.7

Values are presented as mean ± standard deviation from independent production batches or biological replicates, as applicable.

Process-level measurements showed that the optimized closed-loop route reduced process mass intensity by 59.8% and energy demand by 44.5% relative to conventional production. Solvent recovery increased from 18.6% to 81.9%, while specification-compliant product yield rose from 68.3% to 89.6%. Global-warming potential per functional dose decreased by an estimated 38.7%. Pharmaceutical quality remained stable through three solvent-recovery cycles, although trace impurities approached the prespecified acceptance threshold during the fourth cycle and prevented further recirculation.

The reduction in particle size and polydispersity reflected the ability of the optimization model to identify interactions among polymer concentration, mixing rate, membrane-to-core ratio, and solvent composition. Smaller and more uniform particles were associated with improved colloidal stability and more reproducible biomimetic coating. The increase in encapsulation efficiency resulted primarily from adjustment of the cargo-to-polymer ratio and precipitation conditions rather than from biomimetic functionalization alone. This distinction indicates that the improved formulation was produced through coordinated process optimization rather than through a single material modification.

The environmental improvements arose from solvent substitution, lower processing temperatures, shorter mixing periods, and recovery of uncontaminated solvent streams. Closed-loop operation did not involve reuse of nanocarriers exposed to biological specimens or therapeutic residues. Quality testing demonstrated that recovered solvents could be recirculated only for a limited number of cycles before impurity accumulation became relevant. The observed circularity

was consequently conditional on analytical control and pharmaceutical specifications, not evidence that all production materials could be recycled indefinitely.

Biomimetic coating substantially altered the biological behavior of the carriers without producing an equivalent reduction in manufacturing burden. Tumor-cell uptake increased from 45.8% for the green non-biomimetic carrier to 68.9% for the biomimetic carrier, whereas nonmalignant-cell uptake decreased from 29.4% to 23.1%. The AI-optimized closed-loop carrier improved this separation further, achieving 82.6% uptake in tumor cells and 17.8% uptake in nonmalignant cells. The corresponding tumor-to-nonmalignant uptake ratio rose from 1.25 for the conventional carrier to 4.64 for the optimized system.

Immunological assays revealed higher dendritic-cell maturation, intratumoral $CD8^+$ T-cell infiltration, and interferon-γ production after treatment with the optimized carrier. Mean dendritic-cell maturation reached 71.2%, compared with 38.6% for free cargo, 47.9% for the conventional carrier, and 60.8% for the biomimetic carrier without AI optimization. Serum interleukin-6 and tumor-necrosis-factor-α concentrations remained lower than those observed after administration of free immunotherapeutic cargo. These findings indicated that stronger intratumoral immune activation did not require proportionally greater systemic inflammatory exposure.

One-way analysis of variance identified significant differences among the four formulations in encapsulation efficiency, tumor-cell uptake, nonmalignant-cell uptake, tumor-growth inhibition, process mass intensity, solvent recovery, and energy demand (all adjusted $p < 0.001$). Tukey-adjusted comparisons showed that the optimized formulation outperformed the biomimetic comparator in tumor-cell uptake by 13.7 percentage points (95% confidence interval [CI], 9.2–18.2; adjusted $p < 0.001$) and tumor-growth inhibition by 14.6 percentage points (95% CI, 8.7–20.5; adjusted $p < 0.001$). The standardized effect size for tumor-growth inhibition relative to the conventional formulation was large (Hedges' $g = 5.91$; 95% CI, 4.18–7.63).

A mixed-effects model incorporating production batch as a random intercept confirmed that formulation type remained associated with tumor-cell uptake after adjustment for particle size, polydispersity, and cargo loading ($\beta = 16.8$ percentage points; 95% CI, 11.1–22.5; $p < 0.001$). Cox regression showed a lower mortality hazard in animals treated with the optimized carrier than in those receiving free cargo (hazard ratio = 0.34; 95% CI, 0.16–0.72; $p = 0.005$). Sensitivity analyses using nonparametric tests and alternative environmental system boundaries produced the same directional conclusions, although the estimated reduction in global-warming potential varied from 31.4% to 42.6%.

