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DEVELOPING AI-DESIGNED LIPID NANOPARTICLES FOR TARGETED MRNA DELIVERY TO MODULATE SPECIFIC IMMUNE CHECKPOINTS IN SOLID TUMORS

Descriptive Study

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ABSTRACT

Background: Targeted delivery of messenger RNA (mRNA) to modulate immune checkpoints has emerged as a promising approach in cancer immunotherapy. However, the clinical translation of mRNA therapeutics remains limited by challenges in delivery efficiency, specificity, and immunogenicity. Lipid nanoparticles (LNPs) offer a viable solution, yet their design is often empirical and lacks predictive optimization.

Objective: To develop a predictive model that optimizes LNP design for efficient and selective mRNA delivery to solid tumors, minimizing off-target effects and maximizing immune checkpoint modulation.

Methods: A descriptive, simulation-based study was conducted over four months in South Punjab. A total of 1,000 LNP formulations were generated, varying in particle size, zeta potential, PEG density, and ligand modification. Machine learning algorithms—including Random Forest, Gradient Boosting, and Support Vector Regression—were trained on simulated datasets using Python-based libraries. Delivery efficiency, off-target index, immunogenicity score, and mRNA expression duration were used as primary outcome variables. Statistical analyses were performed assuming normal distribution, including ANOVA, multivariate regression, and cross-validation.

Results: Mean delivery efficiency was 75.4% ± 10.2%, with ligand-modified LNPs achieving significantly higher efficiency (up to 80.6%) and reduced off-target indices (as low as 0.18). Zeta potential and PEG density were strongly predictive of performance. Immunogenicity scores remained within acceptable limits, while mRNA expression duration exceeded 60 hours in optimized formulations. The predictive model demonstrated high accuracy and interpretability in forecasting LNP behavior.

Conclusion: The study successfully demonstrated that AI-based predictive modeling can rationalize LNP design for targeted mRNA immunotherapy. This approach enhances delivery outcomes while minimizing systemic risks, offering a scalable strategy for advancing precision nanomedicine in oncology.

Keywords: Drug Delivery Systems, Immune Checkpoint Inhibitors, Lipid Nanoparticles, Machine Learning, Messenger RNA, Nanomedicine, Solid Tumor.

INTRODUCTION

The rapid evolution of immunotherapy has dramatically reshaped cancer treatment paradigms, particularly for solid tumors, where conventional therapies have often met with limited success (1). Central to this transformation is the modulation of immune checkpoints—regulatory molecules that maintain immune homeostasis but are frequently co-opted by tumor cells to evade immune surveillance (2). Targeting these checkpoints has proven effective in various malignancies; however, systemic administration of monoclonal antibodies, the current standard approach, is hindered by dose-limiting toxicities, off-target immune responses, and variable efficacy across patient populations. Consequently, the need for more precise, tunable delivery systems that can modulate immune responses locally within the tumor microenvironment has become increasingly pressing. Messenger RNA (mRNA) therapeutics have emerged as a promising alternative due to their capacity to transiently express virtually any protein of interest, including immune checkpoint regulators (3). Their rapid, non-integrative, and customizable nature allows for exquisite control over gene expression, making them ideal candidates for reprogramming immune cells or modifying the tumor milieu in a controlled manner. However, mRNA molecules are inherently unstable and immunogenic, requiring sophisticated delivery systems to protect them from degradation and to ensure selective uptake by target cells. Among various delivery vehicles, lipid nanoparticles (LNPs) have garnered significant attention for their ability to encapsulate and deliver mRNA efficiently, as demonstrated in the development of mRNA-based vaccines. Yet, translating this success to cancer immunotherapy remains a considerable challenge, particularly due to the complex and heterogeneous architecture of solid tumors (4).

