IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Artificial Intelligence and Machine Learning in Nanomedicine Design

(A COMPREHENSIVE REVIEW)

FINAL YEAR B.PHARM (SEMVIII)

EXECUTED IN ACADEMIC

YEAR 2026-2027

BY

1. MR.SANTOSH DATTARAO GAVALI

(PRN NO: 23025431823506)

2. MS.RUTUJA ANIL KHANDE

(PRN NO:2225431823103)

3. MS.VAISHNAVI BANGAR

(PRN NO. 2225431823102)

4. KHEDKAR SANKET DATTATRAYA

(PRN NO. 23025431823505)

GUIDED BY: DR. SANANSE V.A (DOCTOR OF PHARMACY)

PRINCIPAL : DR. PAWAR D.R (DOCTOR OF PHARMACY)

COLLAGE NAME : ADITYA PHARMACY COLLAGE, BEED

ABSTRACT

Nanomedicine is a rapidly growing area of healthcare that uses nanosized materials for the diagnosis, prevention, and treatment of different diseases, including cancer, infectious diseases, and neurological disorders. Various types of nanoparticles, such as lipid-based, polymeric, and inorganic nanoparticles, are widely explored because of their ability to improve drug delivery and therapeutic effectiveness. However,

despite encouraging research outcomes, converting these nanoparticle systems into approved clinical products is still a difficult process. Several important parameters, including particle size, surface properties, stability, and interaction with biological systems, need proper optimization to achieve safe and effective results in humans. In many cases, positive preclinical findings do not always produce the same success during clinical studies.

In recent years, Artificial Intelligence (AI) and Machine Learning (ML) have emerged as advanced technologies that can significantly improve the development of nanomedicine. These technologies help researchers analyze large amounts of experimental data, identify important relationships between nanoparticle properties and biological performance, and design optimized formulations more efficiently. AI-based computational models can also predict biodistribution, drug release patterns, toxicity, and therapeutic outcomes, helping reduce the time and cost involved in traditional trial-and-error research methods.

Advanced experimental approaches, including high-throughput screening and automated liquid handling systems, generate large datasets that support AI-driven analysis and accelerate nanoparticle discovery. In addition, AI plays an important role in studying protein corona formation on nanoparticle surfaces, which greatly affects immune response, cellular uptake, circulation time, and overall therapeutic performance.

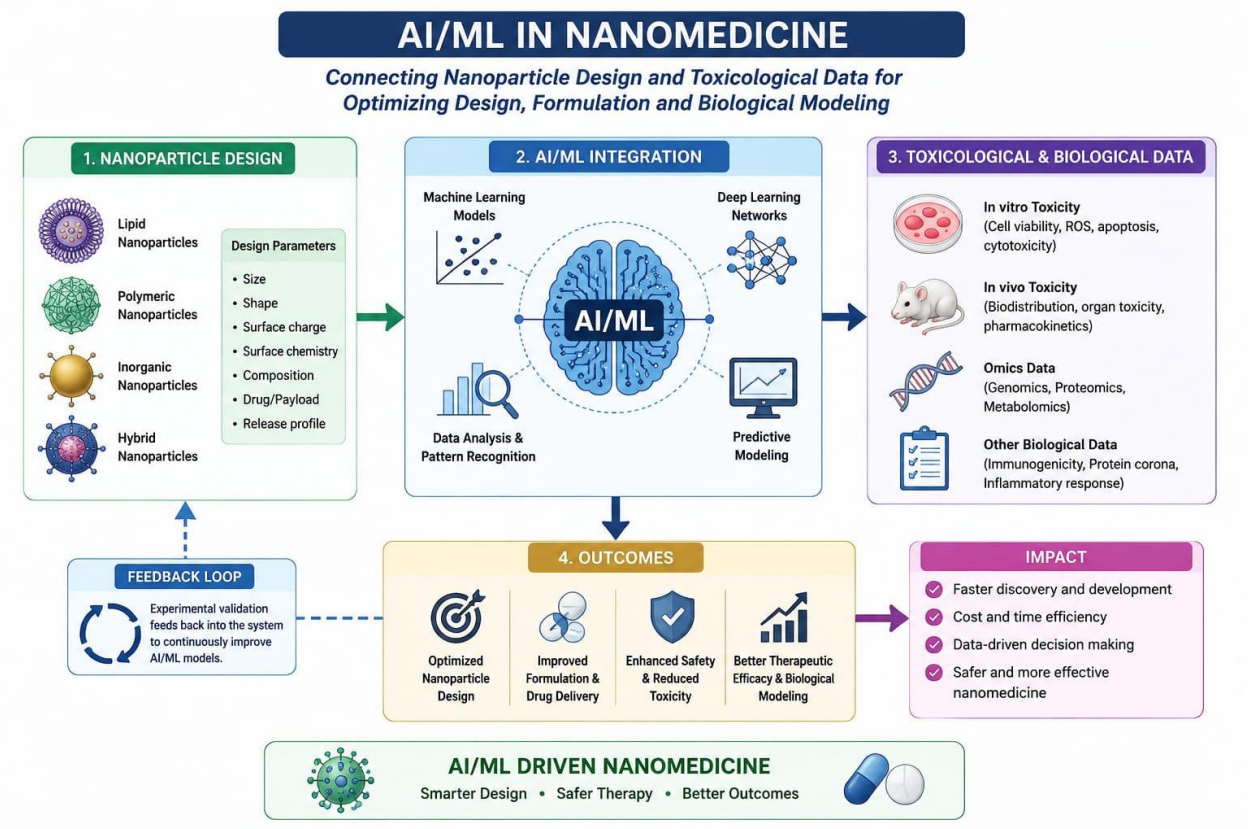
Although AI has shown great potential in nanomedicine research, several challenges still limit its full clinical application. Problems such as lack of standardized datasets, limited reproducibility of computational models, and absence of specific regulatory guidelines for AI-integrated nanomedicine remain major concerns. Therefore, better data sharing systems, accurate in vivo validation, ethical considerations, and clear regulatory frameworks are essential for future advancements in this field.

This review highlights the growing contribution of AI and ML in nanomedicine development, particularly in nanoparticle design, prediction of biological behavior, and optimization of drug delivery systems. It also discusses the present limitations and future opportunities associated with the integration of artificial intelligence into next-generation nanomedicine research.

KEYWORDS:

(Artificial Intelligence (AI),Machine Learning (ML),Nanomedicine,Nanoparticles (NPs),Drug Delivery System (DDS),Lipid Nanoparticles (LNPs),PBPK Modeling,Protein Corona,Generative AI,Targeted Drug Delivery)

- **Graphical Abstract**The integration of Artificial Intelligence (AI) and Machine Learning (ML) in nanomedicine helps establish a connection between nanoparticle design, formulation development, and toxicological analysis. These advanced computational approaches enable researchers to analyze large biological datasets, predict nanoparticle behavior, and optimize formulation parameters more efficiently. AI-driven models also improve the understanding of biological interactions, safety profiles, and therapeutic performance of nanoparticles, thereby supporting the development of safer and more effective nanomedicine systems.



3. Need of the Study

The rapid advancement of nanomedicine has created new opportunities for targeted drug delivery, disease diagnosis, and personalized therapy. However, the development of efficient nanoparticle (NP)-based systems remains highly challenging because nanoparticle behavior inside biological systems is influenced by multiple factors such as particle size, surface chemistry, biodistribution, toxicity, protein corona formation, and immune interactions. Traditional experimental approaches for optimizing nanomedicine formulations are often time-consuming, costly, and dependent on trial-and-error methods.

Artificial Intelligence (AI) and Machine Learning (ML) have emerged as powerful computational tools capable of accelerating nanomedicine research by analyzing large-scale datasets, predicting nanoparticle behavior, optimizing formulations, and improving preclinical predictions. AI-driven approaches can

identify hidden structure–activity relationships, enhance pharmacokinetic modeling, improve protein corona analysis, and support rational nanoparticle design with reduced experimental burden.

Despite these advancements, several challenges still exist regarding data standardization, model validation, biological complexity, and clinical translation of AI-assisted nanomedicine systems. Therefore, there is a strong need to study and understand the integration of AI and ML technologies in nanomedicine development.

This study aims to explore the applications, advantages, computational approaches, challenges, and future prospects of AI and ML in nanomedicine. The study also highlights how AI-driven technologies can improve nanoparticle formulation, biodistribution prediction, nano-bio interaction analysis, and high-throughput nanomedicine optimization for safer and more effective therapeutic applications.

4.INTRODUCTION

Nanomedicine is an emerging and highly flexible field that focuses on the use of nanoscale materials for the delivery of therapeutic and diagnostic agents. It supports the administration of a wide range of treatments, including small-molecule drugs, biologics, proteins, and vaccines. Because of their extremely small size and specialized surface characteristics, nanoparticles (NPs) can effectively move through complex biological systems and cross various physiological barriers such as the blood–brain barrier. These properties also allow NPs to selectively interact with target cells and tissues, improving the efficiency of drug delivery and therapeutic action (Mitchell et al. 2021).