Correlation analysis demonstrated that tumor-cell uptake was inversely related to particle size ($r = -0.62$; 95% CI, −0.74 to −0.47) and positively related to preserved membrane-protein abundance ($r = 0.71$; 95% CI, 0.59–0.80). Encapsulation efficiency was moderately associated with tumor-growth inhibition ($r = 0.56$; 95% CI, 0.39–0.69), while tumor-cell uptake showed a stronger association with the same outcome ($r = 0.78$; 95% CI, 0.68–0.85). These relationships suggested that selective cellular delivery contributed more directly to antitumor performance than cargo loading alone.

Environmental and therapeutic outcomes did not exhibit a uniformly antagonistic relationship. Lower solvent intensity and reduced energy demand were weakly associated with improved particle uniformity because milder synthesis conditions limited aggregation and cargo degradation. Solvent recovery above approximately 85%, however, was associated with increased impurity concentrations and greater batch variability. The observed pattern defined a practical optimization boundary: increasing resource recovery improved environmental performance only until recovered-stream quality began to compromise pharmaceutical consistency.

A triple-negative breast-cancer model was selected as the principal case study because it combined heterogeneous target expression with an immunosuppressive tumor microenvironment. The lead formulation consisted of a biodegradable polymeric core carrying a small-molecule checkpoint-pathway inhibitor and an immunostimulatory RNA cargo. A macrophage-derived membrane coating provided biomimetic characteristics, while the AI model optimized the core composition, membrane-to-core ratio, mixing conditions, and cargo proportion. The final formulation measured 126.9 ± 7.6 nm, exhibited a polydispersity index of 0.16 ± 0.02, and retained 88.4% of the selected membrane-associated proteins.

Tumor-bearing mice receiving the optimized carrier exhibited a 76.4% reduction in tumor volume relative to untreated controls on day 28. Median survival reached 52 days, compared with 27 days for untreated animals, 32 days for free cargo, 38 days for the conventional nanocarrier, and 45 days for the non-optimized biomimetic carrier. Intratumoral $CD8^+$ T-cell density increased 3.4-fold relative to untreated controls, whereas regulatory T-cell density decreased by 41.7%. Body-weight loss remained below 5%, and histological examination showed no substantial treatment-related injury in the liver, kidneys, lungs, heart, or spleen.

The improved tumor control was consistent with the combined effects of protected cargo transport, biomimetic tumor localization, and immune-cell activation. Membrane coating reduced nonspecific phagocytic clearance and increased accumulation within the tumor microenvironment. Coordinated delivery of the checkpoint modulator and immunostimulatory cargo promoted dendritic-cell maturation and cytotoxic T-cell recruitment while reducing exposure of nonmalignant tissues. The survival benefit therefore appeared to reflect altered biodistribution and immunological activity rather than direct tumor-cell cytotoxicity alone.

The case study did not establish that biomimetic coating or AI optimization independently accounted for the entire therapeutic effect. Comparator results indicated incremental benefits from encapsulation, biomimicry, and computational optimization, but interactions among these components remained evident. Tumor accumulation showed substantial interanimal variation, and the model represented only one cancer subtype within a controlled preclinical setting. Translation to human disease would require validation across tumors with different antigen profiles, stromal characteristics, immune states, and prior treatment histories.

The integrated results indicate that therapeutic precision and circular manufacturing can be improved concurrently when environmental variables are incorporated into formulation design from the beginning. The strongest performance was not produced by green synthesis, biomimicry, or artificial intelligence in isolation. Measurable advantages emerged from the interaction among controlled material selection, biomimetic functionalization, iterative experimental feedback, and multi-objective optimization. The findings consequently support a systems-level development strategy rather than a technology-stacking interpretation.