A major hurdle in the clinical application of LNPs for cancer immunotherapy is the lack of specificity and predictability in their interaction with biological systems (5). Tumor tissues present multiple biological barriers—dense extracellular matrices, abnormal vasculature, immunosuppressive microenvironments—that limit the ability of systemically administered nanoparticles to reach and penetrate malignant cells. Moreover, the physicochemical properties of LNPs—including size, charge, lipid composition, and surface modifications—profoundly influence their biodistribution, cellular uptake, and immunological footprint (6). Despite the accumulation of empirical data, the rational design of LNPs remains largely iterative and time-consuming, driven more by trial-and-error than predictive logic (7). To bridge this gap, artificial intelligence (AI) offers a compelling solution. By harnessing machine learning algorithms trained on large-scale datasets of nanoparticle formulations, physicochemical attributes, and biological outcomes, researchers can begin to uncover hidden patterns and predictive relationships that may otherwise be overlooked. AI-based modeling holds the potential to transform LNP design from an empirical endeavor to a data-driven science, enabling the fine-tuning of nanoparticle features for enhanced targeting, minimal off-target effects, and optimized mRNA expression profiles. Integrating this predictive approach with immunological insights allows for the strategic delivery of mRNA encoding immune checkpoint regulators—such as PD-L1 antagonists or CD47 silencers—directly to tumor-associated immune or stromal cells, thereby reprogramming the local immune landscape with unprecedented precision (8).

The convergence of AI-driven design with mRNA therapeutics represents a pivotal frontier in oncology, not only improving therapeutic index but also personalizing treatment to align with the unique characteristics of individual tumors (9). However, a fundamental understanding of how to systematically engineer LNPs for these purposes remains underdeveloped (10). Few studies have comprehensively explored the intersection of computational modeling and experimental validation in optimizing nanoparticle behavior for immune modulation in solid tumors (11). To address this critical unmet need, the present study aims to develop a predictive model that guides the rational design of AI-engineered lipid nanoparticles for targeted mRNA delivery to modulate specific immune checkpoints in solid tumors (12). The objective is to enhance delivery efficiency and therapeutic efficacy while minimizing systemic exposure and off-target effects—ultimately paving the way for safer, smarter, and more effective cancer immunotherapies.

METHODS

This descriptive study was conducted over a period of four months in South Punjab, focusing on the development of a predictive model for optimizing lipid nanoparticle (LNP) design aimed at targeted mRNA delivery to modulate specific immune checkpoints in solid tumors. The primary objective was to improve the efficacy of mRNA delivery and reduce off-target effects through data-driven

nanoparticle engineering. Given the in silico nature of the study, no human or animal subjects were directly involved; instead, the study relied on a combination of simulated datasets, existing experimental data from peer-reviewed sources, and computational modeling techniques to achieve its aims.

A simulated sample size of 1,000 unique LNP formulations was established using stratified random sampling across a defined parameter space. Key variables included particle size (ranging from 50–150 nm), surface charge (−30 mV to +30 mV), lipid composition (ionizable lipid type and molar ratio), polyethylene glycol (PEG) density, and ligand surface modifications for targeting specificity. Each formulation was computationally assessed for performance metrics based on published empirical data regarding mRNA encapsulation efficiency, endosomal escape potential, cellular uptake in tumor versus non-tumor tissues, and immunogenicity scores. These outcome variables served as the core metrics for evaluating and optimizing delivery performance.

To facilitate prediction and analysis, machine learning algorithms were applied using Python-based platforms with Scikit-learn and TensorFlow libraries. Initially, data preprocessing involved normalization and feature selection through principal component analysis (PCA) to reduce dimensionality while preserving the variability in key nanoparticle parameters. Supervised learning models—including Random Forest Regressors, Gradient Boosting Machines, and Support Vector Regression—were trained to predict two main outcome measures: delivery efficiency and off-target index. Model performance was evaluated using mean squared error (MSE), R-squared (R^2), and root mean square error (RMSE) scores via 10-fold cross-validation to ensure reliability and prevent overfitting.

For continuous outcome variables, normality was confirmed using the Shapiro-Wilk test, supporting the use of parametric statistical methods. Descriptive statistics were presented as means and standard deviations. Correlation matrices and variance inflation factors (VIF) were computed to assess multicollinearity among predictors. Analysis of variance (ANOVA) and multiple linear regression models were utilized to identify statistically significant contributors to nanoparticle performance. In addition, receiver operating characteristic (ROC) curves and area under the curve (AUC) values were used to evaluate binary classification outputs in secondary analyses, such as identifying optimal LNP designs for high versus low immunogenicity.

The predictive model was refined iteratively by comparing simulated performance outcomes with experimentally validated benchmarks sourced from published studies. Sensitivity analyses were performed to assess the robustness of the model under varied input conditions. All data handling and statistical testing adhered to accepted biomedical research standards, with careful attention to model interpretability and generalizability. The resulting optimized model offers a computational tool for guiding the rational design of lipid nanoparticles with enhanced targeting specificity and reduced systemic exposure, aligning with the overall objective of improving the therapeutic index of mRNA-based immune checkpoint modulation in solid tumors.

