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# Artificial Intelligence-Driven Nanoarchitectonics for Smart Targeted Drug Delivery

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**The development of data-driven and targeted drug delivery systems is essential for advancing precision therapeutics. Despite substantial progress in nanocarrier development, conventional platforms continue to face major challenges in clinical translation due to biological complexity, off-target accumulation, and limited adaptability to dynamic physiological environments. The integration of nanoarchitectonics and artificial intelligence (AI) offers an advanced strategy for engineering delivery systems that are structurally programmable, stimuli-responsive, and autonomously optimized. Nanoarchitectonics enables the construction of hierarchical nanostructures with precise spatial and temporal control, while AI facilitates modeling, prediction, and iterative optimization throughout the development pipeline. In this perspective, an AI-driven nanoarchitectonics framework is introduced for targeted drug delivery, structured around three key phases: 1) molecular target identification through bioinformatic profiling, 2) machine learning (ML)-guided surface engineering to enhance targeting specificity, and 3) in silico modeling of delivery dynamics and systemic distribution. Drawing on recent advances and representative case studies, how AI tools are illustrated, from generative design algorithms to predictive pharmacokinetic models, are transforming the field from empirical formulation toward mechanism-informed and AI-driven intelligent design. By highlighting current limitations and outlining future directions for the integration of AI and nanoarchitectonics, are concluded with a focus on enabling clinically translatable nanomedicine platforms.**

## 1. Introduction

The development of advanced drug delivery systems plays an increasingly critical role in enhancing therapeutic specificity and reducing off-target effects.[1] Among various strategies, targeted drug delivery has emerged as a particularly promising approach, enabling the precise localization of therapeutic agents to diseased tissues or specific cell populations.[2] Reducing off-target activity enhances both therapeutic precision and tolerability. Yet, conventional nanocarriers frequently fail to achieve optimal performance in physiologically relevant conditions.[3] Poor responsiveness to biological cues, inefficient tissue penetration, suboptimal biodistribution, and premature clearance or degradation frequently lead to reduced therapeutic efficacy and clinical failure.[4]

To address these challenges, a shift in design philosophy is required. This shift involves moving away from traditional material-centric approaches and toward strategies that emphasize complexity, hierarchy, and adaptability.[5] Nanoarchitectonics has emerged as a powerful and

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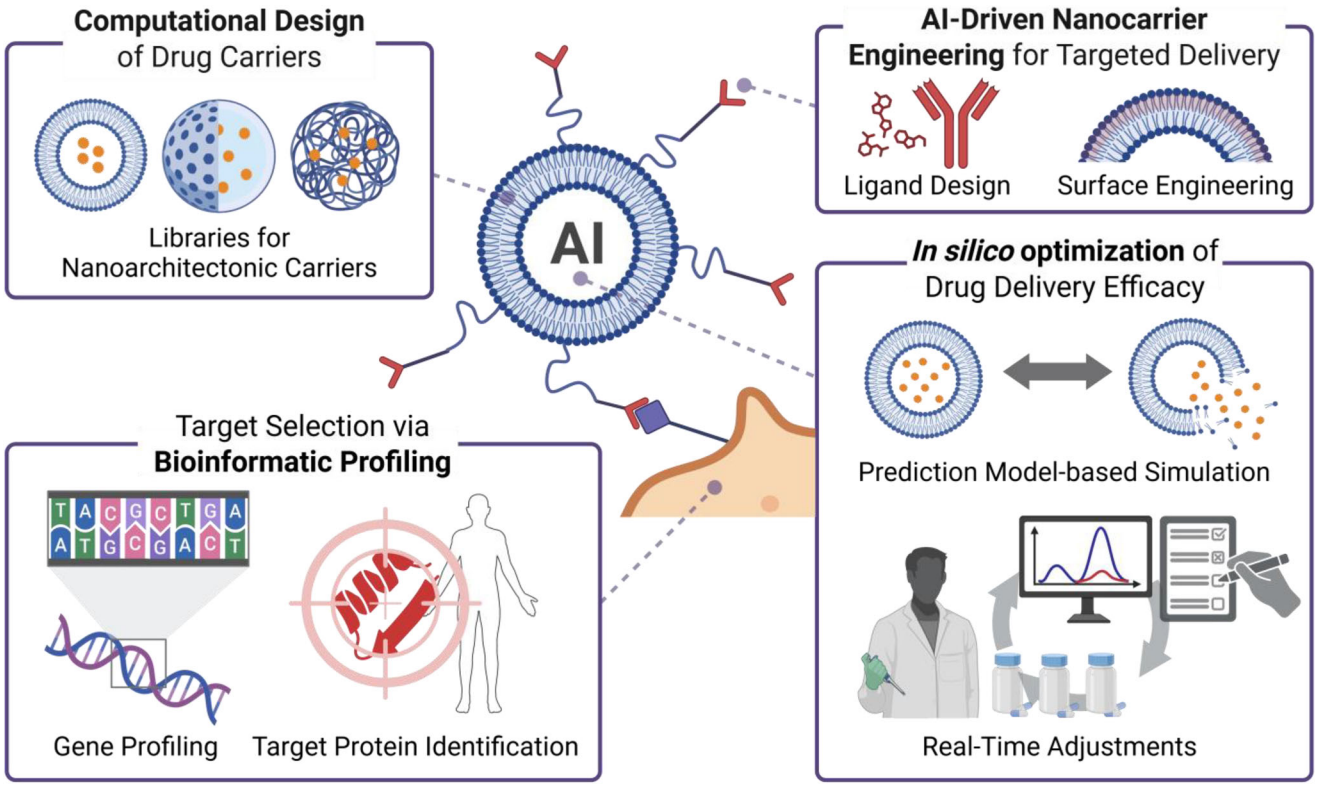


**Figure 1.** Schematic representation of the integration between artificial intelligence (AI) and nanoarchitectonics for intelligent drug delivery. Created with BioRender.com.

integrative strategy to meet this need. Defined as the methodology of architecting functional systems by arranging atoms, molecules, and nanoscale units into well-organized structures, nanoarchitectonics bridges the gap between molecular design and macroscopic function.[6] It is a multidisciplinary framework that integrates nanotechnology, supramolecular chemistry, molecular self-assembly, and bioinspired design to construct functional nanostructures with precisely controlled architectures and dynamic behaviors.[7] Its approach emphasizes the integration of diverse nanoscale processes, including molecular manipulation, self-organization, and alignment under external fields, into multistep, often hierarchical construction strategies.[8] Nanoarchitectonics enables the development of intelligent nanocarriers capable of responding to microenvironmental stimuli, performing logic-gated release, or reorganizing their structure in situ.[9] These systems exhibit emergent functionalities beyond the reach of conventional fabrication, positioning nanoarchitectonics as a versatile platform for programmable drug delivery.[10]

The integration of nanoarchitectonics with artificial intelligence (AI) technologies opens new opportunities in drug delivery.[11] AI encompasses powerful computational tools for analyzing complex, high-dimensional datasets, including multiomics profiles, structural databases, imaging data, and biosensor outputs, and for extracting actionable insights to guide rational material design.[12] Machine learning (ML), a major subset of AI, enables data-driven model development and predictive analysis without explicit programming. Deep learning (DL), a specialized branch of ML rooted in artificial neural networks (ANNs), supports simulation of nanocarrier–biological interactions, identification of optimal surface chemistries, and prediction of in vivo biodistribution patterns from structural features.[13] These capabilities enable hypothesis generation, predictive modeling of physicochemical and pharmacokinetic properties, and autonomous optimization of nanocarrier design.[14] This significant transition from traditional trial-and-error methods to computationally guided, mechanism-informed workflows hold promises for advancing precision and efficacy of targeted drug delivery systems.[15]

This perspective introduces a unified framework in which AI-integrated nanoarchitectonics drives the development of next-generation targeted drug delivery systems. As illustrated in **Figure 1**, the framework emphasizes how artificial intelligence contributes at each step of the nanoarchitectonic design process, from target identification to delivery optimization. The proposed system incorporates bioinformatic profiling for database-guided target discovery, computational design of nanocarriers, AI-driven engineering for targeted delivery, and in silico simulation to optimize therapeutic efficacy. Each component leverages machine learning and data-driven modeling tools to enable adaptive and feedback-informed design. The figure presents a modular and sequential workflow in which AI helps refine surface chemistry, predict biological responses, and customize delivery strategies for enhanced precision. This integrated and recursive architecture supports real-time optimization and reflects biological design principles, offering a systems-level approach to more

personalized and efficient nanomedicine. In the following sections, we elaborate on each element of this framework, review representative case studies, and discuss key challenges and future opportunities in advancing AI-enabled, dynamically tunable drug delivery platforms.

## 2. AI-Driven Workflow for Targeted Drug Delivery Systems

The integration of AI into targeted drug delivery represents a paradigm shift from conventional empirical approaches to an intelligent and closed-loop design framework.[16] This shift enables a dynamic workflow where each phase is informed by data and continuously refined through iterative feedback. The architecture mimics the adaptability of biological systems while accelerating therapeutic innovation. In the context of this framework, "adaptive" refers to three interrelated dimensions. First, material adaptability describes nanocarriers that respond to environmental stimuli such as pH, redox gradients, or enzymatic activity.[17] Second, computational adaptability reflects the iterative learning process of AI models that refine design predictions based on new data.[18] Third, system-level adaptability involves real-time modulation of therapeutic parameters using patient-specific physiological inputs, such as those collected from wearable biosensors.[19] These adaptive layers enable smart, personalized drug delivery strategies that dynamically respond to complex and evolving biological conditions.

The workflow begins with the rational design of nanocarriers tailored to specific therapeutic goals. Formulation follows, involving the synthesis of nanoparticles with controlled size, charge, loading capacity, and release kinetics. These nanocarriers undergo comprehensive characterization and biological verification through in vitro or in vivo studies, generating multi-dimensional datasets on performance metrics such as uptake, biodistribution, and efficacy.[20] Data from each stage is systematically curated and integrated into a comprehensive dataset. This dataset then undergoes processing, including normalization, feature extraction, and data curation, to prepare it for ML. Once processed, the data are used to train and validate predictive models that learn complex relationships between input design parameters and biological outcomes. These models can then generate predictions for new nanocarrier candidates with desirable delivery profiles.

Predicted candidates re-enter the experimental cycle, beginning again with design and formulation, followed by characterization and verification. This iterative loop drives continuous improvement of predictive models and fosters the stepwise evolution of nanocarriers, linking computational design to biological function. It facilitates the adaptive delivery systems that evolve through feedback and intelligently respond to data-driven design adjustments. The loop functions as the engine of a broader workflow that is modular and scalable to diverse material types, therapeutic payloads, and disease contexts.