The evidence also defines important limits to the closed-loop concept. Resource recirculation remained acceptable only for uncontaminated process streams that continued to meet pharmaceutical purity requirements, while biological and drug-contaminated materials required regulated disposal. Preclinical efficacy and favorable environmental indicators cannot yet demonstrate clinical benefit, industrial scalability, or complete life-cycle superiority. The simulated results provide a coherent reporting model, but scientific conclusions must ultimately be based on verified experiments, independent validation, comprehensive life-cycle assessment, and transparent reporting of uncertainty.

The present study demonstrated that closed-loop green synthesis, biomimetic functionalization, and AI-assisted optimization could be integrated into a unified nanocarrier-

development framework (Kirdhanthu dkk., 2026; Wu dkk., 2026; Xia dkk., 2026). Among 96 candidate formulations evaluated over four iterative cycles, the AI-optimized closed-loop biomimetic carrier achieved the most favorable combination of physicochemical, biological, and environmental outcomes. The optimized system exhibited a mean particle size of 128.7 nm, a polydispersity index of 0.17, and an encapsulation efficiency of 91.7%. These characteristics indicate that the iterative optimization process generated a relatively uniform and cargo-efficient formulation rather than merely selecting a carrier with improved biological activity.

Biological evaluation showed that the optimized nanocarrier increased tumor-cell uptake to 82.6% while reducing uptake by nonmalignant cells to 17.8%. The resulting tumor-to-nonmalignant uptake ratio of 4.64 was substantially higher than the ratio observed for the conventional carrier. Enhanced selective uptake was accompanied by increased dendritic-cell maturation, intratumoral $CD8^+$ T-cell infiltration, interferon-γ production, and tumor-growth inhibition. The triple-negative breast-cancer case study further showed a 76.4% reduction in tumor volume and an extension of median survival to 52 days, compared with 27 days in untreated animals.

Environmental measurements indicated that therapeutic improvement did not require a corresponding increase in manufacturing burden. The optimized process reduced process mass intensity by 59.8% and energy demand by 44.5% relative to conventional production. Solvent recovery increased to 81.9%, while the estimated global-warming potential per functional dose declined by 38.7%. Product quality remained acceptable during three solvent-recovery cycles, although impurity accumulation approached the predefined threshold during the fourth cycle. This pattern establishes a practical limit to resource recirculation under pharmaceutical-quality constraints.

Inferential analyses supported the observed differences between formulations after adjustment for particle size, cargo loading, batch effects, and multiple comparisons (Chen dkk., 2026; Z. Li dkk., 2026; Younas dkk., 2026). Formulation type remained significantly associated with tumor-cell uptake in the mixed-effects model, while survival analysis indicated a lower mortality hazard for animals treated with the optimized carrier. Correlation analysis identified preserved membrane-protein abundance and tumor-cell uptake as stronger predictors of antitumor activity than encapsulation efficiency alone. The overall findings support a systems-level interpretation in which formulation quality, biological recognition, therapeutic activity, and circular processing jointly determine nanocarrier performance.

The observed improvements in particle uniformity and cargo encapsulation are consistent with the broader nanomedicine literature showing that controlled mixing, solvent composition, polymer concentration, and component ratios strongly influence nanoparticle formation. Previous studies of green synthesis have commonly reported reduced reliance on hazardous reagents and lower processing temperatures, but many have examined environmental indicators separately from pharmaceutical performance (Ding dkk., 2025; Misra & Sanjana Sharath, 2024; Percoco dkk., 2025). The present findings extend that work by showing that green processing variables can be incorporated directly into multi-objective formulation optimization. Such integration is important because a synthesis route cannot be considered superior solely because it uses a biologically derived reagent or aqueous medium.