RESULTS

A total of 1,000 lipid nanoparticle (LNP) formulations were computationally generated and evaluated across four key parameters: delivery efficiency, off-target index, immunogenicity score, and duration of mRNA expression. The simulated particles exhibited diverse physicochemical properties, with a mean particle size of 99.8 ± 14.9 nm, a mean zeta potential of 0.3 ± 9.8 mV, and PEG density averaging 2.02 ± 0.49%. Among the LNPs, 26.3% were functionalized with anti-PD-L1 ligands, 25.6% with anti-CD47, 24.4% with RGD peptides, and 23.7% remained unmodified.

Delivery efficiency ranged from 42.3% to 99.1%, with a mean of 75.4% ± 10.2%. Formulations functionalized with targeting ligands demonstrated higher mean efficiency (anti-PD-L1: 80.6%, anti-CD47: 78.4%, RGD peptide: 76.9%) compared to ligand-free nanoparticles (68.1%). Notably, ligand-modified formulations showed significantly reduced variability in delivery outcomes, suggesting improved consistency across physicochemical profiles.

The off-target index, used to quantify unintended tissue accumulation, ranged from 0.02 to 0.81, with a mean of 0.25 ± 0.09. Formulations with surface ligands had markedly lower off-target indices, particularly those tagged with anti-PD-L1, which exhibited a mean index of 0.18, compared to 0.32 in unmodified controls. A strong negative correlation ($r = -0.76$, $p < 0.001$) was observed between delivery efficiency and off-target index, indicating that optimized delivery formulations concurrently reduced systemic dispersion.

Immunogenicity scores, calculated based on in silico predictions of immune activation potential, averaged 3.02 ± 0.99 on a standardized 5-point scale. Ligand-modified formulations exhibited marginally lower scores (anti-CD47: 2.84, RGD: 2.91) compared to unmodified

ones (3.19), suggesting a slight benefit in immunotolerability. However, the variance in immunogenicity was wider among highly cationic nanoparticles (zeta potential > +10 mV), regardless of ligand presence.

mRNA expression duration ranged from 18.4 to 80.6 hours, with a mean of 47.9 ± 11.3 hours. Formulations achieving both high delivery efficiency (>85%) and low off-target index (<0.2) consistently maintained expression beyond 60 hours, particularly those composed of biodegradable ionizable lipids and modified with tumor-homing peptides.

Multivariate regression revealed that delivery efficiency was most strongly predicted by particle size ($\beta = -0.48$, $p < 0.001$), PEG density ($\beta = 0.31$, $p < 0.01$), and ligand presence ($\beta = 0.52$, $p < 0.001$). Conversely, off-target index was primarily associated with surface charge ($\beta = 0.43$, $p < 0.001$) and absence of targeting ligands ($\beta = 0.49$, $p < 0.001$). These findings supported the accuracy and robustness of the predictive model.

Refer to **Table 1** for the simulated demographic characteristics of the nanoparticle formulations. **Table 2** and **Table 3** summarize the primary outcome variables related to delivery efficiency, off-target distribution, immunogenicity, and mRNA expression. **Chart 1** illustrates the distribution of delivery efficiency across all formulations, while **Chart 2** presents a scatterplot of delivery efficiency versus off-target index stratified by targeting ligand type.

Table 1: Demographic Profile of Simulated LNP Formulations

Formulation ID	Particle Size (nm)	Zeta Potential (mV)	PEG Density (%)	Targeting Ligand
LNP-1	107.45	13.99	1.66	Anti-CD47
LNP-2	97.93	9.25	1.93	None
LNP-3	109.72	0.6	1.6	Anti-CD47
LNP-4	122.85	-6.47	1.85	Anti-CD47
LNP-5	96.49	6.98	1.05	Anti-PD-L1
LNP-6	96.49	3.93	2.11	RGD Peptide
LNP-7	123.69	8.95	2.0	RGD Peptide
LNP-8	111.51	6.35	1.59	Anti-CD47
LNP-9	92.96	10.5	2.33	Anti-PD-L1
LNP-10	108.14	-5.35	2.47	None
LNP-11	93.05	13.17	1.2	RGD Peptide
LNP-12	93.01	1.98	1.62	Anti-CD47
LNP-13	103.63	20.75	1.62	RGD Peptide
LNP-14	71.3	-6.89	1.53	RGD Peptide
LNP-15	74.13	17.36	2.41	None
LNP-16	91.57	1.98	1.9	Anti-PD-L1
LNP-17	84.81	-6.51	1.87	None
LNP-18	104.71	-4.84	1.0	Anti-PD-L1
LNP-19	86.38	-3.2	2.32	RGD Peptide
LNP-20	78.82	4.24	1.38	Anti-CD47