Due to these advantages, nanomedicine has gained significant attention in the treatment and diagnosis of several diseases, including cancer, infectious diseases, and neurological disorders. NPs improve drug stability, enhance bioavailability, and enable targeted delivery, thereby reducing side effects associated with conventional therapies. Different nanomaterials such as lipid nanoparticles, polymeric nanoparticles, metallic nanoparticles, and hybrid nanocarriers are widely studied for biomedical applications (Huang et al. 2024; Shi et al. 2017; Wang, Hu, et al. 2024).

Despite major scientific advancements, many nanomedicine formulations fail to achieve successful clinical translation. One of the primary reasons behind this challenge is the complexity involved in NP design and optimization. Various physicochemical parameters, including particle size, shape, surface charge, surface chemistry, and payload properties, strongly influence the biological behavior and therapeutic performance of NPs. In addition, experimental in vitro and in vivo models often fail to accurately predict human clinical outcomes, leading to difficulties during later stages of development (Blanco et al. 2015; Chen et al. 2023; Wilhelm et al. 2016; Kim et al. 2024).

Another important factor affecting nanomedicine performance is the nano-bio interface. This refers to the interaction between NP surfaces and biological molecules such as plasma proteins, cell membranes, and immune system components. Even small modifications in NP surface properties can significantly alter biodistribution, cellular uptake, immune responses, circulation time, and therapeutic efficacy. Protein corona formation around NPs further complicates these interactions and directly impacts NP stability and biological activity (Francia et al. 2019; Shaw et al. 2025).

To better understand NP behavior, researchers have developed large databases containing information related to pharmacokinetics, biodistribution, tumor accumulation, toxicity, and physicochemical characteristics of NPs. The availability of these large and complex datasets has created opportunities for the application of AI and ML in nanomedicine research and development (Chen et al. 2023; Cheng et al. 2020; Wilhelm et al. 2016).

Recent advancements in AI and ML have introduced innovative approaches for overcoming many challenges associated with nanomedicine development. By analyzing high-dimensional datasets and identifying hidden patterns, AI-driven systems can optimize NP formulations and improve design strategies more efficiently than conventional experimental methods. ML algorithms are increasingly used to predict important preclinical outcomes such as toxicity, biodistribution, therapeutic efficacy, and drug release behavior. As a result, these computational techniques reduce dependence on costly and time-consuming trial-and-error experimentation (Ho 2022; Li et al. 2024; Mi et al. 2024; Shan et al. 2024).

AI and ML are especially useful in nanomedicine because they can model nonlinear biological relationships, optimize multidimensional formulation parameters, and integrate data obtained from experiments, simulations, and scientific literature. These technologies also assist researchers in predicting protein corona formation and understanding nano-bio interactions under different physiological conditions. High-throughput experimental platforms and automated liquid handling systems further support AI-driven research by generating standardized and reproducible datasets (Ban et al. 2020).

Although AI and ML offer significant advantages, several limitations still restrict their widespread implementation in nanomedicine. Challenges such as insufficient high-quality datasets, algorithmic bias, lack of standardization, and regulatory uncertainties can affect the reliability and practical use of AI-generated predictions. Data scarcity remains one of the major barriers because many available nanomedicine datasets are limited in size and consistency. To overcome these problems, researchers are exploring advanced techniques such as data augmentation and transfer learning to improve model accuracy and generalizability in low-data environments (Bets et al. 2024; Jahandoost et al. 2024).

Furthermore, successful translation of AI-assisted nanomedicine into clinically approved products requires extensive experimental validation and collaboration among researchers, clinicians, pharmaceutical industries, and regulatory authorities. Ethical considerations and proper regulatory

frameworks are also essential for ensuring the safe and effective application of AI technologies in healthcare.

This review focuses on the growing role of AI and ML in nanomedicine development. It highlights their applications in NP design, formulation optimization, toxicity prediction, biological modeling, and preclinical evaluation. In addition, the review discusses current challenges, limitations, and future opportunities associated with integrating AI technologies into next-generation nanomedicine systems for improved therapeutic outcomes and accelerated clinical translation.

5. AIM

To study the application of AI and ML in nanomedicine and evaluate their role in improving NP design, drug delivery, toxicity prediction, biological modeling, and formulation optimization for advanced healthcare applications.

6. OBJECTIVES

- To understand the basic concept and importance of nanomedicine in modern healthcare.
- To study different types of NPs used in drug delivery and disease treatment.
- To analyze the role of AI and ML in the design and optimization of nanomedicine formulations.
- To evaluate how AI and ML help in predicting biodistribution, toxicity, and therapeutic efficacy of NPs.
- To study the importance of nano-bio interactions and protein corona formation in nanomedicine.
- To understand the use of high-throughput screening and automated systems in AI-driven nanomedicine research.
- To identify the major challenges associated with AI-integrated nanomedicine, including data scarcity, algorithmic bias, and regulatory limitations.
- To explore future opportunities and advancements of AI and ML in next-generation nanomedicine development.

7. LITERATURE REVIEW

- **Mitchell et al. (2021)**

  Explained the importance of NPs in targeted drug delivery and their ability to cross biological barriers for improved therapeutic action.

- **Huang et al. (2024)**

  Discussed the applications of nanomedicine in cancer treatment and neurological disorders.

- **Shi et al. (2017)**

  Reported the use of nanomaterials for diagnosis and therapy of infectious and chronic diseases.

- **Blanco et al. (2015)**

  Studied the major challenges associated with clinical translation of nanomedicine formulations.

- **Wilhelm et al. (2016)**

  Analyzed NP delivery efficiency in tumors and limitations in successful clinical outcomes.

- **Chen et al. (2023)**

  Developed databases related to NP biodistribution and highlighted the importance of AI-assisted prediction models.

- **Kim et al. (2024)**

  Explained how physicochemical properties of NPs affect biological performance and clinical success.

- **Francia et al. (2019)**

  Investigated protein corona formation and its influence on NP uptake and immune response.

- **Shaw et al. (2025)**

  Discussed nano-bio interactions and the effects of surface modifications on NP behavior.

- **Ho (2022)**

  Highlighted the growing role of AI in nanomedicine design, optimization, and data analysis.

- **Li et al. (2024)**

  Studied AI-driven approaches for improving NP formulation and therapeutic prediction.

- **Mi et al. (2024)**

  Reported the application of ML techniques in predicting NP toxicity and biodistribution.

- **Shan et al. (2024)**

  Explained advanced AI frameworks for accelerating nanomedicine discovery and optimization.

- **Ban et al. (2020)**

  Focused on AI-based modeling of nano-bio interfaces and biological interactions.

- **Banaye Yazdipour et al. (2023)**

  Discussed ML applications in predicting preclinical outcomes and toxicity profiles of NPs.

- **Chou et al. (2023)**

Highlighted the importance of AI and ML in reducing trial-and-error experimentation in nanomedicine research.

- **Bets et al. (2024)**

  Explained the issue of data scarcity in AI-based nanomedicine research and suggested data augmentation techniques.

- **Jahandoost et al. (2024)**

  Studied transfer learning approaches for improving AI model performance in low-data conditions.

- **Nuhn (2023)**

  Emphasized the future potential of AI and ML in streamlining nanomedicine development and formulation strategies.

8. Limitations of Traditional Medicine System:

- Poor Target Specificity: Drugs distribute throughout the body, affecting both diseased and healthy cells.
- Low Bioavailability: Many drugs are not fully absorbed, reducing effectiveness.
- High Dose Requirement: Larger doses are needed to achieve therapeutic effect.
- Systemic Side Effects: Non-specific distribution leads to toxicity and side effects.
- Rapid Drug Degradation: Drugs may degrade before reaching the target site.
- Frequent Dosing: Short half-life requires repeated administration.
- Poor Solubility: Many drugs have low water solubility, limiting absorption.

Nanomedicine

Nanomedicine involves the use of nanoscale carriers such as nanoparticles, liposomes, dendrimers, and polymeric systems to improve drug delivery and therapeutic outcomes.

- **Advantages of Nanomedicine over Traditional Systems**

1. Targeted Drug Delivery

Delivers drug directly to specific cells or tissue

Reduces damage to healthy cells

Especially useful in cancer therapy

2. Improved Bioavailability

Enhances absorption of poorly soluble drugs

Increases therapeutic efficiency

3. Controlled and Sustained Release

Provides slow and controlled drug release

Reduces dosing frequency

4. Reduced Side Effect

Minimizes systemic toxicity

Improves patient safety

5. Enhanced Drug Stability

Protects drugs from degradation (enzymes, pH, etc.)