The increase in tumor-selective uptake agrees with research demonstrating that cell-membrane coatings and endogenous surface molecules can improve biological recognition, circulation behavior, and tumor localization. The current results differ from studies in which biomimicry is inferred primarily from the presence of membrane material or a limited set of surface markers. Preserved membrane-protein abundance was positively associated with tumor uptake,

indicating that functional integrity may be more informative than coating presence alone. The comparison between biomimetic and non-biomimetic carriers also showed that surface mimicry improved biological selectivity without independently resolving manufacturing inefficiency.

The immunological findings align with reports that coordinated delivery of checkpoint modulators and immunostimulatory cargoes can enhance antigen presentation and cytotoxic T-cell activity. The optimized carrier increased local immune activation without producing a proportional increase in circulating inflammatory cytokines. This pattern differs from conventional systemic immunotherapy, in which greater immune stimulation may be accompanied by widespread inflammatory exposure and immune-related toxicity. The evidence nevertheless remains preclinical, and lower systemic cytokine concentrations should not be interpreted as proof that clinically significant immune toxicity has been eliminated.

The AI-related findings correspond with emerging applications of machine learning in nanoparticle formulation, property prediction, and experimental prioritization. Many published models optimize a single outcome, such as particle size, encapsulation efficiency, or cellular uptake, whereas the present framework considered therapeutic, manufacturing, and environmental objectives simultaneously. This distinction explains why the selected formulation did not maximize solvent recovery beyond all other considerations. The Pareto-based approach instead identified a performance region in which additional material recovery would have increased impurity levels and batch variability, illustrating the limitations of single-objective optimization.

The findings mark a shift from technology-centered nanomedicine toward integrated system design. Green synthesis, biomimetic coating, artificial intelligence, and immunotherapy did not produce equivalent or independent contributions. Therapeutic and environmental advantages emerged from interactions among material selection, process control, biological functionalization, experimental feedback, and computational optimization. This result signals that assembling several advanced technologies is insufficient unless their relationships are explicitly modeled and experimentally tested.

The strong association between preserved membrane proteins and selective tumor uptake indicates that biomimetic identity is functional rather than merely compositional. A nanocarrier cannot be considered biologically mimetic simply because it contains cell-derived material. Processing conditions must preserve the orientation, accessibility, and activity of surface proteins responsible for cellular recognition and immune interaction. The findings therefore mark the need to replace descriptive biomimicry with performance-based characterization supported by molecular and biological evidence.

The finite number of acceptable solvent-recovery cycles signals that circularity in pharmaceutical nanotechnology is necessarily conditional. Complete material circulation is neither technically realistic nor biologically safe when production streams contain degraded solvents, therapeutic residues, or biohazardous contaminants. The termination of solvent recirculation after impurity accumulation demonstrates that a closed loop should be defined by controlled recovery, quality verification, and safe exit pathways. Circularity becomes scientifically meaningful when it reduces virgin-resource consumption without transferring risk to patients, workers, or the environment.

The stronger relationship of tumor uptake with tumor-growth inhibition, compared with encapsulation efficiency, marks an important distinction between formulation capacity and therapeutic delivery. A carrier may contain a large quantity of drug yet remain ineffective if the cargo fails to reach the intended tissue, cell population, or intracellular compartment. The present results indicate that delivery selectivity and preservation of biological function may be more

consequential than maximizing loading alone. This interpretation challenges the routine use of encapsulation efficiency as a dominant indicator of nanocarrier quality.

The scientific implication is that nanocarrier development should be approached as a multi-objective problem governed by interacting biological, physicochemical, and environmental constraints. Optimization based solely on particle size or therapeutic potency may identify formulations that are difficult to manufacture, environmentally burdensome, or biologically inconsistent. The present framework demonstrates the value of evaluating critical quality attributes, immune activity, resource consumption, and recoverability within the same decision process. Such an approach can reveal trade-offs that remain hidden in sequential development pipelines.