As shown in **Figure 2**, the workflow operates as a self-improving, data-driven pipeline that accelerates the convergence of material design, functional evaluation, and therapeutic application. By harnessing the capacity of AI to analyze and integrate high-dimensional data, this workflow facilitates the rapid identification of high-performance, personalized drug delivery solutions while reducing experimental burden. It establishes the operational foundation nanoarchitectonic approach to precision nanomedicine. The general framework introduced here underpins the practical strategies discussed in the following sections. These include AI-guided material selection, model-driven nanocarrier design, and iterative experimental validation, all of which work together to realize and refine the proposed design loop.

## 3. AI-Guided Process for Nanocarrier and Nanomaterial Design

The rational design of nanocarriers for targeted drug delivery requires a deep understanding of material properties, physicochemical interactions, and biological behavior. Traditional formulation development has been largely empirical, often involving time-intensive experimentation with limited predictability. The integration of AI, particularly ML, enables the identification of complex structure–function relationships by analyzing multidimensional datasets. AI-driven approaches allow researchers to accelerate formulation design and guide decision-making through data-driven predictions.[21] This strategy aligns with the core principles of nanoarchitectonics, which emphasize the deliberate, bottom-up assembly of molecular components into functional nanostructures. Within this framework, AI serves as a core tool for high-throughput material screening, formulation optimization, and performance prediction.[22]

As illustrated in **Figure 3**, the AI-guided design process begins by generating diverse candidate formulations from well-curated material libraries, followed by iterative model training, prediction, and experimental validation.[23] These libraries encompass a broad spectrum of chemical and structural features that affect drug loading capacity, release kinetics, targeting ability, and biocompatibility. ML models are iteratively trained on experimental datasets to uncover non-linear relationships between design variables and delivery performance metrics. Once validated, the models inform the design and tuning of nanocarrier structures to achieve specific therapeutic functionalities.[24] By integrating predictive modeling into material selection, AI facilitates a shift from empirical approaches to hypothesis-driven design, promoting the development of more efficient and personalized drug delivery systems.

To provide a structured overview of AI applications in nanoarchitectonics for targeted drug delivery, we categorized representative approaches by their functional roles in the design workflow (**Table 1**). These categories include nanocarrier design, targeting system design, and simulation or predictive modeling. Each AI approach is further classified by type, reflecting its conceptual or operational role within the ML pipeline. **Algorithms** refer to core learning methods used for prediction, classification, or optimization (e.g., random forests (RF), support vector machines (SVMs)).[25] **Models** represent ML architectures capable of learning complex patterns from data (e.g., deep neural networks (DNNs), convolutional neural networks (CNNs), generative models).[26] **Paradigms** describe broader learning strategies that define how models are trained or deployed, such as reinforcement learning (reward-based optimization) or federated learning (distributed learning across decentralized datasets).[27] **Platforms**, such as Automated machine learning (AutoML) tools, provide integrated environments that automate model selection,

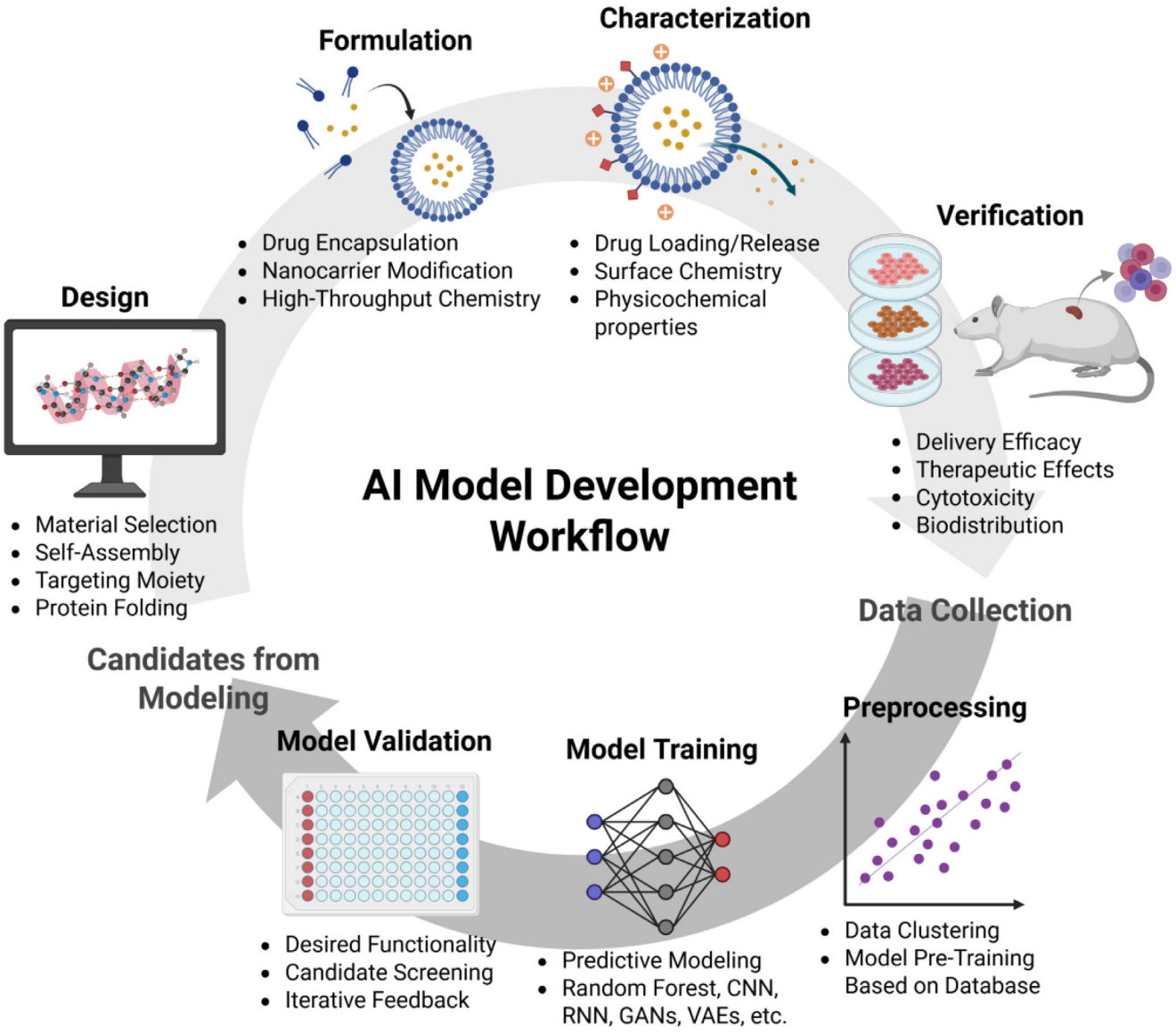


**Figure 2.** Schematic workflow of an AI algorithm for targeted drug delivery. Created with BioRender.com.

training, and tuning, allowing users to deploy robust models with minimal manual effort.[28]

Many of the representative AI tools listed in Table 1 are available as open-source platforms, which significantly enhance accessibility and reproducibility in nanomedicine research. For example, SHAP enables model explainability,[29] AutoKeras supports automated model development,[30] AlphaFold and RFdiffusion are widely used for protein structure prediction and design,[31] and frameworks like PySyft or Flower facilitate the implementation of federated learning. These tools help lower technical barriers and broaden participation in AI-driven nanoarchitectonic drug delivery design.

While numerous AI approaches have been applied to nanoarchitectonic design, their applicability, strengths, and limitations vary significantly depending on the stage and complexity of the drug delivery pipeline (**Table 2**). For instance, RF and SVMs are commonly employed for early-stage classification tasks,[32] such as predicting nanocarrier toxicity or ligand-binding affinity, due to their strong performance on small to medium-sized datasets and high interpretability. However, their ability to model nonlinear, high-dimensional relationships is limited compared to deep learning methods. DNNs, including CNNs, excel at complex pattern recognition tasks, including structure–activity modeling and image-based cellular phenotyping.[33] These models leverage large datasets and can uncover latent features that are otherwise undetectable. Nevertheless, they are often criticized for their "black-box" nature, and they require extensive hyperparameter tuning, high-quality data, and substantial computational resources. Graph Neural Networks (GNNs) and transformer-based models such as AlphaFold and RoseTTAFold are highly effective for 3D structural predictions, particularly of proteins, peptides, and ligand–receptor interactions.[34] These models are