6. Lower Dose Requirement

Efficient delivery reduces required dose

7. Improved Pharmacokinetics

Better distribution, metabolism, and elimination

Increases half-life of drugs

8. Ability to Cross Biological Barriers

Can cross barriers like Blood-Brain Barrier (BBB)

9. Multifunctional Capability

Can combine therapy + diagnosis (Theranostics)

10. Personalized Medicine Support

9. AI-Driven Nanomedicine Design and Formulation

The design and optimization of nanomedicine formulations involve several interconnected factors such as NP size, shape, surface characteristics, and drug loading capacity. Traditionally, researchers depended on trial-and-error methods, where one formulation parameter was changed at a time. These conventional approaches are time-consuming, expensive, and less efficient in handling complex formulation challenges. In many cases, they fail to identify the best nanoparticle design because of limited ability to analyze large chemical design spaces and nonlinear relationships between formulation properties and biological responses.

Recent advancements in AI and ML have significantly improved the process of nanomedicine design and formulation optimization. AI-driven computational models can rapidly analyze large experimental datasets, identify hidden structure–activity relationships, and predict the performance of different NP formulations more accurately. These technologies enable faster screening of nanoparticle libraries and reduce the dependence on labor-intensive experimental methods.

Shan et al. (2024) introduced a directed evolution framework that combines virtual and physical compound libraries, combinatorial synthesis, DNA and peptide barcoding techniques, in vivo screening, and ML-based data analysis. This advanced approach overcomes the limitations of traditional linear screening methods by using an iterative and data-driven optimization strategy. Through continuous feedback from experimental data, researchers can improve NP formulations step-by-step and optimize therapeutic performance more efficiently.

AI-driven systems also help researchers understand nano-bio interactions and improve important formulation characteristics such as NP stability, drug release behavior, cellular uptake, and endosomal escape. High-throughput experimentation and automated screening platforms further accelerate nanomedicine discovery by generating large volumes of standardized data for AI analysis.

Overall, AI-based methodologies are transforming nanomedicine development by enabling faster discovery, improved formulation optimization, reduced experimental costs, and enhanced therapeutic efficiency of nanoparticle systems.

[Reference]

Shan et al. (2024) – Directed evolution framework for AI-driven nanomedicine optimization and formulation development.

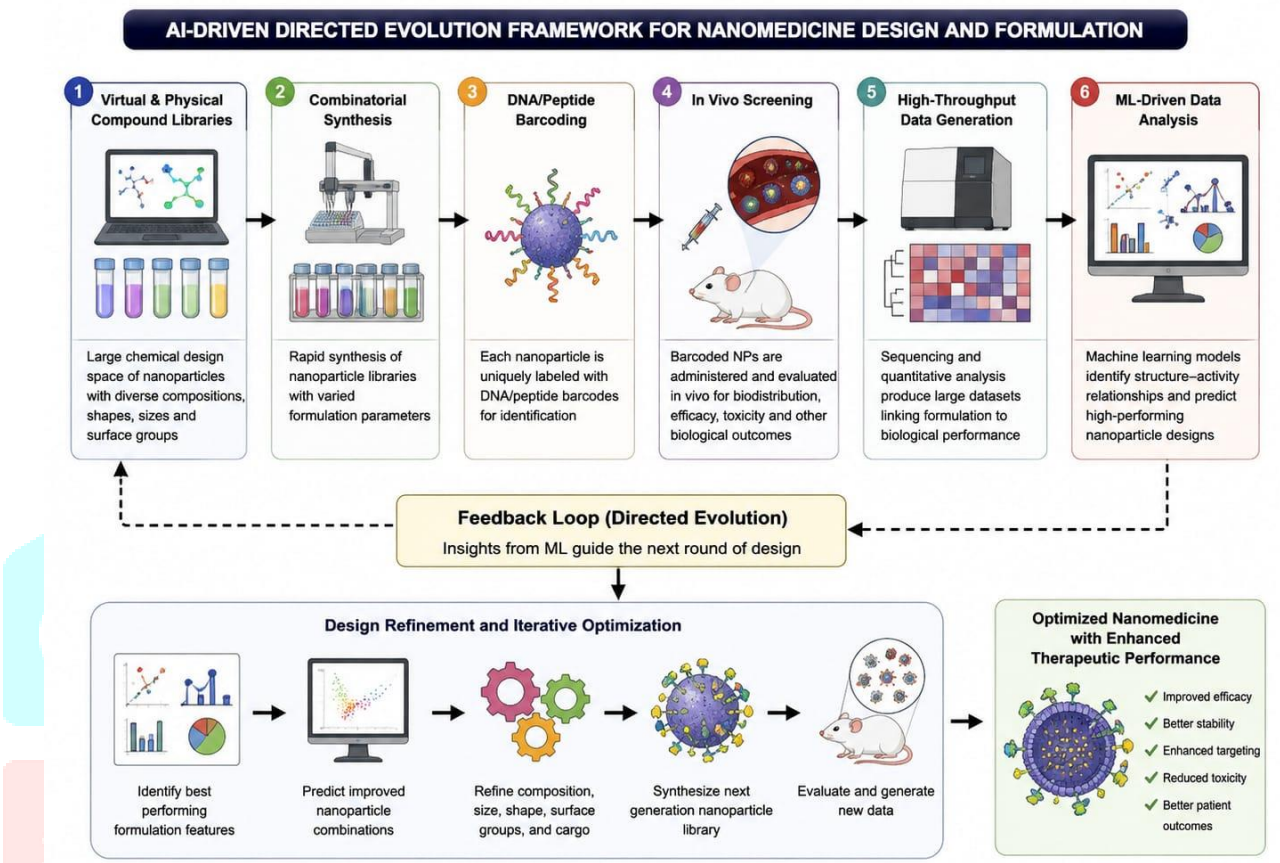


Figure 1. Directed evolution framework for AI-driven nanomedicine design and formulation.
The framework integrates virtual/physical libraries, combinatorial synthesis, barcoding, *in vivo* screening and ML-driven analysis in an iterative feedback loop to accelerate the discovery of optimized nanoparticle formulations.

9.1 Computational Approaches for Nanomedicine Formulation

Recent developments in AI and ML have significantly transformed the formulation and optimization of nanomedicine systems. Traditional formulation methods mainly depended on repeated trial-and-error experiments, which were expensive, time-consuming, and inefficient for handling complex nanoparticle formulations. AI-driven computational techniques now allow researchers to design and optimize nanomedicine formulations more rapidly and accurately by analyzing large experimental datasets and predicting formulation performance.

0(LNPs) used for RNA therapeutics and mRNA delivery. Several studies have demonstrated that ML-based computational models can efficiently screen large libraries of ionizable lipids and identify promising candidates with improved delivery performance (Li et al. 2024; Shan et al. 2024; Wang, Chen, et al. 2024; Witten et al. 2024; Xue et al. 2024).

Li et al. (2024) and Shan et al. (2024) reported ML-driven screening approaches that enhanced mRNA delivery efficiency in LNP systems. Similarly, Wang et al. (2022) performed large-scale in silico screening of nearly 20 million ionizable lipids and identified novel lipid candidates that showed better RNA delivery performance than established benchmark lipids such as MC3 and SM-102. These findings demonstrated the ability of AI models to accelerate lipid discovery and improve therapeutic efficiency.

Xue et al. (2024) introduced the AI-Guided Ionizable Lipid Engineering (AGILE) platform, which combined deep learning techniques, Graph Neural Network (GNN) models, and high-throughput combinatorial lipid synthesis. This platform screened approximately 1200 lipid formulations and further expanded predictions to nearly 12,000 lipid variants for improved mRNA transfection performance.

Witten et al. (2024) developed a large-scale dataset containing more than 9000 LNP activity measurements and demonstrated an AI-guided approach for pulmonary gene therapy applications. These computational pipelines reduced the need for repeated wet-laboratory experiments and enabled rapid identification of optimized nanoparticle formulations. AI and ML models also helped researchers identify nonlinear relationships between molecular structures and biological outcomes that are often difficult to detect using conventional methods.

Apart from LNPs, AI-driven approaches are also applied in the optimization of polymeric micelles, dendrimers, inorganic nanoparticles, and hybrid nanocarriers. Evolutionary algorithms and deep generative models are increasingly used to explore large formulation design spaces involving polymer composition, surface chemistry, and core-shell architecture (Ding et al. 2023; Rezvantalab et al. 2024).

Stillman et al. (2021) utilized reinforcement learning and multiscale simulations to optimize NP properties for improved tumor penetration and controlled drug release. Similarly, deep-learning models have been used to predict colloidal stability and sustained-release behavior, which are important for long-acting therapeutic applications (Kim et al. 2024).

AI-supported formulation platforms such as FormulationAI allow researchers to upload NP descriptors, receive AI-generated performance predictions, and refine formulations using shared datasets and cloud-based computational systems (Ding et al. 2023). Open-source databases and standardized reporting systems are also improving reproducibility and cross-laboratory collaboration in nanomedicine research (Agrahari and Agrahari 2018; Dordevic et al. 2022).