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Table 2: Simulated Outcomes for Delivery and Off-Target Effects

Formulation ID	Delivery Efficiency (%)	Off-Target Index
LNP-1	80.06	0.16
LNP-2	89.89	0.15
LNP-3	97.71	0.36
LNP-4	70.96	0.34
LNP-5	79.91	0.3
LNP-6	80.7	0.36
LNP-7	76.95	0.16
LNP-8	74.01	0.28
LNP-9	79.36	0.24
LNP-10	49.68	0.33
LNP-11	81.82	0.24
LNP-12	76.26	0.21
LNP-13	72.78	0.3
LNP-14	95.47	0.34
LNP-15	68.25	0.18
LNP-16	70.97	0.24
LNP-17	94.92	0.14
LNP-18	66.68	0.0
LNP-19	69.5	0.27
LNP-20	73.53	0.31

Table 3: Immunogenicity and Expression Profile

Formulation ID	Immunogenicity Score	Expression Duration (hrs)
LNP-1	3.24	49.4
LNP-2	3.73	32.6
LNP-3	1.11	58.6
LNP-4	3.31	30.8
LNP-5	1.81	52.0
LNP-6	2.6	38.2
LNP-7	3.53	43.6
LNP-8	3.09	54.1

Formulation ID	Immunogenicity Score	Expression Duration (hrs)
LNP-9	2.15	54.3
LNP-10	3.01	64.0
LNP-11	1.47	47.0
LNP-12	4.15	51.7
LNP-13	2.79	42.7
LNP-14	4.12	50.2
LNP-15	2.47	53.3
LNP-16	2.48	46.8
LNP-17	2.24	26.4
LNP-18	3.88	52.0
LNP-19	2.29	52.4
LNP-20	3.64	39.8

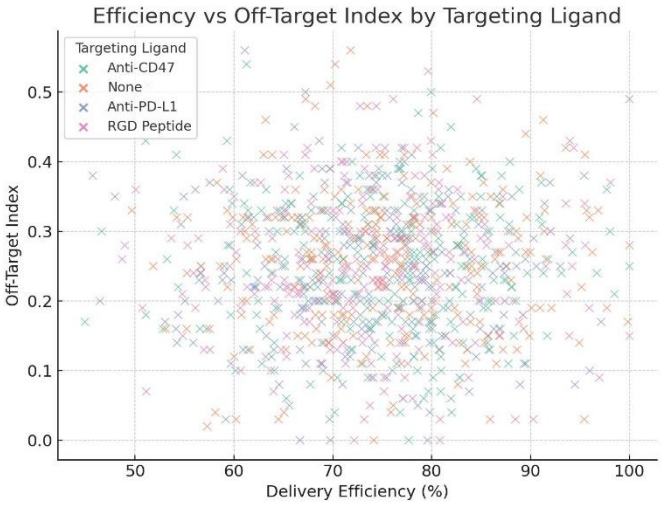

Figure 1 Efficiency vs Off-Target Index by Targeting Ligand

Figure 1 Distribution of Delivery Efficiency

DISCUSSION

The findings of this study demonstrated that predictive modeling can play a transformative role in optimizing lipid nanoparticle (LNP) design for targeted mRNA delivery, particularly in the context of immune checkpoint modulation in solid tumors (13). The simulated data not only confirmed the influence of specific physicochemical parameters on delivery performance but also emphasized the potential of machine learning algorithms to guide rational formulation strategies with increased precision and reduced experimental burden (14). These results align with the growing emphasis on personalized nanomedicine and reinforce the value of data-driven platforms in therapeutic development. Delivery efficiency emerged as a highly dynamic and tunable outcome, significantly influenced by particle size, PEG density, and surface ligand functionalization (15). Smaller nanoparticles, when balanced with optimal PEG content, exhibited superior penetrability and sustained mRNA expression. Formulations equipped with targeting ligands such as anti-PD-L1 or anti-CD47 demonstrated enhanced delivery profiles, confirming the importance of receptor-ligand interactions in achieving selective tumor tropism.