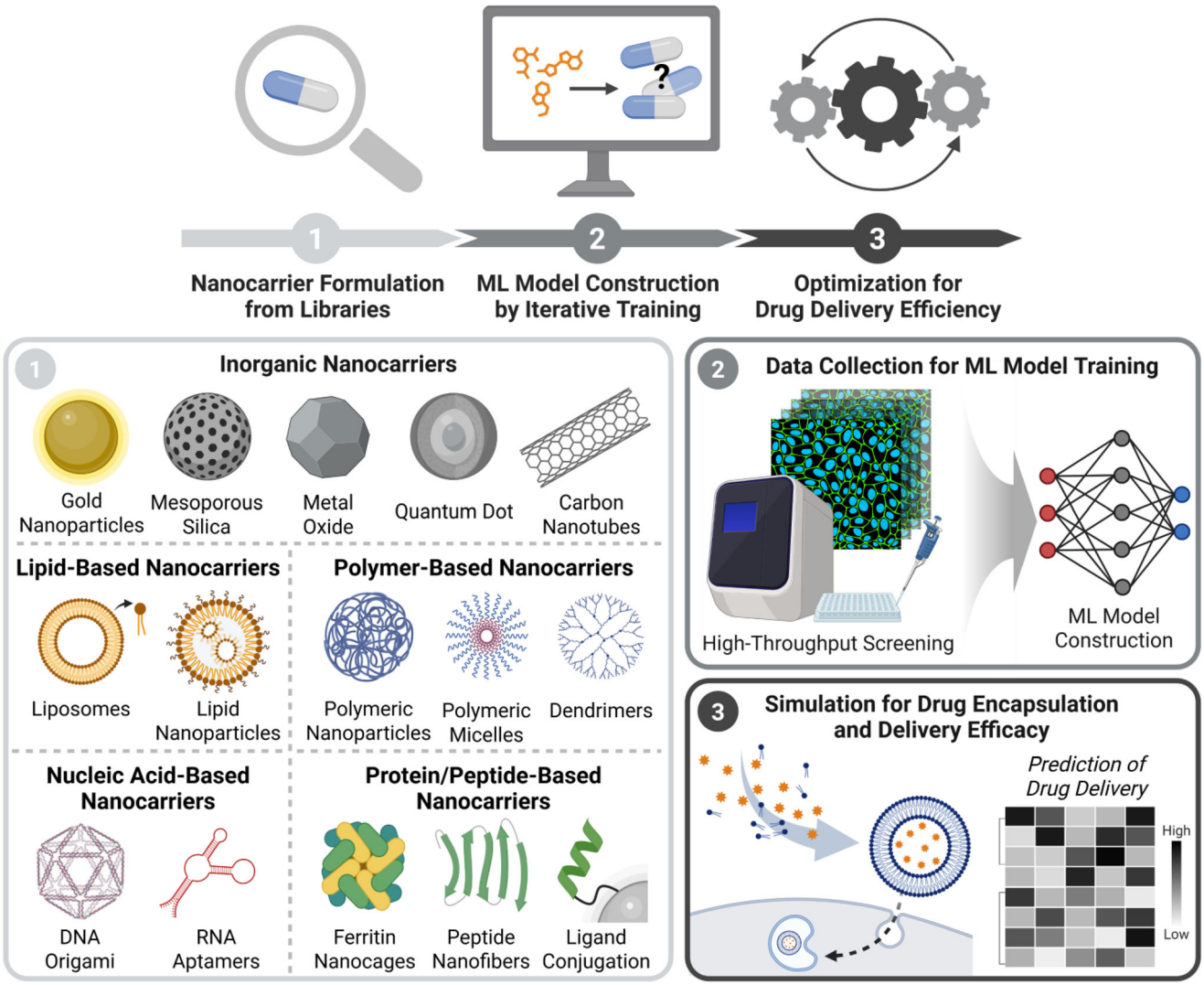


**Figure 3.** AI-guided nanomaterials and nanocarrier design process for targeted drug delivery. Created with BioRender.com.

increasingly applied to the design of targeting domains and binding scaffolds.[30b] Despite their advantages, their complexity and reliance on high-resolution structural data can limit their accessibility in some research contexts. Generative models (e.g., Variational Autoencoders (VAEs), Generative Adversarial Networks (GANs), RoseTTAFold diffusion (RFdiffusion) offer powerful capabilities for inverse design by generating novel nanocarrier architectures with predefined features.[31b] However, these models are data-intensive and often require expert curation and post-processing to identify chemically viable candidates.

To enhance model transparency and interpretability, explainable artificial intelligence (XAI) tools, such as SHAP and Local Interpretable Model–Agnostic Explanations (LIME), are commonly used to attribute importance to input features driving model predictions.[29,35] Frameworks, such as knowledge graphs, support structured reasoning across complex biomedical relationships and facilitate the integration of multi-scale data.[36] Finally, hybrid tools that combine conventional modeling methods, such as molecular dynamics (MD) simulations, with AI acceleration, improve both computational efficiency and predictive performance.[37]

This classification provides a practical lens through which to evaluate and select AI tools suited to specific stages of the nanoarchitectonic drug delivery process, supporting a more modular, scalable, and mechanistically interpretable system design, as discussed in the following sections.

### 3.1. Library-Based Nanocarrier Formulation

From the perspective of nanoarchitectonics, nanocarrier formulation extends beyond material selection to the rational organization of nanoscale building blocks into functional architectures with dynamic and integrated behavior. This approach combines molecular design, self-assembly, interface engineering, and external-field modulation to create adaptive drug delivery systems.[46] To support this goal, extensive libraries of nanocarriers have been developed, comprising a broad spectrum of

**Table 1.** AI approaches in nanoarchitectonics for targeted drug delivery. This table summarizes representative AI methods applied across three stages of nanoarchitectonics for drug delivery: (1) nanocarrier design, (2) targeting system design, and (3) simulation and prediction. Each entry includes the AI approach, its functional classification (Type), a brief description, and representative applications.

| Stage | AI Approach | Type | Description | Example Applications | Refs. |
|---|---|---|---|---|---|
| 1. Nanocarrier Design | Deep Neural Networks (DNNs) | Model | Model complex relationships between formulation parameters and performance | Predict nanocarrier-drug compatibility, optimize nanoparticle synthesis | [26c,d] |
| | Random Forests (RF) | Algorithm | Ensemble method for robust prediction and feature selection | Predict clinically relevant physico-chemical properties of nanoparticles | [25b,c] |
| | AutoML Platforms | Platform | Automated ML for rapid model development | Rapid screening of material nanotoxicity | [28b] |
| | Generative Models (e.g., GANs, VAEs, etc.) | Model | Generate novel data or design candidates based on learned distributions | Design advanced materials; Predict crystal structures or chemical compositions | [26g,h] |
| | Bayesian Optimization | Algorithm | Efficiently optimize hyperparameters or experimental conditions | Optimize nanoparticle synthesis parameters | [38] |
| 2. Targeting System Design | Convolutional Neural Networks (CNNs) | Model | Analyze structural or image-based data | Predict ligand binding motifs, screen aptamer sequences | [26e,f] |
| | Transformer Models (e.g., AlphaFold, RoseTTAFold) | Model | Predict 3D structures of proteins and complexes | Design or predict the structure of targeting peptides and antibodies | [31a,39] |
| | Support Vector Machines (SVMs) | Algorithm | Classification and regression modeling | Predict the binding affinity of ligands for receptors | [25d–f] |
| | Reinforcement Learning (RL) | paradigm | Learning optimal strategies through rewards | Discover optimal ligand structures for specific targets | [27b] |
| 3. Simulation and Prediction | Gaussian Process Regression (GPR) | Algorithm | Probabilistic modeling with uncertainty estimates | Predict binding affinity with confidence intervals | [40] |
| | Molecular Dynamics (MD) Simulation with AI Acceleration | Hybrid tool | Simulate atomic interactions, enhanced by AI-accelerated approximations | Predicting efficacy of nanocarrier designs for cancer treatment | [37] |
| | Federated Learning | Paradigm | Distributed learning across decentralized datasets | Enable large-scale prediction of pharmacokinetics while preserving data privacy | [27c] |
| | Explainable Artificial Intelligence (XAI) (e.g., SHAP, LIME) | Interpretability tool | Interpret model decisions by feature attribution | Understand key factors influencing biodistribution, ADME profiles | [13c,41] |
| | Knowledge Graphs | Framework | Structured integration of multi-domain knowledge | Model relationships between drug, carrier, target, and physiological factors | [42] |
| | Combination ML | Model | Train and validate ML/DL models with diverse algorithms (e.g., DNN, RF, SVM, etc.) | Predict tissue distribution and target delivery efficiency | [43] |
| | Quantitative Structure-Activity Relationship (QSAR) Models | Algorithm | Statistical modeling correlating structural descriptors with biological activity | Predict nanocarrier biodistribution, toxicity, targeting efficiency, or ADME profiles | [44] |
| | k-Nearest Neighbors (k-NN) | Algorithm | Instance-based learning method that classifies or predicts outcomes based on similarity to nearest data points | Predict a consensus RNA secondary structure; Predict early recurrence of disease after resection | [45] |

building blocks including inorganic nanoparticles (e.g., gold nanoparticles, mesoporous silica, metal oxides, etc.), lipid-based systems (e.g., liposomes, lipid nanoparticles (LNPs)), polymer- or nucleic acid-based nanosystems, and peptide- and protein-based nanocages.[47] Each category provides distinct architectural potential, enabling the construction of nanocarriers with tunable size, surface properties, and biological behavior. These materials are engineered as integral components of orchestrated nanosystems, capable of exhibiting stimuli-responsive or environment-adaptive functionalities.

Nanocarrier libraries are formulated with attention to both structural control and emergent functionality. They are built through combinatorial synthesis, high-throughput screening, and systematic annotation of key physicochemical parameters

**Table 2.** Overview of representative AI model types commonly applied in nanoarchitectonic drug delivery design. The table summarizes the core strengths, limitations, and typical use cases of each model class, ranging from traditional machine learning (e.g., RF, SVM) to deep learning architectures (e.g., DNN, CNN, GNN), generative frameworks, and transformer-based models. These models are selected based on their suitability for specific tasks, such as property prediction, structural modeling, or de novo ligand design, and are referenced accordingly for further technical detail.

| Model Type | Strengths | Limitations | Best Use Case | Refs. |
|---|---|---|---|---|
| Random Forests (RFs) | Fast training, good for small data, and interpretable | Limited with high-dimensional or sequential data | Property prediction, feature selection | [32a] |
| Support Vector Machines (SVMs) | Accurate classification, effective for small data | Hard to scale to large datasets, kernel selection | Binding affinity classification | [32b,c] |
| Deep Neural Networks (DNNs) | Powerful nonlinear modeling | Requires large data, less interpretable | Structure–activity prediction | [33b,d] |
| Convolutional Neural Networks (CNNs) | Excellent for image-based analysis | Less effective for tabular data | Phenotypic screening, image classification | [33a,c] |
| Graph Neural Networks (GNNs) | Captures complex molecular graphs | Complex to train, needs structured input | Protein-ligand modeling, binding prediction | [34a,d] |
| Generative Models (GAN, VAE, DDPM) | Enables inverse design, creative exploration | Risk of invalid outputs, needs curation | Novel ligand or carrier design | [31b,34b] |
| Transformers | State-of-the-art for structural prediction | High resource demands, limited generalizability | Protein structure or interaction prediction and design | [31a,34c] |

such as size, zeta potential, drug loading efficiency, release profiles, targeting capability, and biocompatibility.[48] The resulting datasets provide a critical foundation for AI-driven selection and optimization. The effectiveness of AI-assisted design depends significantly on the intrinsic characteristics of each nanocarrier platform. For example, inorganic systems provide high structural stability and well-defined surface properties, which enable precise ligand functionalization and compatibility with imaging applications.[49] Lipid-based carriers are clinically validated, biocompatible, and highly efficient for drug encapsulation, making them well-suited for AI-based modeling of membrane dynamics and release kinetics. Polymeric nanocarriers offer tunable degradation rates, mechanical flexibility, and diverse drug–polymer interactions, which can be leveraged by ML to optimize spatiotemporal release profiles.[50] Meanwhile, nucleic acid-based architectures and protein nanocages offer genetically programmable features that allow AI to assist in folding prediction, sequence optimization, and immunogenicity evaluation.[51]

In addition to conventional nanocarrier types, AI-assisted design is increasingly being applied to more complex delivery platforms such as multi-stage responsive systems and multifunctional synergistic carriers.[52] These advanced architectures are engineered to perform sequential or simultaneous functions, including targeted accumulation, controlled drug release in response to specific stimuli, and integration with diagnostic or therapeutic modalities.[5] The design space for such systems is inherently high-dimensional, making them well-suited for data-driven modeling and optimization. Machine learning algorithms, including deep learning and reinforcement learning, can be used to predict interdependent behaviors among components, optimize spatiotemporal response profiles, and support the inverse design of multifunctional carriers tailored for complex disease contexts.[53]

Recognizing the distinct properties of each nanocarrier class is essential for developing AI models that are appropriately matched to the design complexity and intended function. As a result, nanocarrier formulation libraries serve not only as a foundation for material discovery but also as context-specific environments for AI-based inverse design, optimization, and performance prediction. Among AI techniques, VAEs and GANs have emerged as powerful generative models for the inverse design of inorganic solid materials.[54] ML models trained on nanocarrier libraries can uncover hidden structure–property–function relationships that inform the rational design of next-generation delivery systems. Rather than serving as static material catalogs, formulation libraries function as dynamic design spaces. In these spaces, each nanocarrier is treated as an architectural unit whose form and function can be computationally predicted, experimentally tuned, and systematically improved.