In addition, AI-based protein structure prediction technologies such as AlphaFold have further expanded the scope of targeted nanomedicine development (Jumper et al. 2021; Yang et al. 2023). These AI tools help researchers design peptide ligands and protein-based nanoparticles with specific three-dimensional structures for receptor-targeted drug delivery. Such targeting moieties improve tumor accumulation, cellular uptake, and reduce off-target effects in nanomedicine applications (Gomari et al. 2025).

Overall, AI-integrated computational pipelines are revolutionizing nanomedicine formulation by combining virtual screening, mechanistic modeling, biological simulations, and iterative experimental feedback. These technologies accelerate formulation development, reduce experimental costs, and enable the discovery of advanced nanoparticle systems that were previously difficult to achieve using traditional screening methods alone.

9.2 ML Insights Into Stability, Endosomal Escape, and Beyond

NP stability is one of the most important factors affecting the performance of nanomedicine systems. Stability refers to the ability of NPs to maintain their physicochemical properties such as size, shape, surface charge, and structural integrity under physiological and biological conditions. Poorly stable NPs may undergo aggregation, premature degradation, or rapid clearance from the body, which can reduce therapeutic efficacy and increase unwanted biological interactions (Hou et al. 2021).

Another critical factor in NP-based drug delivery is endosomal escape. After cellular uptake, many NPs become trapped inside endosomal vesicles. Effective endosomal escape allows the therapeutic payload to be released into the cytoplasm before degradation occurs inside lysosomes. Insufficient endosomal escape significantly limits the efficiency of drug and gene delivery systems because the therapeutic agents fail to reach their intracellular targets (Carrasco et al. 2021).

Although NP stability and endosomal escape are different processes, they are closely interconnected. NPs with poor colloidal stability may aggregate or disassemble under endosomal conditions, reducing escape efficiency. In contrast, specially designed stimuli-responsive NPs can undergo controlled destabilization in acidic endosomal environments, improving intracellular release of therapeutic agents. Materials with proton-sponge effects or membrane-disruptive properties are commonly used to enhance endosomal esca by responding to pH changes inside cells (Nayanathara et al. 2025; Smith et al. 2019).

Recent advancements in ML have provided powerful tools for understanding and optimizing NP stability and endosomal escape mechanisms. ML models can analyze large datasets containing NP physicochemical descriptors such as particle size, zeta potential, shape, surface chemistry, and material composition. These computational approaches help researchers identify hidden patterns and relationships that are difficult to detect using traditional experimental methods alone.

AI- and ML-driven predictive models assist in designing NPs with improved colloidal stability, reduced aggregation, controlled drug release, and enhanced intracellular delivery. Although direct studies simultaneously focusing on NP stability and endosomal escape are still limited, several related investigations have demonstrated the usefulness of data-driven approaches in nanomedicine optimization.

Chen and Lv (2022) reviewed ML-assisted NP synthesis strategies and highlighted how ML techniques improve control over NP stability, structural properties, and formulation parameters. Their work also emphasized the importance of understanding reaction conditions and material characteristics during NP fabrication.

Researchers are also exploring the integration of additional biological parameters such as proton-buffering capacity, ligand interactions, and intracellular trafficking behavior into ML-based predictive models. These improvements may help bridge the gap between in vitro characterization and in vivo therapeutic performance.

Furthermore, the growing use of stimuli-responsive nanomaterials introduces additional complexity into nanomedicine systems. These advanced materials respond to environmental triggers such as pH variations, temperature changes, or enzymatic activity for controlled drug release and targeted delivery. ML-based computational models are particularly useful for analyzing and optimizing these highly dynamic systems because they can process multidimensional datasets and predict biological responses more accurately (Fatima et al. 2024).

Overall, AI and ML are becoming valuable tools for improving NP stability, optimizing endosomal escape, and enhancing intracellular drug delivery. These technologies support the rational design of safer, more efficient, and highly targeted nanomedicine formulations for future therapeutic applications.

10.The Role of AI in NP Pharmacokinetics and Biodistribution

10.1 AI-Powered PBPK Modeling for Predicting NP Pharmacokinetics

Understanding NP pharmacokinetics (PK), biodistribution, and safety is essential for the successful development of nanomedicine systems. However, predicting NP behavior inside biological systems is highly complex because NPs interact with multiple biological barriers, tissues, cells, and biomolecules simultaneously (Mahmoudi et al. 2023; Park 2020; Yuan et al. 2023). In many cases, preclinical animal studies fail to accurately predict human outcomes because of differences in immune response, tissue permeability, protein interactions, and clearance mechanisms between species.

To overcome these limitations, PBPK modeling has emerged as an effective computational approach for predicting NP biodistribution and PK behavior (Chou et al. 2022; Chou et al. 2023; Dogra et al. 2020; Li et al. 2010; Lin, Aryal, et al. 2022; Yuan et al. 2019). Unlike traditional empirical methods, PBPK models divide the body into physiologically relevant compartments such as liver, spleen, blood, lungs, and tumors. These models incorporate physiological parameters including tissue volume, blood flow rate, permeability, plasma protein binding, and elimination rates to simulate NP movement throughout the body.

PBPK models can integrate large amounts of experimental information obtained from in vitro studies, animal experiments, and literature-based datasets to generate high-fidelity simulations of NP behavior. However, constructing PBPK models for nanomedicine requires several kinetic parameters such as cellular uptake rates and permeability coefficients, which are often difficult to measure experimentally (Le et al. 2022).

Recent advancements in AI and ML have significantly improved PBPK modeling by predicting these missing parameters and enhancing simulation accuracy. AI-assisted PBPK systems combine ML algorithms with mechanistic biological models to improve prediction of NP biodistribution and therapeutic performance (Chou et al. 2023; Chou and Lin 2023).

Chou et al. (2023) developed an AI-PBPK workflow that integrated a deep neural QSAR model with a mouse PBPK model. Their system achieved high prediction accuracy for 24-hour tumor delivery across 378 datasets without requiring additional animal calibration experiments. Similarly, Mi et al. (2024) collected 534 mouse biodistribution profiles from 10 different NP platforms and used deep neural network (DNN) models to predict tumor delivery and tissue distribution. Their analysis identified hydrodynamic size and zeta potential as major factors influencing NP biodistribution.

Khakpour et al. (2025) further improved prediction performance using a multi-view cross-attention network combined with RF and XGB ensemble models. Their results demonstrated lower prediction errors compared to traditional multilayer perceptron (MLP) models, while hydrodynamic diameter was identified as a dominant factor affecting tumor accumulation and NP kinetics.

AI also plays an important role in cross-species translation by learning patterns from both animal and human datasets. AI-assisted models can estimate human-specific kinetic parameters using in vitro experimental data and physicochemical descriptors. Although most current studies are still based on animal models, these approaches provide a strong foundation for future human-specific PBPK predictions (Mi et al. 2024; Chou and Lin 2023).

When integrated with QSAR modeling, AI-assisted PBPK simulations become highly valuable for rational NP design. QSAR models establish relationships between NP physicochemical properties and experimentally measured kinetic parameters. Using these computational approaches, researchers can predict how changes in NP size, surface charge, or shape may influence biodistribution, toxicity, tumor accumulation, and therapeutic efficiency without performing extensive wet-laboratory experiments (Lin, Chou, et al. 2022; Mi et al. 2024).

For example, Chou et al. (2023) utilized a Nano-Tumor Database containing NP descriptors such as particle size, surface charge, and shape to train an AI-QSAR model. The predicted kinetic parameters were then incorporated into a PBPK model to create an AI-assisted PBPK simulation system for NP

biodistribution analysis. These simulations helped identify the most promising NP candidates before experimental validation in animal studies.

Overall, AI-powered PBPK modeling is becoming a powerful tool for predicting NP PK behavior, optimizing biodistribution, reducing experimental costs, and accelerating nanomedicine development. The integration of AI, QSAR, and PBPK frameworks provides a more efficient and mechanistic approach for designing safer and more effective nanomedicine systems.