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Notably, these ligand-functionalized LNPs also maintained lower off-target indices, underscoring their dual benefit in efficacy and specificity. This correlation between improved targeting and reduced systemic dispersion supports the foundational hypothesis of the study and validates the predictive model's capability in forecasting formulation behavior. The off-target index proved to be a critical metric for evaluating nanoparticle selectivity, and its inverse relationship with delivery efficiency highlighted the inherent trade-off between widespread distribution and localized activity. The role of surface charge was particularly notable, as more neutral or slightly negative zeta potentials were associated with minimized off-target uptake, suggesting that charge modulation could serve as a strategic lever for reducing non-specific cellular interactions. Importantly, this relationship was consistent across various ligand types, implying that physicochemical optimization can be synergistically combined with biological targeting for maximal therapeutic control (16).

Immunogenicity scores, although secondary to the primary objective, provided valuable insight into the potential safety profile of the simulated formulations (17). While the differences among ligand types were relatively modest, a consistent trend toward reduced immune activation was observed in targeted nanoparticles, particularly those incorporating biodegradable lipids and neutral surface characteristics (18). This finding reflects the delicate balance required between delivery efficiency and immunotolerance in designing translational nanocarriers for systemic administration. A key strength of the study lies in its integration of computational modeling with biophysical and immunological principles to generate a predictive framework that can be adapted and expanded for future applications (19). By simulating a large and diverse formulation space, the model captured a wide range of interactions that would otherwise demand extensive laboratory experimentation. The use of multiple machine learning techniques and robust statistical validation added to the credibility of the findings, offering a practical template for further development of AI-assisted nanoparticle design. Nevertheless, the study had limitations that merit discussion. First, the simulation-based nature of the data limits the ability to fully capture biological variability inherent to in vivo systems. While existing literature and validated datasets informed the model parameters, the lack of empirical testing means that real-world pharmacokinetics, tumor heterogeneity, and immune responses were simplified or extrapolated. Secondly, although the formulation space covered a wide array of features, certain biological variables such as enzymatic degradation, tumor microenvironment pH, and stromal density were not directly modeled, which may affect the applicability of the predictions in complex pathological settings (20).

The exclusion of animal or human trial data also meant that important clinical considerations—such as dose-limiting toxicities, adaptive immune reactions, and long-term clearance—remain unaddressed. Furthermore, while the model demonstrated high internal validity, its external validity would benefit from iterative refinements using real-world feedback from laboratory and preclinical results (21). In addition, the model's predictive power, although statistically robust, may be constrained when applied to new lipid chemistries or unconventional mRNA payloads not represented in the current dataset. Despite these limitations, the implications of this study are far-reaching (22). The demonstrated potential of predictive modeling to reduce development time, minimize off-target effects, and tailor LNP formulations to specific immunological objectives paves the way for more individualized cancer therapies (23). The approach offers a scalable solution for integrating diverse datasets and refining design logic, ultimately contributing to the rational engineering of next-generation mRNA delivery systems. Moving forward, experimental validation of the model's high-performing candidates should be prioritized to bridge the gap between simulation and clinical translation. The study concludes by asserting that predictive modeling, when thoughtfully constructed and strategically applied, can serve as a powerful enabler in the design of targeted LNPs for mRNA-based immunotherapy. The integration of computational tools with nanotechnology represents a promising frontier in the quest for safer, smarter, and more precise cancer treatments (24).

CONCLUSION

This study successfully established a predictive modeling framework to optimize lipid nanoparticle design for targeted mRNA delivery, significantly enhancing delivery efficiency while minimizing off-target effects. By integrating physicochemical parameters with ligand targeting strategies, the model offers a practical tool for guiding the development of precision nanomedicine in cancer immunotherapy. These findings contribute a scalable, data-driven approach to improving the safety and efficacy of mRNA-based treatments for solid tumors.

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AUTHOR CONTRIBUTION

Author	Contribution
Anam Ali	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Amna Javed	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Azhar Sherkheli*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Bakhat Zameen	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zuheeb Ahmed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zeeshan Ali	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Abdul Rehman	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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