### 3.2. Iterative ML Model Development

While earlier sections have emphasized predictive modeling for formulation optimization, recent advances have expanded the role of AI in nanoarchitectonics from performance estimation to autonomous design generation. Building on data from nanocarrier libraries, machine learning models are developed through iterative training cycles that integrate experimental feedback. These models predict key delivery metrics such as encapsulation efficiency, circulation half-life, tissue-specific accumulation, and therapeutic efficacy based on design parameters.[12a,55] Algorithms such as random forests, SVMs, gradient boosting, and DNNs are commonly used to capture nonlinear relationships between formulation features and biological outcomes (Table 1).

In nanoarchitectonics, model construction extends beyond conventional regression or classification tasks. AI functions as a computational orchestrator, harmonizing design elements from molecular building blocks to complete nanosystems by learning how small-scale attributes, such as surface ligands, charge distribution, or core structure, translate into emergent behaviors like tumor-specific accumulation or endosomal escape.

Recent breakthroughs in generative and structure-predictive AI have enabled the bottom-up design of molecular

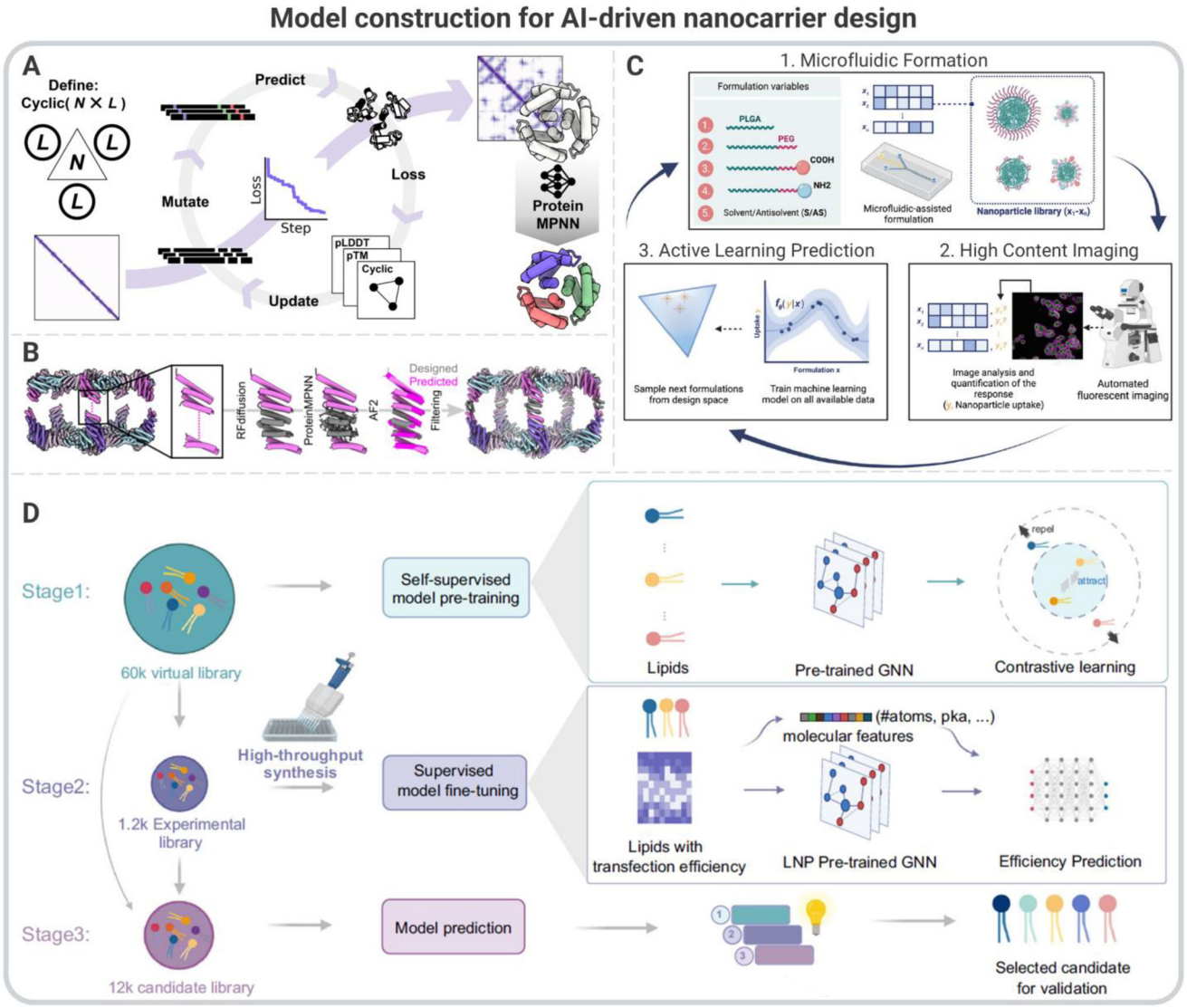


**Figure 4.** Representative examples of model construction for AI-driven nanomedicine design. A) Generative design of cyclic symmetric protein nanostructures using a Monte Carlo sampling approach guided by AlphaFold2 (AF2) structure predictions and ProteinMPNN-based sequence refinement. A random sequence is iteratively optimized to fit target symmetry and structural confidence. Reproduced with permission.[56] Copyright 2022, AAAS. B) Fine-tuning of bifaceted protein nanoparticle subunits using RFdiffusion. Backbone structures connecting functional motifs are generated de novo, followed by sequence design with ProteinMPNN and structural validation via AF2. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[57] Copyright 2024, bioRxiv. C) Iterative optimization of polymeric nanoparticle formulations via a closed-loop system. Microfluidic-assisted nanoprecipitation produces formulation variants, which are screened using high-content imaging (HCI). An ML model is trained to relate formulation variables to biological responses, enabling active learning and rapid design cycles. Reproduced under the terms of the CC-BY Creative Commons Attribution 3.0 Unported License[25c] Copyright 2024, RSC. D) A three-stage nanoparticle discovery pipeline leveraging self-supervised and supervised learning for ionizable LNP design. The AGILE framework pre-trains on virtual libraries, fine-tunes with high-throughput data, and deploys predictive models for candidate ranking in mRNA delivery applications. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[58] Copyright 2024, Springer Nature. Created with BioRender.com.

architectures with predefined structural and functional properties. For instance, Markov chain Monte Carlo (MCMC)-driven AlphaFold2 pipelines can generate novel protein nanostructures starting from minimal constraints such as cyclic symmetry and chain length, with sequence optimization by Protein Message-Passing Neural Network (ProteinMPNN) ensuring stable folding and functional interfaces (**Figure** 4A).[56] These models not only classify or regress known formulations but also create entirely new molecular architectures with defined structural motifs and self-assembly capabilities, embodying the principles of bottom-up functional design. Similarly, RFdiffusion, a denoising diffusion probabilistic model, has been applied to design bifunctional protein nanoparticles by generating backbone structures that bridge functional domains, followed by closed-loop sequence refinement and verification using AlphaFold2 (Figure 4B).[57]

These approaches demonstrate how AI can act as a digital architect, combining structural biology, computational design, and materials science to accelerate nanoarchitectonic innovation. Further integration with active learning strategies enables ML models to prioritize high-value data points for experimental testing, closing the loop between computational prediction, nanoscale synthesis, and biological validation. This approach not only enhances efficiency but also advances the vision of self-refining, adaptive design systems in AI-driven nanomedicine.

### 3.3. Optimization of Nanocarrier Delivery Performance

Integrated experimental-AI pipelines have emerged that combine formulation, high-throughput screening, and ML-guided iteration. These systems reflect the principles of nanoarchitectonics by establishing tightly coupled loops of design, construction, and evaluation that drive emergent, system-level behavior. This approach enables data-driven refinement of nanocarrier systems, leading to improved targeting, bioavailability, and therapeutic performance.

One representative approach utilizes microfluidics-assisted nanoprecipitation to generate nanoparticles with controlled variations in composition and structure, forming a dynamic library of candidate formulations (Figure 4C).[25c] These particles are then evaluated using high-content imaging (HCI) to extract phenotypic data such as cellular uptake, intracellular trafficking, and cytotoxicity. The resulting data feeds into an ML model, which learns the relationship between formulation variables and biological outcomes. The model then suggests new formulations predicted to improve desired properties, thereby guiding the next experimental cycle in an active learning loop. This strategy has been successfully applied to discover poly(lactide-co-glycolic acid)(PLGA)- polyethylene glycol (PEG) nanoparticles with enhanced uptake in breast cancer cells and holds promise for diverse nanocarrier platforms.

Advanced AI frameworks such as the AI-guided ionizable lipid engineering (AGILE) platform, based on a GNN architecture, implement a modular, staged approach that mirrors nanoarchitectonic construction (Figure 4D).[58] In this system, a virtual library of ionizable lipids is first used to pretrain a DL model in a self-supervised manner. This is followed by supervised fine-tuning using high-throughput experimental data to capture real-world performance trends. The trained model is then deployed to predict optimal lipid compositions for mRNA delivery via LNPs. By learning the complex structure–function relationships that govern transfection efficiency, membrane interaction, and immunogenicity, AGILE accelerates the identification of high-performance nanocarriers across vast chemical design spaces.