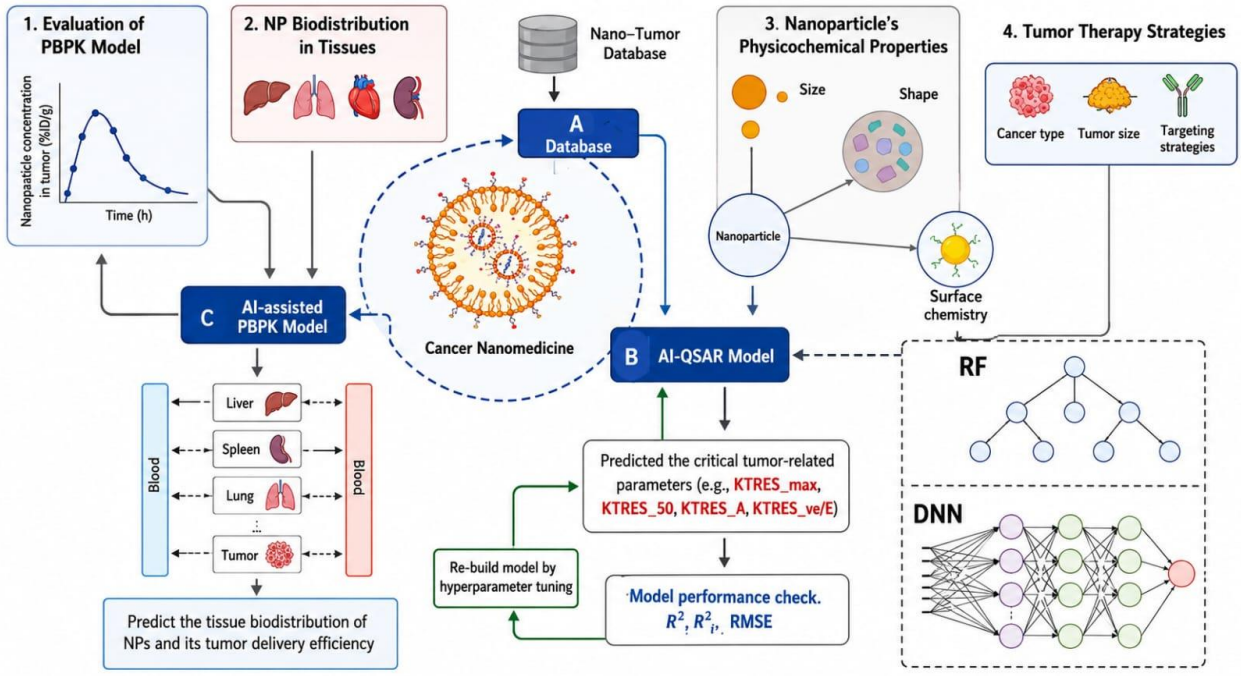


Figure-2 [AI ACCOCIATED MODEL]

10.2Data-Driven Models for NP Pharmacokinetics

Recent advancements in AI have introduced advanced data-driven approaches for improving NP pharmacokinetic modeling beyond traditional PBPK systems. Among these modern approaches, Neural Ordinary Differential Equations (NODEs) and Physics-Informed Neural Networks (PINNs) have gained significant attention because they combine mechanistic biological understanding with deep learning techniques (Bram et al. 2024; Karniadakis et al. 2021).

Traditional PBPK models use compartmental ordinary differential equations (ODEs) to describe the movement of NPs through different organs and tissues over time. Although these models are useful, they often require predefined equations and assumptions that may not fully capture the highly dynamic and nonlinear behavior of NP systems.

NODEs extend conventional ODE-based models by allowing AI systems to directly learn biological dynamics from experimental data while preserving continuous-time mathematical relationships. This combination improves both interpretability and predictive flexibility. Lu et al. (2021) demonstrated that NODE-based approaches could predict drug concentration profiles more accurately than traditional compartmental PK models, especially when working with sparse and noisy patient datasets.

In their study, NODEs dynamically adjusted ADME-related parameters and successfully learned nonlinear drug kinetics from real-world patient information. This approach is particularly useful for NP-based drug delivery because NP degradation, biodistribution, and drug release behavior often differ from classical pharmacokinetic assumptions.

For example, in NP-based cancer therapy, tumor permeability and the enhanced permeability and retention (EPR) effect strongly influence drug accumulation within tumors. NODE-driven systems can continuously refine predictions using patient-specific PK data, resulting in more accurate and personalized therapeutic modeling.

Another important AI-based approach is the use of PINNs. Unlike conventional neural networks, PINNs incorporate known physiological and pharmacokinetic principles directly into the training process. These models include biological constraints such as blood flow rate, tissue permeability, and compartmental PK equations within the loss function itself, ensuring that predictions remain biologically meaningful.

Ahmadi Daryakenari et al. (2025) developed a PINN-based model called CMINNs (Compartment Model Informed Neural Networks) to study the long-term PK behavior of amiodarone, a drug with complex absorption and elimination characteristics. Their model introduced time-dependent absorption rates and successfully captured fluctuations in drug concentration more accurately while maintaining consistency with known pharmacokinetic principles.

PINNs are especially valuable in nanomedicine because they can utilize limited but high-quality in vivo data, such as NP concentrations in blood or tissues measured at specific time points, and predict unmeasured biological dynamics while still following physiological rules. These approaches reduce the need for extensive experimental datasets and improve prediction accuracy for new dosing strategies and NP formulations (Ahmadi Daryakenari et al. 2025).

By integrating NODEs, PINNs, AI-assisted parameter estimation, and mechanistic PBPK frameworks, researchers are developing powerful hybrid computational systems for NP pharmacokinetics and biodistribution analysis. These advanced models improve simulation accuracy, reduce experimental costs, support personalized nanomedicine design, and accelerate the development of safer and more effective NP-based therapeutics.

Overall, data-driven AI models are transforming NP pharmacokinetic research by combining deep learning with biological principles, providing a more flexible, interpretable, and efficient framework for future nanomedicine development.

11. AI and Computational Modeling for Analyzing Nano-Bio Interactions

11.1 AI-Driven Analysis of Nano-Bio Interactions and Protein Corona Formation

When NPs enter biological fluids such as blood plasma, proteins and biomolecules rapidly attach to their surfaces, forming a structure known as the protein corona. This corona changes the original biological identity of NPs and significantly affects their biodistribution, immune recognition, cellular uptake, and therapeutic performance (Hajipour et al. 2023; Monopoli et al. 2012).

Protein corona formation strongly influences opsonization, immune clearance, circulation time, and localization of NPs within target tissues (Cai et al. 2022; Chou and Lin 2024; Corbo et al. 2016; Francia et al. 2019). Traditional experimental studies related to protein corona analysis are often slow and low-throughput. However, AI and ML techniques can efficiently process complex proteomic datasets and identify hidden relationships between NP properties and protein adsorption behavior.

ML algorithms can correlate NP physicochemical characteristics such as size, surface charge, hydrophobicity, and surface chemistry with specific protein corona profiles (Ban et al. 2020; Duan et al. 2020; Findlay et al. 2018; Fu et al. 2024; Huzar et al. 2025; Saeedimasine et al. 2024). These computational approaches help researchers understand how different NP surface properties influence electrostatic, hydrophobic, and steric interactions with plasma proteins.

For example, positively charged NPs preferentially attract negatively charged proteins such as albumin, whereas hydrophobic NP surfaces often adsorb apolipoproteins and immunoglobulins more efficiently (Lundqvist et al. 2008; Walkey et al. 2012). Experimental techniques such as fluorescence correlation spectroscopy, isothermal titration calorimetry, and surface plasmon resonance are commonly used to study protein binding affinity and protein exchange kinetics, helping researchers distinguish between hard and soft corona layers (Cedervall et al. 2007; Monopoli et al. 2012).

Advanced AI methods including RF, DNNs, and support vector machines are increasingly applied to identify the NP properties that most strongly influence protein corona formation, cellular trafficking, immune responses, and intracellular uptake.

Findlay et al. (2018) applied RF models to study silver NP-protein corona formation and achieved high prediction accuracy using NP size, surface charge, and ionic strength as major input features. Ban et al. (2020) further developed RF meta-models using large protein corona datasets to predict functional protein

categories such as immunoglobulins and apolipoproteins. Their work also demonstrated important relationships between protein corona composition, macrophage uptake, and cytokine release.

Similarly, Cao et al. (2025) used RF-based models to predict NP-induced pulmonary fibrosis by integrating NP descriptors, cytokine profiles, and cellular signaling data. These findings show that AI models can move beyond simple protein corona prediction and help connect protein signatures with immunological responses, toxicity, and therapeutic outcomes.

11.2 Computational Modeling and Predictive Insights Into Protein Corona Dynamics

Computational simulations combined with experimental protein-binding data provide important insights into protein corona dynamics and competitive protein adsorption on NP surfaces over time (Salvati et al. 2013).

Wei et al. (2017) used coarse-grained molecular simulations together with experimentally measured protein-NP binding affinities to study dynamic protein exchange on silica NP surfaces. Their work demonstrated how proteins compete and replace each other under biological conditions, significantly affecting NP interactions with cells and tissues.

The composition and structural arrangement of the protein corona strongly influence receptor-mediated endocytosis, intracellular trafficking pathways, immune clearance, and biodistribution. AI-based predictive models are therefore increasingly used to determine which proteins are most likely to adsorb onto specific NP surfaces (Ban et al. 2020; Fu et al. 2024; Huzar et al. 2025).

Ban et al. (2020) trained RF models using large-scale mass spectrometry datasets to predict protein binding profiles for different NP systems. Their study highlighted how small modifications in NP surface properties could significantly alter protein adsorption patterns and biological behavior.

Huzar et al. (2025) investigated protein corona formation on DNA nanostructures using XGBoost models and demonstrated that NP design characteristics strongly influence protein corona composition and functionality.

AI-driven protein corona prediction models are also linked with functional biological assays such as cellular uptake analysis and cytotoxicity testing. These combined approaches help researchers determine whether specific protein corona compositions improve receptor-mediated internalization or instead trigger rapid immune clearance and opsonization.