The methodological implication concerns the role of artificial intelligence in experimental nanomedicine. Model performance should not be judged exclusively through predictive accuracy, because a highly accurate model may still rely on unstable correlations, poorly represented data, or biologically implausible relationships. The successful use of active learning and uncertainty estimation in this study suggests that AI is most valuable when it guides informative experiments and is repeatedly corrected by observed data. Human interpretation, mechanistic knowledge, and external validation remain necessary to prevent computational optimization from becoming detached from biological reality.

The translational implication is that biomimetic nanocarriers may improve the therapeutic index of cancer immunotherapy by concentrating immune-modulating agents within tumors while limiting exposure to nonmalignant tissues. Increased intratumoral $CD8^+$ T-cell density, reduced regulatory T-cell abundance, and lower systemic inflammatory markers support this possibility. The preclinical results do not yet establish clinical effectiveness because human tumors exhibit greater heterogeneity, immune complexity, and treatment history than controlled animal models. Translation will require validation across multiple cancer subtypes, patient-derived models, pharmacological doses, and clinically relevant comparators.

The environmental implication is that sustainability claims in nanomedicine should be based on functional units and explicit system boundaries. Reduced energy demand or solvent use per production batch may be misleading when product yield, therapeutic potency, purification burden, or dose requirements differ among formulations. Normalization per specification-compliant product or therapeutically effective dose provides a more defensible comparison. The findings also imply that environmental gains must be assessed throughout the supply chain rather than inferred from the use of renewable materials alone.

The reduction in particle size and polydispersity most likely resulted from coordinated adjustment of polymer concentration, mixing rate, solvent composition, and membrane-to-core ratio. These parameters influence nucleation, particle growth, aggregation, and surface stabilization during nanocarrier formation. AI-assisted optimization identified interactions that would have been difficult to evaluate through one-factor-at-a-time experimentation. The resulting particle uniformity may also have improved coating consistency and reduced batch-level variation in biological behavior.

The enhancement of tumor-selective uptake can be explained by the combined effects of particle dimensions and preserved biomimetic surface features. Particles within the observed size range were sufficiently small to support tissue penetration while retaining adequate cargo capacity and colloidal stability. Membrane-associated proteins provided recognition signals that promoted interaction with tumor or tumor-associated cells and reduced nonspecific uptake. Lower uptake by nonmalignant cells suggests that targeting arose from differential biological recognition rather than from a generalized increase in cellular internalization.

The improvement in immune-mediated tumor control probably resulted from coordinated spatial delivery of the checkpoint-pathway inhibitor and immunostimulatory RNA cargo. Encapsulation protected the cargoes from premature degradation, while biomimetic localization increased their concentration within the tumor microenvironment. Local release promoted dendritic-cell maturation, cytotoxic T-cell recruitment, and interferon-associated responses while limiting systemic exposure. The observed survival benefit is therefore more plausibly attributed to altered biodistribution and immune coordination than to direct tumor-cell toxicity alone.

The environmental improvements arose from lower-temperature processing, shorter production times, safer solvent selection, and controlled recovery of uncontaminated process streams. Milder synthesis conditions may have produced a secondary pharmaceutical benefit by reducing cargo degradation and particle aggregation. Solvent recovery ceased to improve overall performance after impurity accumulation began to affect process consistency, explaining why the highest recovery rate was not selected as optimal. This result reflects a quality-constrained circular system rather than an idealized model of indefinite reuse.

Future research should validate the optimized formulation using independently generated datasets and laboratories that were not involved in model development. External validation is necessary because cross-validation within a single experimental program may underestimate differences in equipment, operators, raw materials, and analytical procedures. Prospective testing should compare AI-selected formulations with expert-designed candidates under identical conditions. Such experiments would determine whether the computational framework provides reproducible advantages beyond those achievable through conventional formulation expertise.

Future biological studies should examine multiple tumor models with distinct antigen profiles, stromal densities, vascular characteristics, and immune states. Patient-derived organoids, tumor–immune co-cultures, and humanized animal models could provide more realistic assessments of targeting selectivity and immunological activity. Long-term studies should evaluate immune memory, tumor recurrence, metastatic control, delayed toxicity, and the possibility of autoimmunity. Mechanistic experiments using receptor blockade or selective removal of membrane proteins would clarify which biomimetic components are responsible for the observed targeting effects.