Through such frameworks, AI-driven optimization transcends conventional screening by enabling a convergence of computation and experimentation. Complex design objectives, such as target selectivity, stimuli-responsiveness, or multi-drug coordination, can be addressed through intelligent iteration within a multidimensional design space. A real-world demonstration of this approach is the development of LNP-based mRNA COVID-19 vaccines by Pfizer-BioNTech and Moderna.[59] In these platforms, AI and ML techniques were employed to optimize the composition of ionizable lipids, PEG-lipids, and cholesterol derivatives, which are crucial for ensuring efficient mRNA encapsulation, endosomal escape, and reduced immunogenicity. Computational screening methods, including Bayesian optimization and GNNs, facilitated the rapid evaluation of vast lipid libraries to predict candidate formulations with favorable biophysical properties and high transfection efficiency.[60] These AI-accelerated pipelines significantly shortened the formulation timeline and improved in vivo performance, enabling rapid clinical translation. However, this process still required extensive experimental validation, adaptation to Good Manufacturing Practice (GMP) protocols, and regulatory engagement to address safety, scalability, and batch consistency, which underscores the real-world hurdles that exist even in successful translation cases.[61] This paradigm has also been extended to siRNA-based nanocarrier systems, with several candidates designed using predictive modeling tools advancing into early-phase clinical trials, highlighting their translational potential. Nevertheless, translation of AI-designed siRNA carriers faces challenges such as interpatient variability in immune responses, difficulty in predicting long-term pharmacokinetics, and regulatory uncertainty regarding model interpretability and reproducibility.

In a typical implementation, DNNs are trained on datasets comprising nanoparticle descriptors such as size, surface charge (zeta potential), PEG density, hydrophilicity, ligand valency, and encapsulation efficiency. These features are paired with experimental outcomes, including cellular uptake rates, biodistribution profiles, or in vivo therapeutic response. GNNs are particularly suited for modeling polymeric or lipid structural relationships and can predict self-assembly behavior or membrane interaction potential. Trained models are used to rank or generate candidate formulations with optimized delivery profiles, which are experimentally validated and used to refine future predictions in a closed-loop system.

Collectively, these model-based strategies illustrate how AI can not only interpret but also generate and optimize nanocarrier systems with minimal human intervention. The synergy between design algorithms, predictive analytics, and experimental feedback loops is reshaping the landscape of nanomedicine development, enabling faster, smarter, and more personalized drug delivery platforms. These AI-guided optimization strategies set the stage for a more structured approach to smart nanocarrier design. In the following section, we present a three-phase framework that integrates these methodologies into a coherent strategy for precision targeting.

## 4. A Three-Step Strategy for AI-Driven Smart Nanoarchitectonics

This section introduces a structured, AI-enabled framework for the rational design of advanced targeted drug delivery systems. The proposed strategy consists of three interlinked phases that incorporate AI at every stage of the design pipeline to enhance specificity, adaptability, and therapeutic efficacy (**Figure 5**). The first phase focuses on molecular target identification through bioinformatic profiling and ML-based analysis of high-dimensional omics data. The second phase involves predictive surface engineering, where ML models guide the structural tuning and functionalization of nanocarriers to achieve selective targeting and immune compatibility. The third phase centers on

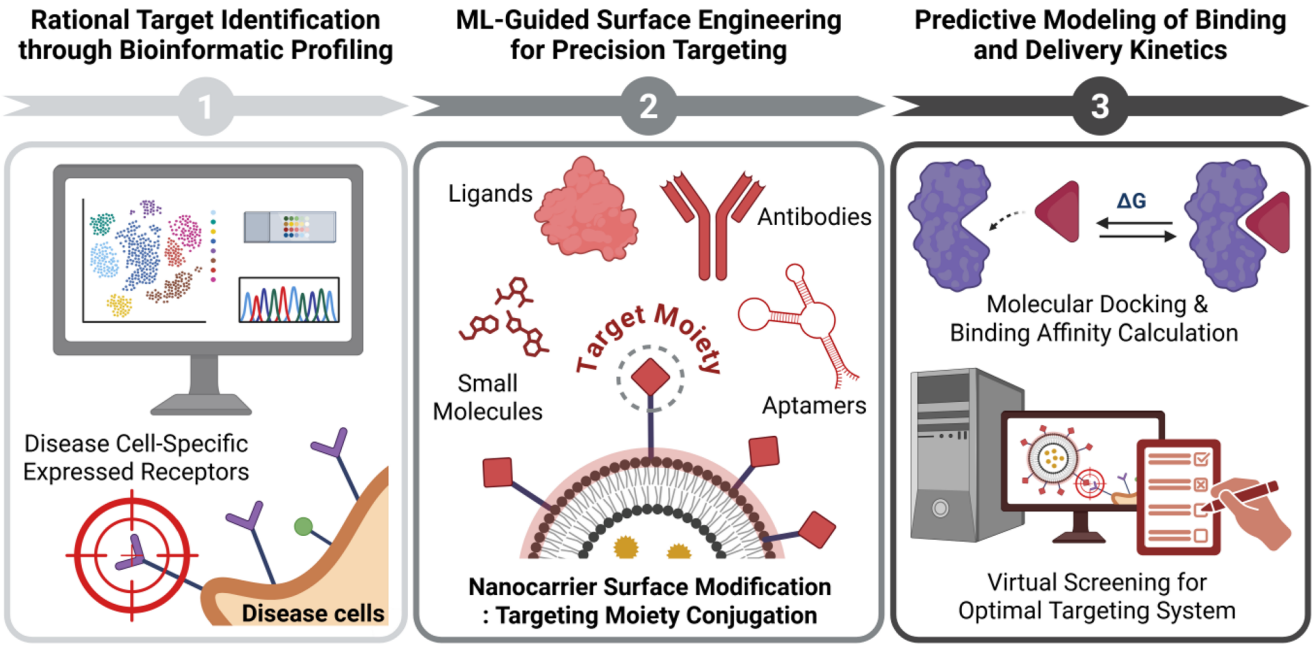


**Figure 5.** AI-driven prediction and optimization of smart targeted drug delivery. Created with BioRender.com.

delivery optimization, employing in silico simulations and data-informed pharmacokinetic modeling to refine biodistribution, binding kinetics, and systemic performance. Collectively, these steps provide a mechanistically grounded and data-driven framework that aligns with the principles of nanoarchitectonics and supports adaptive design across molecular, structural, and physiological scales.

Each phase comprises distinct but interconnected computational and experimental tasks. Rather than following a strictly linear sequence, the workflow operates iteratively: findings from surface functionalization or delivery modeling can inform earlier-stage decisions, including target prioritization and ligand selection. Such feedback-driven refinement increases responsiveness to biological complexity and supports context-sensitive design decisions. By reflecting the self-regulating nature of living systems, the recursive architecture exemplifies nanoarchitectonic principles that emphasize functional integration, scalability, and structural adaptability.

AI integration across the design pipeline not only enhances prediction accuracy but also accelerates translation from in silico models to in vivo performance. The sections that follow examine each phase in detail, including (Section 4.1) target identification, (Section 4.2) precision surface engineering, and (Section 4.3) dynamic delivery optimization, highlighting how AI and ML methodologies enable hypothesis generation, feature extraction, system-level learning, and iterative model refinement to support the creation of next-generation, intelligent drug delivery systems.

### 4.1. Rational Target Identification through Bioinformatic Profiling

The initial phase of AI-driven targeted drug delivery centers on selecting biologically meaningful targets, which is a decision that defines the entire trajectory of nanocarrier design. Traditional target identification relies on experimentally validated markers or phenotypic screening, which are often labor-intensive and limited in scope. However, recent advances in data science have enabled the analysis of high-dimensional, multi-omics datasets, such as genomic, transcriptomic, proteomic, and metabolomic profiles, to uncover previously unrecognized biomarkers and disease-specific pathways.[62] Techniques such as unsupervised clustering, principal component analysis, and feature selection algorithms allow for patient stratification and identification of conserved molecular patterns suitable for targeting, thereby enhancing therapeutic precision.

Single-cell RNA sequencing (scRNA-seq) has emerged as a powerful tool to resolve human disease heterogeneity at cellular resolution, particularly when conventional models are insufficient.[63] By applying scRNA-seq to patient-derived samples, researchers can identify disease-associated gene expression signatures and determine which genes or proteins might serve as optimal therapeutic targets. For example, analysis of patient-derived samples in drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DIHS/DRESS) revealed distinct immune cell signatures and upregulation of the JAK-STAT signaling pathway, pinpointing it as a potential therapeutic target (**Figure 6A**).[64] This case exemplifies how bioinformatic profiling via scRNA-seq can guide rational target selection for immune-mediated diseases.

Natural language processing (NLP) tools further enhance target discovery by mining scientific literature and clinical trial databases to contextualize candidate genes within disease ontologies.[65] When combined with biological network analyses, such as protein–protein interaction mapping or pathway enrichment models, these tools strengthen target prioritization by