Boehnke et al. (2022) identified the SLC46A3 gene as an important biomarker associated with LNP uptake pathways through high-throughput protein interaction analysis. Similarly, Voke et al. (2025) demonstrated that proteins such as vitronectin, alpha-2-macroglobulin, and C-reactive protein enhanced LNP uptake in

HepG2 cells, although increased uptake did not always improve mRNA expression because certain protein coronas promoted lysosomal trafficking.

These findings highlight the importance of carefully controlling protein corona formation during nanomedicine development since higher NP uptake alone does not guarantee efficient therapeutic outcomes.

11.3 Possibilities of Generative AI for Inverse Nanomedicine Design

Recent advancements in generative AI technologies such as GANs and RL have introduced new possibilities for inverse NP design and nano-bio interaction optimization (Atz et al. 2024; Korshunova et al. 2022; Popova et al. 2018).

GANs, which are widely used in drug discovery and molecular design, can generate novel NP formulations with optimized physicochemical and biological properties (Rahman et al. 2025). By training AI models on datasets containing NP size, shape, surface chemistry, toxicity, and biodistribution profiles, GANs can propose new NP structures aimed at improving tumor targeting while minimizing immune recognition (Hasanzadeh et al. 2022).

RL further improves NP optimization by continuously refining NP formulations through feedback-based learning systems. These models reward NP designs that achieve desirable properties such as low off-target accumulation, enhanced cellular uptake, and improved therapeutic efficiency (Tao et al. 2021).

Researchers are also exploring generative AI systems for designing NP surfaces that selectively adsorb beneficial proteins while avoiding highly immunogenic proteins. Although direct applications for protein corona-specific NP design are still limited, similar AI-based inverse design approaches have already shown success in porous materials, photonic materials, and molecular synthesis (Yao et al. 2021; Liu et al. 2023; Sanchez-Lengeling and Aspuru-Guzik 2018).

By integrating generative AI with large-scale proteomic datasets, researchers aim to develop safer and more effective NPs with optimized protein corona profiles, enhanced tumor accumulation, reduced immunogenicity, and improved therapeutic performance (Canchola et al. 2025).

Another emerging development is the use of autonomous research systems or “robot scientists,” which combine AI-driven modeling with automated experimentation and active learning algorithms (Hickman et al. 2023; Rapp et al. 2024). These systems continuously refine NP properties through iterative feedback loops, improving protein corona composition, circulation stability, immune compatibility, and therapeutic activity over successive experimental cycles.

Overall, AI-driven computational modeling and generative AI technologies are transforming the understanding of nano-bio interactions and protein corona dynamics. These approaches provide powerful tools for designing safer, more targeted, and clinically effective nanomedicine systems

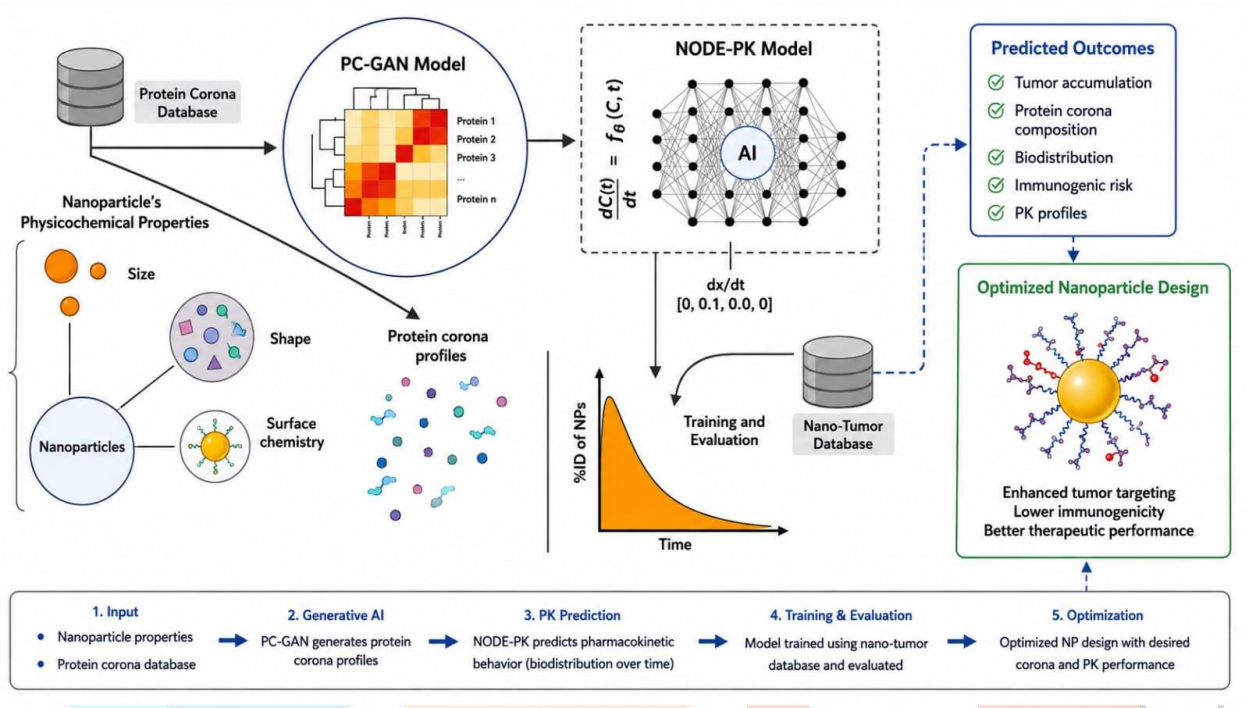


Figure-3

12. High-Throughput Platforms and Database Curation for Nanomaterials

12.1 High-Throughput NP Formulation and AI-Driven Optimization

High-throughput experimental technologies such as DNA barcoding, microfluidic automation, and combinatorial synthesis have significantly improved NP formulation, characterization, and performance analysis (Dahlman et al. 2017; Gimondi et al. 2023; Xue et al. 2024). These advanced platforms allow researchers to rapidly generate and evaluate large numbers of NP formulations by systematically modifying parameters such as particle size, surface chemistry, and drug loading capacity.

DNA barcoding is one of the most important high-throughput techniques used in nanomedicine research. In this approach, each NP formulation is tagged with a unique DNA barcode, allowing hundreds or thousands of NP variants to be tested simultaneously within a single biological experiment (Dahlman et al. 2017). Combined with automated liquid handling systems, multi-well plate readers, and next-generation sequencing technologies, researchers can efficiently evaluate NP uptake, biodistribution, therapeutic efficacy, and cellular interactions across multiple cell lines and animal models.

Guimaraes et al. (2024) demonstrated the effectiveness of this approach in SARS-CoV-2 vaccine development. In their study, barcoded DNA-loaded LNPs were formulated using microfluidic mixing techniques and administered to mice. Deep sequencing analysis was then used to identify LNP formulations with superior tissue-specific delivery, enhanced antigen uptake, and strong immunogenic responses against SARS-CoV-2 variants.

High-throughput chemical synthesis methods also allow rapid development of large NP libraries by screening various lipid, polymer, chemical, and small-molecule precursors (Shan et al. 2024). As a result, large formulation databases are continuously expanding, providing valuable information for identifying NP design principles and optimizing nanomedicine performance.

AI and ML models play a major role in analyzing these large-scale experimental datasets generated through high-throughput platforms. One important example is the AGILE platform developed by Xu et al. (2024), which combines deep learning algorithms with combinatorial lipid libraries for optimizing mRNA delivery systems.

The AGILE framework uses iterative feedback loops in which initial experimental data are used to train predictive AI models. These models then guide subsequent rounds of NP synthesis and optimization. This AI-assisted workflow significantly accelerates nanomedicine discovery and reduces reliance on traditional trial-and-error experimentation.

Overall, high-throughput screening platforms combined with AI-driven computational analysis are transforming nanomedicine development by enabling faster formulation optimization, large-scale data generation, and rational NP design.