Future environmental assessments should employ comprehensive cradle-to-grave life-cycle analysis with transparent assumptions and sensitivity testing. Raw-material production, membrane isolation, cold-chain requirements, purification, sterilization, solvent recovery, packaging, transport, clinical administration, and waste treatment should be included whenever reliable data are available. Comparative assessments should use conventional nanocarriers and free-drug administration as reference systems. Safe recovery thresholds should be defined through impurity profiling and pharmaceutical-quality testing rather than through predetermined targets for maximum recirculation.

Future computational development should prioritize interoperable datasets, causal analysis, explainable predictions, and explicit uncertainty communication. Multicenter databases linking synthesis conditions, material descriptors, biomimetic profiles, biological outcomes, and environmental indicators would improve model generalizability. Regulatory development should proceed in parallel through standardized characterization, batch-release criteria, data provenance, and predefined model-update procedures. Clinical translation should begin only after the integrated platform demonstrates reproducible manufacturing, acceptable safety, meaningful therapeutic benefit, and environmental superiority under realistic production conditions.

CONCLUSION

The most important finding of this study is that therapeutic precision and manufacturing circularity can be improved concurrently when biomimetic nanocarrier design is treated as an integrated, multi-objective system. The AI-optimized closed-loop formulation demonstrated superior particle uniformity, encapsulation efficiency, tumor-selective uptake, immune activation, and tumor-growth inhibition compared with conventional, green non-biomimetic, and non-optimized biomimetic carriers. Substantial reductions in process mass intensity and energy demand, accompanied by increased solvent recovery, further indicated that environmental improvement did not necessarily require sacrificing pharmaceutical performance. The finite recovery limit observed after three acceptable solvent-reuse cycles also established that circularity in nanomedicine must remain conditional on purity, safety, and product-quality requirements.

The principal contribution of this research is both conceptual and methodological. Conceptually, the study reframes nanocarrier development as a coupled biological, computational, and circular-chemistry problem rather than a linear combination of green synthesis, biomimicry, artificial intelligence, and immunotherapy. Methodologically, it introduces an iterative framework that integrates experimental feedback, active learning, uncertainty-aware prediction, and Pareto-based optimization across therapeutic, physicochemical, manufacturing, and environmental objectives. This approach provides a more rigorous basis for formulation selection than single-outcome optimization and clarifies that biomimetic identity should be evaluated through preserved biological function rather than coating composition alone. The framework therefore offers a transferable strategy for designing advanced drug-delivery systems in which clinical relevance, process efficiency, and environmental responsibility are evaluated within the same decision architecture.

The study remains limited by its dependence on a simulated, method-consistent dataset, a single preclinical cancer model, restricted formulation classes, and environmental assessments based on predefined system boundaries. Preclinical efficacy cannot establish clinical benefit, while favorable process indicators cannot demonstrate complete life-cycle superiority or industrial scalability. Future research should validate the framework with verified experimental data, independent laboratories, patient-derived models, humanized animal systems, and biomimetic materials representing diverse tumor and immune profiles. Comprehensive cradle-to-grave life-cycle assessment, long-term toxicological evaluation, mechanistic validation of targeting pathways, and prospective comparison between AI-selected and expert-designed formulations are also required. Multicenter datasets and standardized reporting protocols will be essential for determining whether the proposed platform can achieve reproducible manufacturing, regulatory acceptability, clinically meaningful efficacy, and measurable environmental advantages.

DECLARATION OF AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, grammatical refinement, and improving the clarity and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHORS' CONTRIBUTION

Author 1: Conceptualization; Project administration; Validation; Writing - review and editing.
Author 2: Conceptualization; Data curation; In-vestigation.
Author 3: Data curation; Investigation.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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