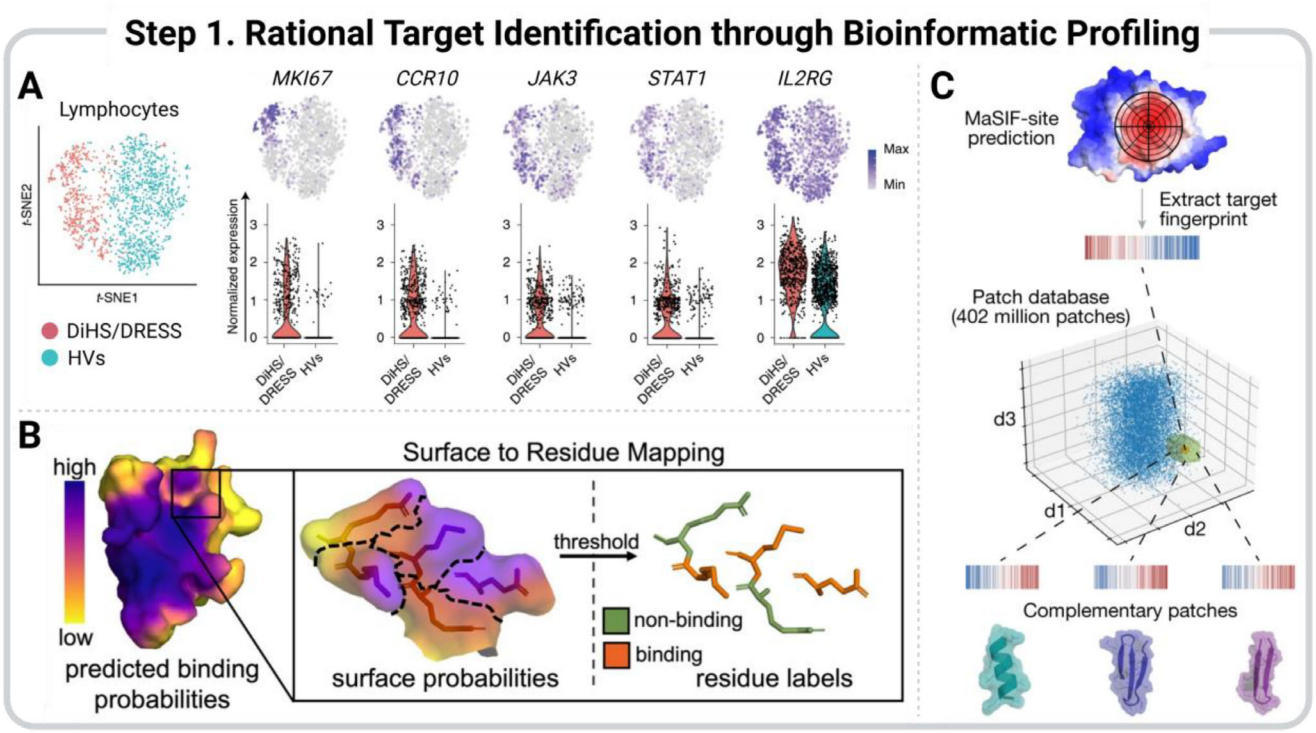


**Figure 6.** Representative examples for rational target identification through bioinformatic profiling. A) Single-cell RNA sequencing (scRNA-seq) analysis enables high-resolution profiling of patient-derived samples, revealing disease-specific cellular states and transcriptomic signatures. In the example shown, scRNA-seq of skin and blood samples from patients with refractory DiHS/DRESS identified an enrichment of keratinocytes and immune cell subpopulations, highlighting potential cellular targets. Reproduced with permission.[64] Copyright 2020, Springer Nature. B) PNAbind, a GNN model, predicts protein binding sites for peptide nucleic acids (PNAs) based on structural and physicochemical properties, allowing identification of therapeutically relevant interaction residues. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[67] Copyright 2024, Springer Nature. C) MaSIF (Molecular Surface Interaction Fingerprinting) detects targetable surface patches and evaluates interaction complementarity through DL. MaSIF-site identifies interface-prone regions, while MaSIF-seed screens a database of millions of patches to rank potential binding partners, accelerating rational binder design. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[68] Copyright 2023, Springer Nature. Created with BioRender.com.

identifying high centrality nodes with therapeutic relevance. MarkerGeneBERT, an NLP-based model trained on curated biomedical corpora, automatically extracts cell marker genes from single-cell sequencing studies, improving annotation accuracy and accelerating scRNA-seq interpretation.[66] This exemplifies how NLP methods can systematically augment early-stage target validation, forming part of a broader informatics pipeline that enhances the specificity and robustness of nanocarrier targeting strategies.

Once a target protein has been identified for therapeutic or diagnostic purposes, it is essential to assess its druggability and identify optimal binding interfaces. DL tools such as PNAbind employ GNNs to predict protein binding sites for peptide nucleic acids (PNAs) by analyzing structural and physicochemical features (Figure 6B).[67] Similarly, Molecular Surface Interaction Fingerprinting (MaSIF) uses DL to identify interface-prone surface patches and evaluate their compatibility with potential binders (Figure 6C).[68] The MaSIF-site module predicts regions likely to form buried protein–protein interfaces, while MaSIF-seed compares these patches to a database of over 400 million interaction motifs, aligning and rescoring the top candidates to identify viable seed structures. Together, these tools provide a robust and scalable platform for structure-based ligand design using only the structural information of the target protein.

In parallel, bioinformatic profiling should also account for delivery-related biological constraints. These include heterogeneous receptor expression across patient populations, off-target cell interactions, stromal barriers, elevated interstitial pressure, and the presence of immune cells that can rapidly clear nanoparticles.[2b] Identifying these obstacles early helps inform downstream design decisions such as surface modification or choice of delivery route. For example, physiological barriers, including plasma opsonization, tumor stroma density, and interstitial fluid pressure, can influence nanoparticle accumulation and distribution.[69] Furthermore, transcriptomic and proteomic analyses can be leveraged not only to pinpoint overexpressed surface receptors (e.g., HER2, EGFR, CD44), but also to uncover local microenvironmental stimuli such as hypoxia, acidic pH, or redox imbalance. These features can serve as activation triggers for smart, stimuli-responsive nanocarriers.[70] Incorporating both target recognition and biological barriers into the profiling stage enables more accurate and context-specific design of AI-guided delivery systems.

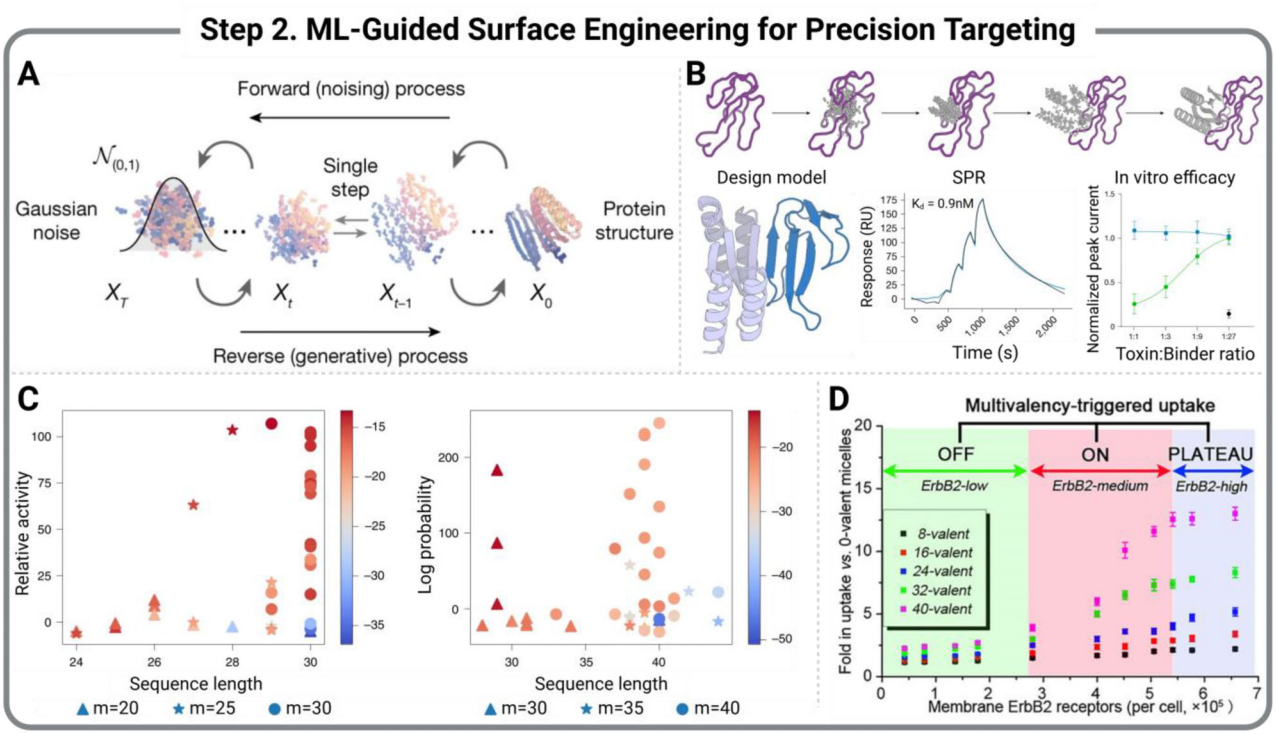


**Figure 7.** Representative examples of ML-guided surface engineering for nanocarrier targeting precision. A) RFdiffusion, a generative protein design model built upon RoseTTAFold, enables the de novo creation of receptor-binding proteins through iterative denoising of random structural inputs. The model generates folded backbones with user-defined topologies, facilitating high-specificity ligand design. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License. [31b] Copyright 2023, Springer Nature. B) Application of RFdiffusion to design a binder against the neurotoxin $\alpha$-cobratoxin. Starting from randomized residue placement near target $\beta$-strands, the model iteratively refines structures to produce a high-affinity binding protein. In vitro validation confirms strong neutralization comparable to monoclonal antibodies. Reproduced under the terms of the CC BY-NC-ND Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.[72] Copyright 2025, Springer Nature. C) RaptGen, a generative model trained on SELEX datasets, designs aptamers by encoding motif features into a latent space using a profile HMM decoder. The model predicts activity of novel sequences and uses Bayesian optimization to guide aptamer refinement across varying nucleotide lengths. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[38] Copyright 2022, Springer Nature. D) Surface ligand density optimization on nanocarriers. AI-guided modeling highlights the importance of matching ligand presentation to receptor density for maximizing cellular internalization, as demonstrated in ErbB2-targeting systems. Design variables include ligand type, spatial distribution, linker length, and surface charge. Reprinted with permission.[74] Copyright 2020, American Chemical Society. Created with BioRender.com.