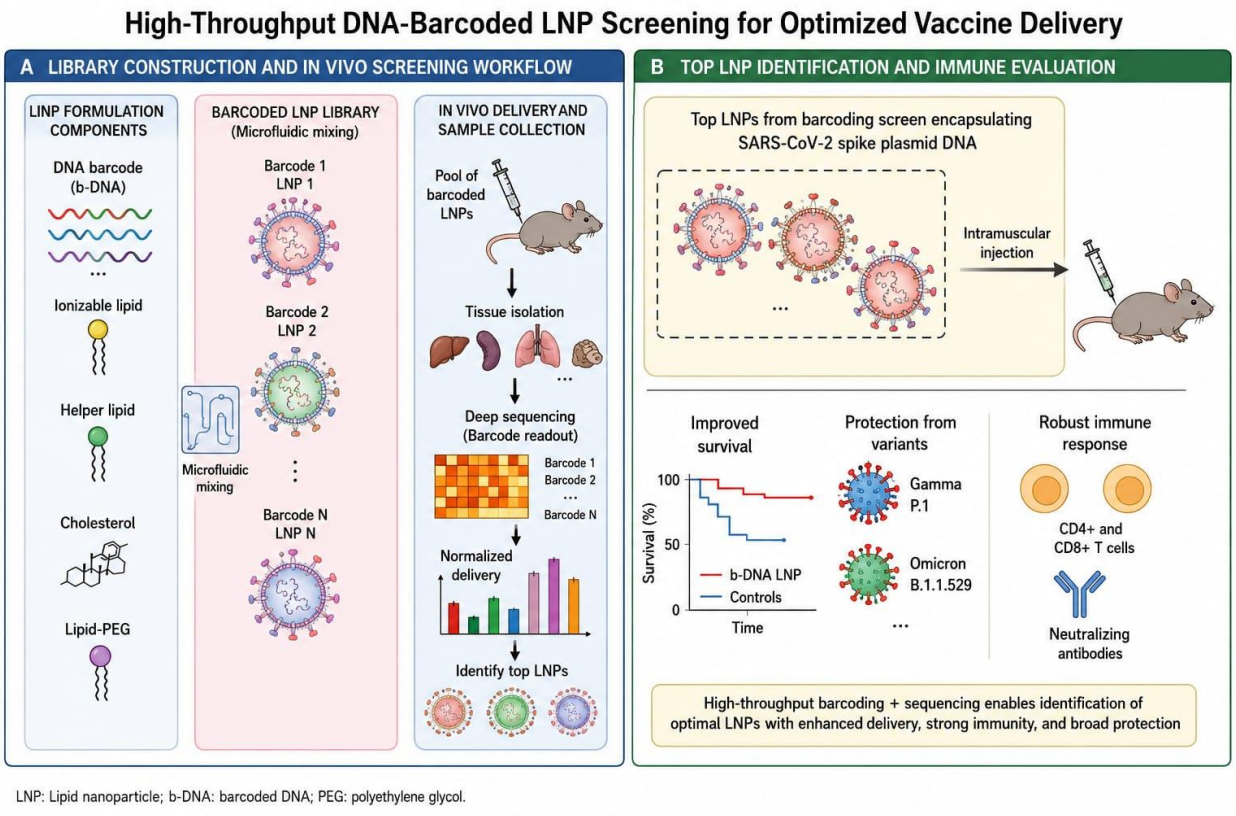


Figure-4

12.2 Advanced Proteomics and Predictive Protein Corona Profiling

High-throughput proteomics platforms have also become essential tools for studying protein corona formation and analyzing NP interactions within biological systems. These technologies help researchers investigate how different NP formulations interact with complex protein mixtures and how these interactions influence biodistribution, cellular uptake, immune response, and therapeutic efficacy (Ban et al. 2020; Blume et al. 2020; Gharibi et al. 2024; Liessi et al. 2021; Ouassil et al. 2022).

Gharibi et al. (2024) developed a standardized data-processing pipeline for harmonizing protein corona analysis across different proteomics laboratories. Their work highlighted the importance of consistent experimental protocols and data standardization for achieving reproducible and reliable cross-laboratory results.

Blume et al. (2020) introduced a multi-NP profiling strategy for rapid plasma proteome characterization. Their study demonstrated that even small modifications in NP surface chemistry could significantly alter the composition of adsorbed proteins on NP surfaces.

Beyond identifying protein adsorption, researchers are increasingly focusing on understanding protein binding orientation and molecular interactions on NP surfaces. Liessi et al. (2021) used isobaric labeling proteomics techniques to study protein corona orientation and showed that protein binding orientation strongly affects NP-biological interactions, immune recognition, and opsonization processes.

Ban et al. (2020) further integrated ML approaches with proteomics data to correlate protein corona composition with downstream cellular recognition and immune responses. Their findings demonstrated that AI-based predictive models could estimate how protein corona formation influences therapeutic performance and toxicological outcomes of NPs.

Similarly, Ouassil et al. (2022) applied supervised learning models to predict protein adsorption behavior on carbon nanotubes. Their study showed that AI-driven predictive systems can efficiently forecast preferential protein binding patterns for various nanomaterials.

Overall, advances in high-throughput proteomics, standardized data processing, and AI-based predictive modeling are shifting protein corona research from simple observational analysis toward highly predictive and mechanistic computational frameworks. These integrated approaches improve understanding of NP behavior in biological environments and support the development of safer, more targeted, and clinically effective nanomedicine systems.

13. Challenges and Limitations of AI/ML in Nanomedicine

Although AI and ML have significantly improved nanomedicine research, several important challenges still limit their widespread clinical application. These limitations include issues related to data quality, dataset standardization, model validation, algorithmic bias, regulatory uncertainty, and experimental scalability. Addressing these problems is essential for achieving reliable and clinically successful AI-driven nanomedicine systems.

13.1 Data Constraints and Standardization

One of the major challenges in AI/ML-based nanomedicine research is the limited availability of high-quality, diverse, and standardized datasets. AI models require large amounts of accurate and well-annotated data for effective training and prediction. However, many nanomedicine studies do not publicly share raw datasets or detailed experimental protocols, making it difficult to build robust and reproducible computational models.

Gharibi et al. (2024) demonstrated that standardized processing pipelines for protein corona analysis can significantly improve reproducibility and consistency across different laboratories. Their study highlighted the importance of uniform metadata collection and analytical standards in multi-laboratory nanomedicine research.

Another major issue is data inconsistency. Even when datasets are available, they are often stored in different formats and may lack critical experimental details such as NP size distribution, surface chemistry, or biological conditions. These inconsistencies complicate data integration and reduce model reliability.

To address these challenges, several specialized nanomedicine databases have been developed for data curation and sharing. One important example is caNanoLab, established by the National Cancer Institute (NCI) in 2007 (Gaheen et al. 2013). This database collects information related to nano-bio interactions, drug efficacy, safety studies, and NP characterization to support AI-assisted nanomedicine development and clinical translation.

Bender and Cortes-Ciriano (2021a) emphasized that comprehensive, bias-free, and standardized datasets are essential for accurate ML predictions. Limited or incomplete datasets may cause AI systems to overlook potentially effective NP formulations or produce unreliable predictions.

Therefore, large-scale open-access databases, standardized reporting systems, FAIR data-sharing principles, and collaborative multi-laboratory research are essential for advancing AI/ML applications in nanomedicine.

13.2 Model Generalizability and Validation

Another critical challenge in AI-driven nanomedicine is model generalizability. Many AI and ML models perform well under controlled laboratory conditions but fail to accurately predict outcomes under complex in vivo biological environments (Bender and Cortes-Ciriano 2021a).

Most current AI models are trained primarily using in vitro datasets such as NP transfection efficiency or cellular uptake measurements obtained from specific cell lines (Ding et al. 2023; Wu et al. 2024). However, these simplified experimental systems cannot fully represent the biological complexity of living organisms.

When translating NP formulations from in vitro studies to animal models or human clinical trials, additional factors such as immune response, tissue barriers, biodistribution variability, and off-target accumulation significantly influence NP behavior (Carrasco et al. 2021). As a result, many AI models struggle to accurately predict real-world therapeutic outcomes.

To overcome this problem, researchers are increasingly using transfer learning and pre-training strategies. In these approaches, AI models are initially trained using large in vitro datasets and later fine-tuned using smaller in vivo datasets (Bae et al. 2025; Shan et al. 2024). However, the limited availability of high-quality in vivo data remains a major obstacle.

Few-shot learning approaches are also gaining attention because they allow AI models to maintain prediction accuracy even when trained on relatively small datasets.

- Researchers suggest that improving model generalizability will require:
  - Multi-platform validation across different NP systems
  - Testing under multiple administration routes
  - Integration of mechanistic biological knowledge
  - Physics-informed AI frameworks
  - Continuous refinement of computational models

(Wang, Chen, et al. 2024)

Overall, despite the significant advantages of AI and ML in nanomedicine development, major improvements in data quality, model validation, regulatory frameworks, and experimental scalability are still required. Addressing these limitations will help accelerate the development of safer, more reliable, and clinically successful AI-driven nanomedicine systems.

Table 2. Key Challenges and Potential Solutions in AI/ML-Driven Nanomedicine

Challenge	Impact on Research	Potential Solutions / Strategies
Data Scarcity and Quality	Limited, inconsistent, and poorly annotated datasets reduce AI model accuracy and predictive performance.	Develop centralized databases such as caNanoLab and eNanoMapper; follow FAIR data-sharing principles; encourage multi-laboratory collaborations and standardized protocols.
Model Generalizability	AI models trained on in vitro datasets often fail to accurately predict in vivo biological outcomes.	Apply transfer learning, physics-informed AI models, and multi-stage validation from cell culture studies to animal and clinical studies.
Algorithmic Bias	Overfitting and biased datasets may favor common NP formulations while ignoring rare or novel nanomaterials.	Use diverse datasets, cross-validation techniques, explainable AI methods (e.g., SHAP), and incorporate biological domain knowledge.
Regulatory and Ethical Challenges	Lack of clear FDA guidelines and concerns related to patient-data privacy slow clinical translation.	Develop transparent and explainable AI frameworks; establish ethical guidelines;

Challenge	Impact on Research	Potential Solutions / Strategies
		involve regulatory agencies during early-stage development.