### 4.2. ML-Guided Surface Engineering for Precision Targeting

Following target identification, selective ligand design is essential to ensure precise and efficient drug delivery. These strategies are generally categorized into passive and active targeting. Among them, active targeting, which is based on ligand–receptor interactions, plays a key role in precision medicine, offering advantages over passive strategies like the enhanced permeability and retention (EPR) effect or liver-specific uptake by LNPs, which are limited to certain physiological contexts.[71]

Recent advances in DL have enabled the *de novo* design of high-affinity targeting moieties, including small molecules, peptides, and antibodies. One example is RFdiffusion, a generative protein design tool built on the RoseTTAFold architecture. Fine-tuned for structural denoising tasks, it generates folded protein backbones with defined topologies by iteratively refining random sequences. RFdiffusion has been used to design receptor-binding proteins, enzyme scaffolds, and therapeutic motifs (**Figure 7A**).[31b] Notably, it produced a high-affinity binder against the neurotoxin $\alpha$-cobratoxin, with in vitro validation confirming strong neutralization comparable to that of monoclonal antibodies (Figure 7B).[72] Simultaneously, RaptGen, a generative model trained on SELEX (Systematic Evolution of Ligands by EXponential enrichment) datasets, designs aptamer sequences by embedding motif features into a latent space and optimizing candidates through Bayesian approaches, producing short, functional sequences with high binding activity (Figure 7C).[38]

Once designed, targeting ligands are conjugated to nanocarrier surfaces, where spatial configuration, ligand density, and surface chemistry critically influence cellular targeting and uptake.[73] For instance, Figure 7D illustrates how optimized ligand-to-receptor ratios enhance internalization in ErbB2-targeting systems, highlighting the importance of nanoscale precision.[74] The design space for nanoparticle surfaces is complex, involving variables such as ligand type, linker length, spatial density, hydrophilic–hydrophobic balance, and overall surface charge.[75]

Stealth functionality is another critical aspect of surface design, as it determines nanoparticle circulation time and immune evasion. Without effective surface shielding, nanocarriers are

rapidly cleared by the mononuclear phagocyte system. Strategies such as PEGylation and zwitterionic coatings are commonly employed to reduce opsonization and enhance systemic stability.[76] Designing such surfaces involves tuning parameters like charge, hydrophilicity, steric effects, and ligand presentation. This task is challenging due to the vast design space and the dynamic nature of biological environments. ML provides a powerful tool to streamline this process. ML models trained on in vivo data can predict how variations in PEG density, chain length, or spatial arrangement influence stealth performance and targeting efficiency.[4a,77]

In addition to stealth optimization, AI is increasingly applied to fine-tune other biophysical surface properties. ML algorithms can predict ligand–receptor binding affinity and simulate cellular uptake across various surface configurations. Techniques such as genetic algorithms and Bayesian optimization enable multi-parameter refinement under physiological constraints, allowing for precise control over ligand orientation, multivalency, and surface charge to enhance specificity and reduce off-target effects.[26f,44c,78]

Recent studies have also applied ML methods like random forests, k-nearest neighbors (k-NN), and SVM to predict nanoparticle dispersibility in solvents, using molecular descriptors such as Hansen solubility parameters, COSMO-based quantum chemical properties, and MACCSKeys fingerprints.[79] These tools are increasingly important in streamlining formulation and scaling in industrial contexts. Together, AI-enabled surface engineering streamlines the development of dynamic and adaptive nanocarrier systems, advancing the field toward more precise and customizable drug delivery platforms.

### 4.3. Predictive Modeling of Binding and Delivery Kinetics

While surface design determines the physical interface for cellular recognition, the dynamic interactions involved in drug delivery must be evaluated computationally. This section focuses on predictive modeling of nanocarrier behavior across biological systems, including molecular recognition such as ligand–receptor binding, as well as broader processes like membrane translocation, intracellular trafficking, and endosomal escape.[80] In silico approaches support early-stage screening by identifying promising candidates before laboratory validation, which reduces development time and resource requirements.

At the molecular scale, recent progress in DL has significantly improved the prediction of binding interactions. For instance, SurfDock combines protein sequences, 3D structural graphs, and surface features within a generative diffusion framework to predict ligand–receptor binding poses with high accuracy, outperforming traditional docking algorithms (**Figure** 8A).[81] Simultaneously, MD simulations remain essential for understanding the binding behavior of ligands. They provide atomistic insights into stability, energy landscapes, and the effects of solvent environments or external stimuli. These simulations are particularly helpful in refining ligand orientation and assessing how structural flexibility or multivalency influences binding efficiency.[37]

To model larger-scale interactions, coarse-grained methods such as the Martini force field are used to simulate nanoparticle interactions with cell membranes, including adhesion, endocytosis, and release into the cytoplasm. Potential of mean force (PMF) simulations further quantify energy barriers associated with membrane penetration and molecular binding, informing the thermodynamic feasibility of specific delivery routes (Figure 8B).[82]

AI-guided simulations are increasingly integrated with traditional modeling techniques to improve efficiency and accuracy. These hybrid methods can accelerate sampling, learn potential energy surfaces, and identify stable configurations with greater precision. For example, AlphaFold3 exhibits remarkably high accuracy in predicting complex biomolecular structures, including proteins, nucleic acids, and ligand assemblies (Figure 8C).[31a] These AI-driven structural prediction tools support structure-based nanocarrier design and enable more refined modeling of interactions between ligands and dynamic biological interfaces. AI-guided force field tuning also helps capture subtle interactions that are difficult to model with conventional parameters.

In the case of LNP-based systems, in silico models are being used to predict transfection efficiency by correlating structural properties with functional outcomes (Figure 8D).[58] These predictions are often supported by experimental studies measuring mRNA expression, cellular uptake, or protein production. This continuous exchange between in silico predictions and laboratory validation enables rapid refinement of LNP formulations for gene delivery applications.[83]

Importantly, accurate prediction of binding and delivery kinetics also requires consideration of complex biological barriers that influence nanocarrier transport and function.[84] Interactions with plasma proteins, such as albumin and immunoglobulins, can lead to opsonization and formation of a protein corona, which significantly alters the pharmacokinetic profile and targeting efficiency of nanoarchitectures. Likewise, the accessibility and expression pattern of cellular surface receptors at the disease site can impact ligand–receptor recognition, internalization, and tissue specificity. Other microenvironmental components, including the extracellular matrix, glycocalyx, and interstitial fluid pressure, may impede diffusion or promote non-specific uptake.[85] Incorporating these parameters into AI and simulation frameworks is crucial to achieving physiologically relevant predictions and to supporting the rational design of robust and translatable delivery systems.[86]

Beyond physics-based modeling, data-driven approaches such as quantitative structure–activity relationship (QSAR) modeling and ML algorithms constitute a critical factor. While QSAR is not inherently AI-based, it is increasingly combined with ML to correlate physicochemical features, such as size, surface charge, and hydrophobicity, to biological responses, including cellular uptake, toxicity, and biodistribution. By learning from these relationships, QSAR and AI-based models can prioritize virtual candidates that are likely to exhibit favorable performance in vitro and/or in vivo.[87] For instance, QSAR models have been applied to predict tumor accumulation of polymeric nanoparticles based on surface chemistry and mechanical properties.[88] Classification algorithms, such as SVMs and random forests, have distinguished between high- and low-performing formulations, while DL models have predicted cytotoxicity and trafficking behaviors in lipid-based carriers with notable accuracy.[89]

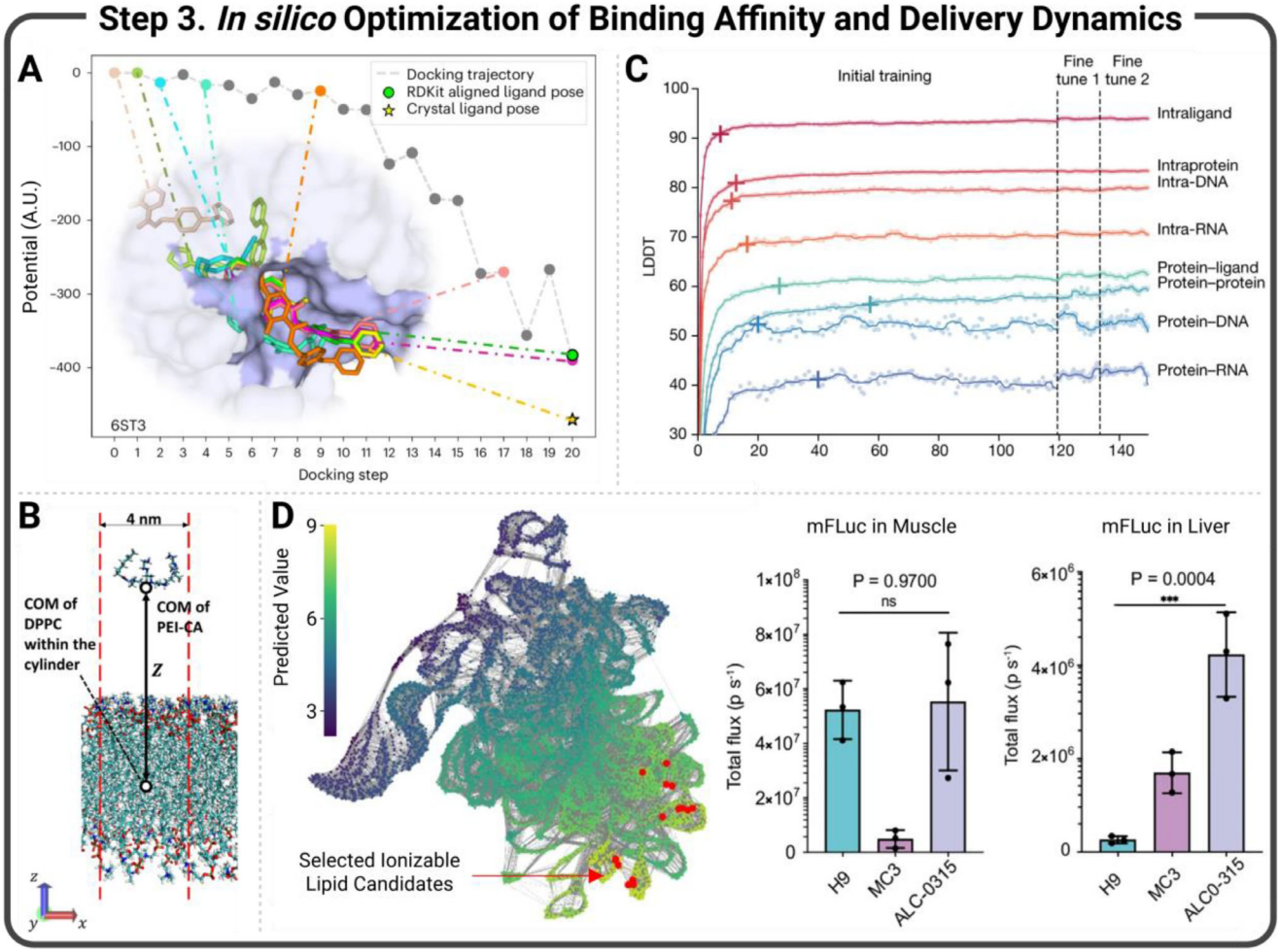


**Figure 8.** Computational strategies for in silico optimization of nanocarrier binding and delivery dynamics. A) SurfDock, a deep-learning-based method that integrates protein sequences, 3D structural graphs, and surface-level features within an equivariant architecture to predict ligand–receptor binding poses. Reproduced with permission.[81] Copyright 2025, Springer Nature. B) Potential of mean force (PMF) profiles derived from umbrella sampling simulations to quantify energy barriers associated with membrane translocation and molecular binding. Reproduced under the terms of the CC BY-NC-ND Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.[82] Copyright 2025, Springer Nature. C) AlphaFold3 model capable of high-accuracy prediction of protein–ligand, protein–nucleic acid, and antibody–antigen interactions within a unified DL architecture, surpassing previous specialized tools in structural accuracy. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[31a] Copyright 2024, Springer Nature. D) In silico prediction of lipid nanoparticle (LNP) transfection efficiency based on structure–function relationships, forming an iterative design–validation loop with experimental readouts such as mRNA expression and protein production. Reproduced under the terms of the CC-BY Creative Commons Attribution 4.0 International License.[58] Copyright 2024, Springer Nature. Created with BioRender.com.

Model interpretability is an important consideration. Methods such as SHAP provide insights into which molecular or structural features most strongly influence model predictions.[90] These tools not only enhance transparency but also help guide mechanistic understanding and experimental design. Additionally, pharmacokinetic and pharmacodynamic (PK/PD) modeling can be integrated with AI to optimize dose schedules, improve delivery efficiency, and tailor therapies to specific disease contexts.[91] AI-powered ADME (Absorption, Distribution, Metabolism, and Excretion) simulations further provide mechanistic insights into in vivo drug behavior, informing the rational design of delivery systems and reducing systemic toxicity through improved targeting.[13c,41,44b] These computational strategies support precise modeling of nanocarrier interactions and facilitate the rational design of adaptive delivery systems within the broader framework of nanoarchitectonics.

Furthermore, targeted delivery can be conceptualized as a multiscale cascade encompassing organ-level biodistribution, cell-specific targeting, and intracellular trafficking to functional compartments such as the cytosol or nucleus.[4a] AI models contribute at each of these levels by predicting systemic distribution from formulation attributes, guiding ligand selection for receptor-mediated endocytosis, and simulating membrane translocation or endosomal escape through in silico approaches.[44b,92] Key performance metrics, including targeting efficiency, cellular uptake rate, binding affinity, and endosomal escape probability, serve both as design objectives and as feedback variables for iterative refinement of AI models.

## 5. Challenges and Future Outlook

The integration of AI with nanoarchitectonics offers unprecedented opportunities for precision drug delivery but also presents several foundational challenges. Among these, data quality, model interpretability, regulatory readiness, and ethical deployment stand out as critical areas that require coordinated solutions.[93]

**Data Scarcity**: The development of accurate and generalizable AI models in nanomedicine is hindered by a lack of high-quality and standardized datasets. Current data are often fragmented, inconsistently reported, and lack harmonization across key parameters such as surface chemistry, pharmacokinetics, and therapeutic outcomes. There is also a pronounced gap between preclinical and clinical datasets, which complicates model transferability and real-world validation. To address these issues, FAIR (Findable, Accessible, Interoperable, and Reusable) data principles must be considered through community-driven curation initiatives. Federated learning offers a compelling solution by allowing decentralized model training across multiple institutions without compromising data privacy or ownership, thereby enabling secure and large-scale collaboration.

**Model Interpretability**: Although DL models demonstrate strong predictive capabilities in nanomedicine, their internal decision-making processes are often difficult to interpret, especially in complex biomedical systems. This limited transparency presents challenges for clinical translation and regulatory approval, where understanding how input features influence model outputs is essential for error detection, hypothesis generation, and risk assessment. To address this issue, XAI frameworks and interpretable model architectures are increasingly used to clarify how specific nanocarrier attributes, such as particle size, charge, or morphology, contribute to biological responses like biodistribution and immune evasion. Techniques such as saliency mapping, feature attribution (e.g., SHAP values), and counterfactual analysis enable researchers to visualize feature relevance and extract mechanistic insight from trained models. For example, SHAP can quantify the relative influence of design parameters such as zeta potential, PEG density, and particle diameter on predicted biodistribution profiles. These insights not only support rational nanocarrier optimization but also improve model transparency in the context of regulatory review.

In parallel, federated learning architectures are gaining attention as a means to enhance model reproducibility and generalizability. These frameworks allow multiple institutions to collaboratively train AI models on decentralized yet harmonized datasets, supporting robust validation across diverse clinical environments while maintaining data privacy and compliance with regulatory standards.[94]

**Regulatory Hurdles**: Current regulatory frameworks were not designed to accommodate adaptive, continuously learning therapeutic platforms. Unlike conventional drug formulations, AI-driven systems evolve based on newly acquired data, which challenges existing standards for validation, reproducibility, and safety assessment.

Recognizing these complexities, regulatory bodies are beginning to issue AI-specific guidance. For example, the U.S. Food and Drug Administration (FDA) released a draft guidance in 2024 outlining key considerations for the use of AI in drug and biological product development. This includes expectations for data quality, model transparency, explainability, generalizability, and lifecycle management.[95] Similarly, the European Medicines Agency (EMA) published its Network Data Steering Group (NDSG) Workplan 2025–2028, emphasizing the integration of AI governance into the medicinal product lifecycle and aligning with broader regulations such as the EU AI Act and GDPR. These efforts reflect a global shift toward regulatory innovation in response to AI-driven technologies.[96]

Continued progress will require adaptive guidelines, regulatory sandboxes, and standardized validation pipelines. Interdisciplinary working groups that include experts in regulatory science, computational modeling, clinical pharmacology, and ethics can help establish risk-informed pathways that ensure both safety and innovation. The growing use of AI platforms in nanomedicine also presents new risks in intellectual property protection. Premature disclosure of AI-generated designs, ambiguous inventorship, or third-party platform data rights may compromise novelty or ownership. These risks highlight the need for legal and institutional safeguards to protect innovation while ensuring responsible development.[97]

**Ethical Concerns**: Algorithmic bias, data security, and informed consent are especially relevant in AI-enabled nanomedicine. Models trained on non-representative or historically biased datasets may reinforce existing health disparities, resulting in inaccurate risk stratification, suboptimal drug recommendations, or even harmful clinical decisions for underrepresented populations. Furthermore, sensor-integrated and feedback-driven systems raise concerns around continuous surveillance, loss of autonomy, and the adequacy of one-time consent in the context of dynamic, adaptive technologies. These risks call for ethical design principles to be embedded early in development through frameworks such as ethics-by-design and algorithmic auditing. Transparent data governance, inclusive design practices, and stakeholder engagement are required for maintaining equity and accountability as technology evolves.[98]

**Strategic Directions**: To address these multidimensional challenges, innovation must occur at both technical and systemic levels. The development of interpretable and context-aware AI models is critical. These models should not only deliver predictive accuracy but also contribute to hypothesis generation, formulation optimization, and therapeutic decision-making. Advances in federated learning, synthetic data generation using models such as GANs or diffusion algorithms, and multimodal data integration that combines omics, imaging, and biophysical inputs will strengthen model robustness and applicability across diverse biological contexts. AI-driven nanocarrier design platforms, which integrate autonomous laboratories, robotic synthesis, and closed-loop experimentation, offer opportunities to accelerate the iterative design process. These systems can efficiently couple simulation and real-time experimentation, reducing development time and improving candidate prioritization (**Figure 9**)

The emergence of real-time optimized delivery systems represents a major leap forward. These platforms use biosensor feedback to dynamically adjust dosing, targeting, and release in response to patient-specific signals. Such adaptability enables unprecedented therapeutic precision. Additionally, the convergence of AI with multimodal nanomedicine, which integrates genomics, transcriptomics, imaging, and biomechanical data, will

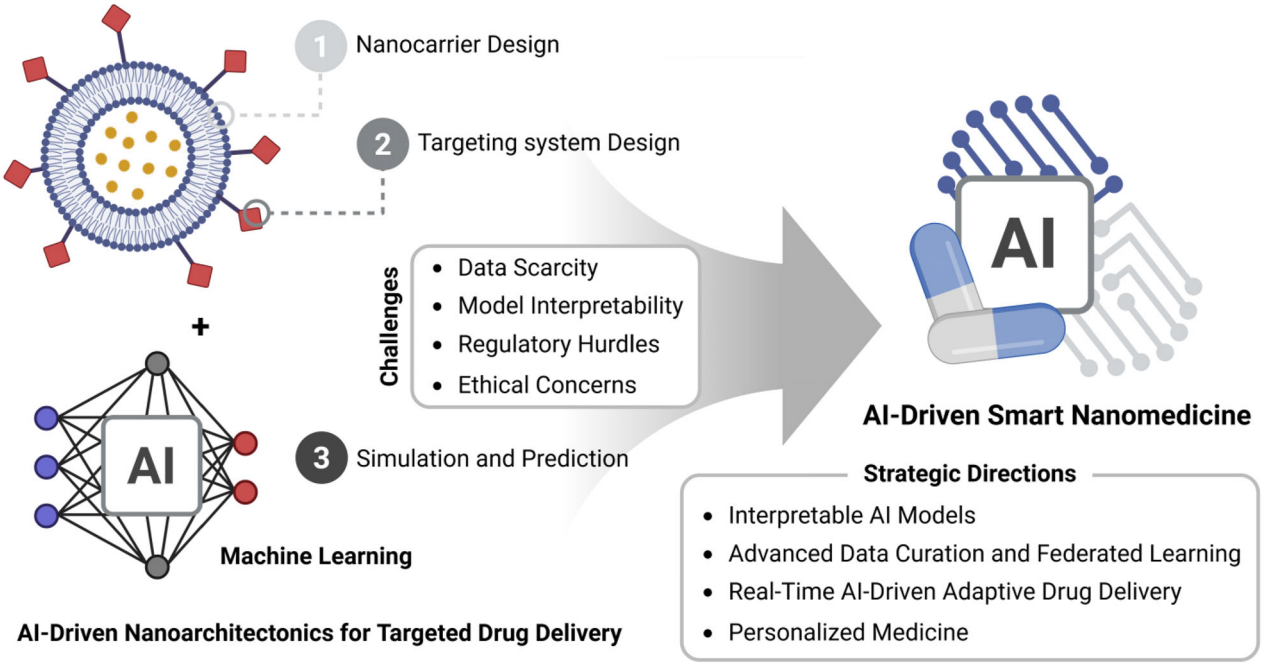


**Figure 9.** Conceptual framework summarizing the key challenges and future directions in AI-integrated nanoarchitectonics for targeted drug delivery. Created with BioRender.com.

support the creation of multifunctional nanocarriers capable of simultaneous diagnosis and treatment. Achieving this vision requires regulatory and ethical frameworks that are as adaptive and integrated as the technologies they aim to govern. By viewing current challenges not as barriers but as design constraints, the field can foster a more resilient and innovative ecosystem. In this context, AI-integrated nanoarchitectonics has the potential to shape a new paradigm in precision medicine that is both intelligent and ethically grounded.

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## Conflict of Interest

The authors declare no conflict of interest.

## Keywords

artificial intelligence, in silico optimization, machine learning, nanocarrier design, nanomedicine, targeted drug delivery

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