14. Conclusion

Nanomedicine has emerged as a highly promising approach for precision drug delivery and advanced therapeutic applications. However, the development of effective NP systems remains challenging because of complex formulation parameters, unpredictable in vivo behavior, and limited predictive capabilities of traditional experimental methods.Recent advancements in AI and ML have significantly transformed nanomedicine research by accelerating NP design, improving formulation optimization, analyzing large-scale biological datasets, and enhancing prediction of biodistribution, toxicity, and therapeutic efficacy. AI-driven computational models, high-throughput screening platforms, DNA barcoding technologies, and proteomics-based protein corona analysis have enabled more rational and data-driven nanomedicine development.

Advanced computational frameworks integrating PBPK modeling, QSAR analysis, deep learning, NODEs, PINNs, and generative AI approaches have further improved the ability to predict NP behavior under complex biological conditions. These technologies support the optimization of NP stability, endosomal escape, targeted delivery, and nano-bio interactions while reducing dependence on traditional trial-and-error experimentation.Despite these advancements, several challenges still remain, including limited data availability, lack of standardized datasets, model generalizability issues, algorithmic bias, regulatory uncertainty, and ethical concerns related to AI-driven healthcare systems. Successful clinical translation of AI-assisted nanomedicine will require transparent data sharing, standardized reporting protocols, interdisciplinary collaboration, and well-defined regulatory frameworks.

Future research is expected to focus on integrating physics-informed AI models, autonomous experimental platforms, high-throughput validation systems, and adaptive real-time AI technologies for next-generation nanomedicine development. As AI and nanomedicine continue to evolve together, the possibility of developing highly personalized, safer, and more efficient NP-based therapeutics is becoming increasingly achievable.Overall, the integration of AI and ML with nanomedicine represents a major step toward a more intelligent, efficient, and precision-driven future in drug delivery and therapeutic development.

15. REFERENCES

1. Mitchell MJ, Billingsley MM, Haley RM, et al. Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery. 2021.
2. Huang X, et al. Applications of nanomedicine in cancer and neurological disorders. 2024.
3. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nature Reviews Cancer. 2017.
4. Wang H, Hu Y, et al. Nanomedicine applications in infectious and neurological diseases. 2024.
5. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature Biotechnology. 2015.
6. Chen K, et al. AI-assisted prediction models in nanomedicine development. 2023.
7. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumors. Nature Reviews Materials. 2016.
8. Kim J, et al. Nanoparticle physicochemical properties and biological performance. 2024.
9. Francia V, Yang K, Deville S, et al. Corona composition can affect nanoparticle uptake and targeting. Nature Nanotechnology. 2019.
10. Shaw A, et al. Nano-bio interactions and nanoparticle surface modifications. 2025.
11. Cheng Y, et al. Nanoparticle biodistribution and pharmacokinetics database studies. 2020.
12. Nuhn L. Artificial intelligence in nanomedicine development. 2023.
13. Ho D. Artificial intelligence in nanomedicine. Advanced Drug Delivery Reviews. 2022.
14. Li Y, et al. Machine learning-guided optimization of lipid nanoparticles for RNA delivery. 2024.
15. Mi P, et al. Deep learning models for nanoparticle biodistribution prediction. 2024.
16. Shan W, et al. Directed evolution framework for AI-driven nanomedicine optimization. 2024.
17. Banaye Yazdipour A, et al. ML applications in nanoparticle toxicity prediction. 2023.
18. Chou WC, Lin Z, et al. AI-PBPK and QSAR modeling for nanoparticle pharmacokinetics. 2023.
19. Ban M, et al. Machine learning analysis of protein corona formation and immune interactions. 2020.
20. Bets K, et al. Data augmentation strategies in AI-assisted nanomedicine. 2024.
21. Jahandoost M, et al. Transfer learning approaches in nanomedicine AI models. 2024.
22. Xue L, et al. AI-Guided Ionizable Lipid Engineering (AGILE) platform for mRNA delivery. 2024.
23. Witten J, et al. AI-guided lipid nanoparticle design for pulmonary gene therapy. 2024.
24. Wang Y, Chen X, et al. Large-scale in silico screening of ionizable lipids for RNA therapeutics. 2022.
25. Ding Y, et al. FormulationAI and computational optimization of nanomedicine formulations. 2023.
26. Rezvantalab S, et al. Deep generative models for nanocarrier optimization. 2024.
27. Stillman Z, et al. Reinforcement learning and multiscale simulation for nanoparticle optimization. 2021.
28. Agrahari V, Agrahari V. Open-source databases and nanomedicine standardization frameworks. 2018.
29. Dordevic L, et al. Standardized reporting systems for nanomedicine datasets. 2022.

30. Jumper J, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021.
31. Yang M, et al. AI-assisted protein and peptide structure prediction in nanomedicine. 2023.
32. Gomari H, et al. Protein-based targeting ligands for nanoparticle drug delivery. 2025.
33. Hou X, et al. Nanoparticle stability and biological performance. 2021.
34. Carrasco MJ, et al. Endosomal escape mechanisms in nanoparticle therapeutics. 2021.
35. Nayanathara A, et al. Stimuli-responsive nanoparticles for intracellular delivery. 2025.
36. Smith SA, et al. Proton sponge effect and membrane-disruptive nanomaterials. 2019.
37. Chen L, Lv Y. Machine learning-assisted nanoparticle synthesis and optimization. 2022.
38. Fatima N, et al. ML optimization of stimuli-responsive nanomaterials. 2024.
39. Mahmoudi M, et al. Biological barriers and nanoparticle pharmacokinetics. 2023.
40. Park K. Nanoparticle biodistribution and translational challenges. 2020.
41. Yuan H, et al. Physiologically based pharmacokinetic modeling of nanoparticles. 2023.
42. Dogra P, et al. PBPK modeling approaches in nanomedicine. 2020.
43. Lin Z, Aryal B, et al. AI-assisted PBPK modeling for nanoparticle biodistribution. 2022.
44. Le T, et al. Challenges in PBPK parameter estimation for nanoparticles. 2022.
45. Khakpour S, et al. Multi-view cross-attention AI models for tumor biodistribution prediction. 2025.
46. Lu J, et al. Neural ordinary differential equations in pharmacokinetic modeling. 2021.
47. Bram R, et al. Physics-informed neural networks and AI pharmacokinetic models. 2024.
48. Karniadakis GE, et al. Physics-informed machine learning approaches. 2021.
49. Ahmadi Daryakenari A, et al. CMINNs model for pharmacokinetic prediction. 2025.
50. Dahlman JE, et al. DNA barcoding and high-throughput nanoparticle screening. 2017.
51. Gimondi S, et al. Microfluidic automation in nanomedicine research. 2023.
52. Guimaraes P, et al. DNA-barcoded LNP screening for SARS-CoV-2 vaccine development. 2024.
53. Gharibi H, et al. Standardized proteomics pipelines for protein corona analysis. 2024.
54. Blume JE, et al. Multi-nanoparticle plasma proteome profiling. 2020.
55. Liessi N, et al. Protein corona orientation and nanoparticle interactions. 2021.
56. Ouassil N, et al. Supervised learning prediction of protein adsorption on carbon nanotubes. 2022.
57. Huzar TF, et al. XGBoost prediction of protein corona formation on DNA nanostructures. 2025.
58. Findlay MR, et al. Random forest prediction of silver nanoparticle protein corona formation. 2018.
59. Cao Y, et al. AI prediction of nanoparticle-induced pulmonary fibrosis. 2025.
60. Atz K, et al. Generative AI and GAN applications in drug discovery. 2024.
61. Korshunova M, et al. Reinforcement learning approaches in molecular and nanoparticle design. 2022.
62. Popova M, et al. Deep reinforcement learning for molecular optimization. 2018.
63. Rahman MM, et al. GAN-based inverse nanoparticle design strategies. 2025.
64. Hasanzadeh A, et al. AI optimization of nanoparticle targeting and biodistribution. 2022.
65. Tao H, et al. Reinforcement learning for nanoparticle optimization. 2021.

66. Yao Z, et al. Generative AI applications in porous material design. 2021.
67. Liu Y, et al. AI-driven photonic material optimization. 2023.
68. Sanchez-Lengeling B, Aspuru-Guzik A. Inverse molecular design using generative models. 2018.
69. Canchola J, et al. Generative AI optimization of protein corona formation for tumor targeting. 2025.
70. Hickman R, et al. Robot scientist systems and active learning in nanomedicine. 2023.
71. Rapp M, et al. Autonomous AI-driven experimental platforms for nanoparticle optimization. 2024.